

CHAPTER NINE

What Limitations Are Inherent in Informed Consent?

To give effective protection to the subject's rights and the integrity of the human experimentation process, the concept of informed consent must take into account the limitations on the subject's ability to make "intelligent" and "insightful" decisions. In this chapter we examine the impediments to self-determination and informed consent inherent in the intellectual capacities, psychological forces, and social pressures operating in and on man. More specifically, we ask whether an awareness of these problems on the part of investigators and subjects can overcome the failures of communication, understanding, and intelligent decisionmaking which now plague the research process.

The limitations of informed consent discussed in this and the following chapters raise questions which go far beyond the human experimentation process. Like the larger issues underlying experimentation, which were presented in Chapter Three, the definitions of these limits reflect contradictory assumptions about the nature and rights of man. These assumptions are only touched upon here, but they should be kept in mind in order not to isolate human experimentation from other societal practices nor, in turn, to neglect questioning those practices in light of our explorations.

In studying these materials, re-evaluate the answers already given to the questions posed in Chapter Eight. In addition, consider the following questions:

1. How and to what extent should the dynamics of the inner and outer world, inherent in the nature of man as an individual and social being, be taken into account in defining his capacity for self-determination and informed consent?

2. How and to what extent are these dynamics affected by the nature and extent of the communications given to subjects?
3. To what extent can and should the investigator ascertain from the subject that informed consent has been obtained?
4. How should the authority of the subject to make decisions be affected by any limitations inherent in informed consent?
5. What implications do the answers to the previous questions have for the formulation, administration, and review of the human experimentation process?

A. Barriers to Achieving Autonomy

1.

The Impact of the Inner World

a.

Sigmund Freud Introductory Lectures on Psycho-analysis (1916)*

[M]ental processes are in themselves unconscious and . . . of all mental life it is only certain individual acts and portions that are conscious. [P]sychoanalysis . . . cannot accept the identity of the conscious and the mental. It defines what is mental as processes, such as, feeling, thinking, and willing, and it is obliged to maintain that there is unconscious thinking and unapprehended willing. . . . The question whether we are to make the psychical coincide with the conscious or make it extend further sounds like an empty dispute about words; yet I can assure you that the hypothesis of there being unconscious mental processes paves the way to a decisive new orientation in the world and in science.

* * *

We will not start with postulates but with an investigation. Let us choose as its subject certain phenomena which are very common and very familiar but which have been very little examined, and which, since they can be observed in any healthy person, have nothing to do with illnesses. They are what are known as "parapraxes," to

which everyone is liable. It may happen, for instance, that a person who intends to say something may use another word instead (a *slip of the tongue*) . . . or he may do the same thing in writing, and may or may not notice what he has done. Or a person may read something, whether in print or manuscript, different from what is actually before his eyes (a *misreading*) . . . or he may hear wrongly something that has been said to him (a *mishearing*). . . . Another group of these phenomena has as its basis *forgetting* . . . not, however, a permanent forgetting but only a temporary one. Thus a person may be unable to get hold of a *name* which he nevertheless knows and which he recognizes at once, or he may forget to carry out an *intention*, though he remembers it later and has thus only forgotten it at that particular moment. In a third group the temporary character is absent—for instance, in the case of *mislaying* . . . when a person has put something somewhere and cannot find it again, or in the precisely analogous case of *losing*. . . . Here we have a forgetting which we treat differently from other kinds of forgetting, one at which we are surprised or annoyed instead of finding it understandable. . . .

* * *

The most usual, and at the same time the most striking kind of slips of the tongue . . . are those in which one says the precise opposite of what one intended to say. Here, of course, we are very remote from relations between sounds and the effects of similarity; and instead we can appeal to the fact that contraries have a strong conceptual kinship with each other and stand in a particularly close psychological association with each other. There are historical examples of such occurrences. A president of the Lower House of

* James Strachey, ed.: 15 *The Standard Edition of the Complete Psychological Works of Sigmund Freud*. London: The Hogarth Press and the Institute of Psychoanalysis 21–22, 25–26, 33–35, 44–45, 52–53, 57–58, 60, 64–66, 72–74 (1963). Reprinted by permission of George Allen & Unwin Ltd., London, and Liveright Publishing Corp., N.Y.

our Parliament once opened the sitting with the words: "Gentlemen, I take notice that a full quorum of members is present and herewith declare the sitting *closed*."

* * *

[W]hat results from the slip of the tongue has a sense of its own. What do we mean by "has a sense"? That the product of the slip of the tongue may perhaps itself have a right to be regarded as a completely valid psychical act, pursuing an aim of its own, as a statement with a content and significance. So far we have always spoken of "parapraxes [faulty acts]," but it seems now as though sometimes the faulty act was itself quite a *normal* act, which merely took the place of the other act which was the one expected or intended.

The fact of the parapraxis having a sense of its own seems in certain cases evident and unmistakable. When the president of the Lower House with his first words *closed* the sitting instead of opening it, we feel inclined, in view of our knowledge of the circumstances in which the slip of the tongue occurred, to recognize that the parapraxis had a sense. The president expected nothing good of the sitting and would have been glad if he could have brought it to an immediate end. We have no difficulty in pointing to the sense of this slip of the tongue. [Or] we are told that a lady who was well known for her energy remarked on one occasion: "My husband asked his doctor what diet he ought to follow; but the doctor told him he had no need to diet: he could eat and drink what I want." Here again the slip of the tongue has an unmistakable other side to it: It was giving expression to a consistently planned program.

* * *

[P]arapraxes . . . are not chance events but serious mental acts: they have a sense; they arise from the concurrent action—or perhaps rather, the mutually opposing action—of two different intentions. . . .

* * *

[I]s this the explanation of *all* cases of slips of the tongue? I am very much inclined to think so, and my reason is that every time one investigates an instance of a slip of the tongue an explanation of this kind is forthcoming. But it is also true that there is no way of proving that a slip of the tongue cannot occur without this mechanism. It may be so; but theoretically it is

a matter of indifference to us, since the conclusions we want to draw for our introduction to psychoanalysis remain, even though—which is certainly not the case—our view holds good of only a minority of cases of slips of the tongue. The next question—whether we may extend our view to other sorts of parapraxis—I will answer in advance with a "yes". . . .

* * *

[A] lady inquired from her doctor for news of a common acquaintance, but called her by her maiden name. She had forgotten her friend's married name. She admitted afterwards that she had been very unhappy about the marriage and disliked her friend's husband.

* * *

The forgetting of intentions can in general be traced to an opposing current of thought, which is unwilling to carry out the intention. But this view is not only held by us psychoanalysts; it is the general opinion, accepted by everyone in their daily lives and only denied when it comes to theory. A patron who gives his protégé the excuse of having forgotten his request fails to justify himself. The protégé immediately thinks: "It means nothing to him; it's true he promised, but he doesn't really want to do it." For that reason forgetting is banned in certain circumstances of ordinary life; the distinction between the popular and the psychoanalytic view of the parapraxes seems to have disappeared. Imagine the lady of the house receiving her guest with the words: "What? Have you come today? I'd quite forgotten I invited you for today." Or imagine a young man confessing to his fiancée that he had forgotten to keep their last rendezvous. He will certainly not confess it; he will prefer to invent on the spur of the moment the most improbable obstacles which prevented his appearing at the time and afterwards made it impossible for him to let her know. We all know, too, that in military affairs the excuse of having forgotten something is of no help and is no protection against punishment, and we must all feel that that is justified. Here all at once everyone is united in thinking that a particular parapraxis has a sense and in knowing what that sense is. . . .

* * *

. . . The governing condition of these cases, it will be realized, is that the present psychical situation is unknown to us or inaccessible to our inquiries. Our interpretation is consequently no

more than a suspicion to which we ourselves do not attach too much importance. Later, however, something happens which shows us how well-justified our interpretation had been. I was once the guest of a young married couple and heard the young woman laughingly describe her latest experience. The day after her return from the honeymoon she had called for her unmarried sister to go shopping with her as she used to do, while her husband went to his business. Suddenly she noticed a gentleman on the other side of the street, and nudging her sister had cried: "Look, there goes Herr L." She had forgotten that this gentleman had been her husband for some weeks. I shuddered as I heard the story, but I did not dare to draw the inference. The little incident only occurred to my mind some years later when the marriage had come to a most unhappy end.

* * *

... We may take it as the outcome of our efforts so far and the basis of our further investigations that parapraxes have a sense. Let me insist once again that I am not asserting—and for our purposes there is no need to do so—that every single parapraxis that occurs has a sense, even though I regard that as probably the case. It is enough for us if we can point to such a sense relatively often in the different forms of parapraxis. Moreover, in this respect these different forms behave differently. Cases of slips of the tongue and of the pen, etc., may occur on a purely physiological basis. I cannot believe that this is so in the types depending on *forgetting* (forgetting names or intentions, mislaying, etc.). It is very probable that there are cases of *losing* which can be regarded as unintended. It is in general true that only a certain proportion of the *errors* that occur in ordinary life can be looked at from our point of view. ...

* * *

We can now turn ... to the main question, which we have long postponed, of what sort of intentions these are, which find expression in this unusual fashion as disturbers of other intentions. Well, they are obviously of very different sorts, among which we must look for the common factor. If we examine a number of examples with this in view, they will soon fall into three groups. The first group contains those cases in which the disturbing purpose is known to the speaker and, moreover, had been noticed by him before he made the slip of the tongue. ... A second group is made up of other cases in which the disturbing purpose is equally recognized as his

by the speaker, but in which he was unaware that it was active in him just before he made the slip. Thus, he accepts our interpretation of his slip, but nevertheless remains to some extent surprised at it. ... In a third group the interpretation of the disturbing intention is vigorously rejected by the speaker; he not only denies that it was active in him before he made the slip, but seeks to maintain that it is entirely foreign to him. ...

* * *

[W]hat distinguishes these three groups from one another is the differing extent to which the intention is forced back. In the first group the intention is there and makes itself noticed before the speaker's remark; only then is it rejected; and it takes its revenge in the slip of the tongue. In the second group the rejection goes further; the intention has already ceased to be noticeable before the remark is made. Strangely enough, this does not in the least prevent it from playing its part in causing the slip. But this behavior makes it easier for us to explain what happens in the third group. I shall venture to assume that a purpose can also find expression in a parapraxis when it has been forced back and not noticed for a considerable time, for a very long time perhaps, and can for that reason be denied straight out by the speaker. But even if you leave the problem of the third group on one side, you are bound to conclude from the observations we have made in the other cases that *the suppression of the speaker's intention to say something is the indispensable condition for the occurrence of a slip of the tongue*.

[P]arapraxes are the outcome of a compromise: They constitute a half-success and a half-failure for each of the two intentions; the intention which is being challenged is neither completely suppressed nor, apart from special cases, carried through quite unscathed. ...

* * *

The instances of forgetting an intention are in general so uniform and so conspicuous that for that very reason they are of no interest for our investigation. Nevertheless there are two points at which we can learn something new from a study of these parapraxes. Forgetting—that is, failure to carry out—an intention points, as we have said, to a counter-will that is hostile to it. This is no doubt true; but our inquiries show that the counter-will can be of two kinds—direct or indirect. What I mean by the latter will best appear from one or two examples. ... [S]uppos-

ing someone forgets an appointment which he has promised someone else to keep, the most frequent reason for it will be, no doubt, a direct disinclination to meeting this person. But in such a case analysis might show that the disturbing purpose did not relate to him but was directed against the place at which the meeting was planned to happen and was avoided on account of a distressing memory attaching to it. Or, again, if someone forgets to post a letter, the counter-purpose may be based on the contents of the letter; but it is by no means out of the question that the letter may be harmless in itself and may only be subject to the counter-purpose because something about it recalls another letter which had been written on some earlier occasion and which offered the counter-will a direct point of attack. It can be said, therefore, that here the counter-will was transferred from the earlier letter, which justified it, to the present one, which it had in fact no grounds for concern about. . . .

Phenomena such as these last may seem to you most unusual, and you will perhaps be inclined to suppose that an "indirect" counter-will already indicates that the process is a pathological one. But I can assure you that it occurs as well within the limits of what is normal and healthy. . . .

The second point I have in mind is this. If in a large majority of instances we find confirmation of the fact that the forgetting of an intention goes back to a counter-will, we grow bold enough to extend the solution to another set of instances in which the person under analysis does not confirm but denies the counter-will we have inferred. Take as examples of this such extremely common events as forgetting to return books one has been lent or to pay bills or debts. We shall venture to insist to the person concerned that an intention exists in him to keep the books and not to pay the debts, while he will deny this intention but will not be able to produce any other explanation of his behavior. Thereupon we shall go on to say that he has this intention but knows nothing about it, but that it is enough for us that it reveals its presence by producing the forgetting in him. He may repeat to us that he has in fact forgotten. You will now recognize the situation as one in which we found ourselves once before. If we want to pursue our interpretations of parapraxes, which have so frequently proved justified, to a consistent conclusion, we are forced to the inescapable hypothesis that there are purposes in people which can become operative without their knowing about them. . . .

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NOTES

NOTE 1.

ERNEST JONES
THE REPRESSION THEORY IN ITS
RELATION TO MEMORY*

. . . In working with psychoanalysis one finds that the unconscious material in the mind is very much more extensive than might have been surmised, that the assimilative capacity of the complexes, due to the radiation of affect, is very much greater, and that, therefore, the number of associations that are established in the unconscious is simply enormous. That being so, it is extremely difficult, and at present impossible, to set any limits to the extent to which operations characteristically applying to unconscious material, such as repression does, are in action. One is practically never in a position, for instance, to assert that such and such an idea cannot have been associated with any "unpleasant" buried complex, for to be so would necessitate a most searching investigation of all its associations, both conscious and unconscious. It is rather like the question of the alleged destruction or fading of forgotten memories, a negative proposition that it is impossible to prove. One can only say, with considerable emphasis, that the more extensive the investigation the greater is the number of forgotten ideas that prove to be affectively connected with repressed complexes, so that the possibility is at least open that they all are.

NOTE 2.

SIGMUND FREUD
A DIFFICULTY IN THE PATH OF
PSYCHO-ANALYSIS (1917)†

* * *

[T]he universal narcissism of men, their self-love, has up to the present suffered three severe blows from the researches of science.

(a) In the early stages of his researches, man believed at first that his dwelling-place, the earth, was the stationary centre of the universe,

* *Papers on Psychoanalysis*. London: Baillière, Tindall & Cox 117 (1920). Reprinted by permission of Baillière, Tindall & Cassell, Ltd.

† James Strachey, ed.: *The Standard Edition of the Complete Psychological Works of Sigmund Freud*. London: The Hogarth Press and the Institute of Psychoanalysis 139-143 (1955). Reprinted by permission of Sigmund Freud Copyrights, Ltd., the Institute of Psychoanalysis and the Hogarth Press, Ltd., London, and of Basic Books, Inc., N.Y.

with the sun, moon and planets circling round it. In this he was naively following the dictates of his sense-perceptions, for he felt no movement of the earth, and wherever he had an unimpeded view he found himself in the centre of a circle that enclosed the external world. The central position of the earth, moreover, was a token to him of the dominating part played by it in the universe and appeared to fit in very well with his inclination to regard himself as lord of the world.

The destruction of this narcissistic illusion is associated in our minds with the name and work of Copernicus in the sixteenth century. . . .

(b) In the course of the development of civilization man acquired a dominating position over his fellow-creatures in the animal kingdom. Not content with this supremacy, however, he began to place a gulf between his nature and theirs. He denied the possession of reason to them, and to himself he attributed an immortal soul, and made claims to a divine descent which permitted him to break the bond of community between him and the animal kingdom. . . .

We all know that little more than half a century ago the researches of Charles Darwin and his collaborators and forerunners put an end to this presumption on the part of man. . . .

(c) The third blow, which is psychological in nature, is probably the most wounding.

Although thus humbled in his external relations, man feels himself to be supreme within his own mind. Somewhere in the core of his ego he has developed an organ of observation to keep a watch on his impulses and actions and see whether they harmonize with its demands. If they do not, they are ruthlessly inhibited and withdrawn. His internal perception, consciousness, gives the ego news of all the important occurrences in the mind's working, and the will, directed by these reports, carries out what the ego orders and modifies anything that seeks to accomplish itself spontaneously. For this mind is not a simple thing; on the contrary, it is a hierarchy of superordinated and subordinated agencies, a labyrinth of impulses striving independently of one another towards action, corresponding with the multiplicity of instincts and of the relations with the external world, many of which are antagonistic to one another and incompatible. For proper functioning it is necessary that the highest of these agencies should have knowledge of all that is going forward and that its will should penetrate everywhere, so as to exert its influence. And in fact the ego feels secure both as to the completeness and trustworthi-

ness of the reports it receives and as to the openness of the channels through which it enforces its commands.

In certain diseases—including the very neuroses of which we have made special study—things are different. The ego feels uneasy; it comes up against limits to its power in its own house, the mind. Thoughts emerge suddenly without one's knowing where they come from, nor can one do anything to drive them away. These alien guests even seem to be more powerful than those which are at the ego's command. They resist all the well-proved measures of enforcement used by the will, remain unmoved by logical refutation, and are unaffected by the contradictory assertions of reality. Or else impulses appear which seem like those of a stranger, so that the ego disowns them; yet it has to fear them and take precautions against them. The ego says to itself: "This is an illness, a foreign invasion." It increases its vigilance, but cannot understand why it feels so strangely paralysed.

Psychiatry, it is true, denies that such things mean the intrusion into the mind of evil spirits from without; beyond this, however, it can only say with a shrug: "Degeneracy, hereditary disposition, constitutional inferiority!" Psycho-analysis sets out to explain these uncanny disorders; it engages in careful and laborious investigations, devises hypotheses and scientific constructions, until at length it can speak thus to the ego:—

"Nothing has entered into you from without: a part of the activity of your own mind has been withdrawn from your knowledge and from the command of your will. That, too, is why you are so weak in your defence: you are using one part of your force to fight the other part and you cannot concentrate the whole of your force as you would against an external enemy. And it is not even the worst or least important part of your mental forces that has thus become antagonistic to you and independent of you. The blame, I am bound to say, lies with yourself. You over-estimated your strength when you thought you could treat your sexual instincts as you liked and could utterly ignore their intentions. The result is that they have rebelled and have taken their own obscure paths to escape this suppression; they have established their rights in a manner you cannot approve. How they have achieved this, and the paths which they have taken, have not come to your knowledge. All you have learned is the *outcome* of their work—the symptom which you experience as suffering. Thus you do not recognize it as a derivative of

your own rejected instincts and do not know that it is a substitutive satisfaction of them.

"The whole process, however, only becomes possible through the single circumstance that you are mistaken in another important point as well. You feel sure that you are informed of all that goes on in your mind if it is of any importance at all, because in that case, you believe, your consciousness gives you news of it. And if you have had no information of something in your mind you confidently assume that it does not exist there. Indeed, you go so far as to regard what is 'mental' as identical with what is 'conscious'—that is, with what is known to you—in spite of the most obvious evidence that a great deal more must constantly be going on in your mind than can be known to your consciousness. Come, let yourself be taught something on this one point! What is in your mind does not coincide with what you are conscious of; whether something is going on in your mind and whether you hear of it, are two different things. In the ordinary way, I will admit, the intelligence which reaches your consciousness is enough for your needs; and you may cherish the illusion that you learn of all the more important things. But in some cases, as in that of an instinctual conflict such as I have described, your intelligence service breaks down and your will then extends no further than your knowledge. In every case, however, the news that reaches your consciousness is incomplete and often not to be relied on. Often enough, too, it happens that you get news of events only when they are over and when you can no longer do anything to change them. Even if you are not ill, who can tell all that is stirring in your mind of which you know nothing or are falsely informed? You behave like an absolute ruler who is content with the information supplied him by his highest officials and never goes among the people to hear their voice. Turn your eyes inward, look into your own depths, learn first to know yourself! Then you will understand why you were bound to fall ill; and, perhaps you will avoid falling ill in future."

It is thus that psycho-analysis has sought to educate the ego. But these two discoveries—that the life of our sexual instincts cannot be wholly tamed, and that mental processes are in themselves unconscious and only reach the ego and come under its control through incomplete and untrustworthy perceptions—these two discoveries amount to a statement that *the ego is not master in its own house*. Together they represent the third blow to man's self-love, what I may call

the *psychological* one. No wonder, then, that the ego does not look favourably upon psycho-analysis and obstinately refuses to believe in it.

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NOTE 3.

ROBERT P. KNIGHT
DETERMINISM, "FREEDOM," AND
PSYCHOTHERAPY*

* * *

The first step in extricating ourselves from the confusion inherent in the determinism versus free will debate lies in clarifying the terms. Determinism in the physical world is no longer seriously questioned by scientists or philosophers. Its alternative, indeterminism—pure chance, accident, unpredictability—represents chaos. "Indeterminacy" in modern (post-Newtonian) physics, simply refers to the fact that human limits of perception and their intrusion into the field of the experimental measuring instruments make absolute precision impossible. Rigorous physical determinism is not contested by Heisenberg's principle of indeterminacy. In the psychological and philosophical realm there is also no real alternative to psychic determinism. To defend "free will" as an alternative is to be guilty of semantic confusion. Determinism refers to the complex of causal factors, hereditary and environmental, internal and external, past and present, conscious and unconscious, which combine to produce a certain resultant in a given individual. Determinism is thus a theoretical construct which fits the observed data, as demonstrated by predictions which were fulfilled, and which is essential to any psychology which claims to be scientific. The antithesis to this construct is the construct, indeterminism—pure chance, chaos. "Free will," on the other hand, is not on the same conceptual level as are these constructs. It refers to a subjective psychological experience, and to compare it to determinism is like comparing the enjoyment of flying to the law of gravity.

... A scrutiny of this matter of "choice" may lead us to further understanding. When such choices involve only trivial matters, the mentally healthy person has the subjective sense of complete freedom of choice, and hence feels

* 9 *Psychiatry* 251-259 (1946). Copyright 1946 by the William Alanson White Psychiatric Foundation. Reprinted by special permission of the William Alanson White Psychiatric Foundation, Inc.

that he has acted of his own free will. Indeed, were a person not to feel free to choose in trivial matters, but instead feel powerfully compelled toward a single course, and experience anxiety if prevented from completing his choice, we would suspect him of suffering from a compulsion neurosis. Or if he were unable to choose quickly and lightly—that is, with a sense of freedom of choice—in unimportant matters we would suspect the presence of obsessional doubt. In weightier matters, however, the healthy person has a combined feeling of freedom and of inner compulsion. He feels that his course is determined by standards, beliefs, knowledge, aspirations that are an integral part of himself and he can do no other; yet at the same time he feels free. A decision or course of action that is in harmony with his character seems to carry with it the reward of a pleasurable sense of freedom. It is not easy to analyze the sense of freedom as it is used in this context but it can be described more fully. In a negative sense it means absence of anxiety, of irrational doubt, and of those inhibitions and restrictions which paralyze both choice and action. In a positive sense it connotes feelings of well-being, of self-esteem, of confidence, of inner satisfaction based on successful use of one's energies for achievement that promotes the best interests of one's fellow men as well as one's own.

It is a part of the thesis of this essay that this kind of "freedom" is experienced only by emotionally mature, well-integrated persons: it is the goal sought for one's patients in psychotherapy; and this freedom has nothing whatever to do with free will as a principle governing human behavior, but is a subjective experience which is itself causally determined. This subjective experience, however, is subjective in a special sense, not in the one which equates "subjective" with "spurious." The behavior of a well-integrated, civilized person can be objectively assessed as "free." Observers see that such a person makes ego syntonic choices, that his motives are "good," and that he is able to carry out what he wills to do.

There are, however, experiences of freedom which are illusions to the persons experiencing them. They are subjective in the sense of spuriousness. Critical examination of the nature of such varieties of the subjective experience of freedom, and objective assessment of their relationship to the actualities of life, distinguish them readily from the freedom defined above. There is, for example, the sense of freedom in

children or immature adults which occurs with the removal of external pressure or with solitary flights of fantasy of being omnipotent. The release from inner checks and restraints that occurs in mania likewise conveys a sense of complete freedom. There is a spurious sense of freedom in those persons, who, unconsciously driven by intense defiance, carry out criminal acts, acts of libertinism, and acts of spurious independence and self-assertion. One of the first tasks in the psychotherapy of such persons is to show them that they are not free, as they have thought, but are enslaved and driven by their compulsion to defy others. There is also the spurious sense of freedom that accompanies the hypocritically righteous decision in a person who perceives that a nefarious purpose may be executed under the cloak of righteousness. In such persons closer scrutiny will reveal a complicated scheme of balances between well-rationalized, sadistically motivated acts of aggression and compulsive acts and rituals of penance. Many other examples could be cited to illustrate varieties of subjective freedom which are illusions to the subject, and are vulnerable to objective assessment.

The genuine freedom which is a mark of mental health and emotional maturity is best expressed by the following quotation, whose authorship I do not know: "That man is free who is conscious of being the author of the law that he obeys." This definition includes both the sense of freedom and the sense of inner compulsion which we have designated as inseparable subjective feelings in matters of real importance in life. It also includes the concept of integration of the personality, that is, the individual's energies and impulses are subject to conscious control but are capable of satisfying discharge according to standards which the ego accepts. If it is correct to assume that this linkage of subjective freedom with inner acceptable compulsion is a criterion of mental health and of emotional and intellectual maturity in human beings, and that other experiences of subjective freedom which do not meet the test of linkage with acceptable inner compulsion and of objective assessment are psychiatrically suspect, then we have narrowed down the problem of freedom by eliminating from further consideration the spurious varieties of subjective freedom. It is sufficient to say, then, that all of the subjective experiences of freedom are, like every other psychological datum, understandable as causally determined products of many factors—hereditary, experiential, biological, cultural, and so on. "Free will" is

thus reduced from its presumptuous position as a real threat or alternative to determinism, and is demoted to the position of a variety of subjective experience—one which is itself causally determined.

[D]ynamic psychology has been able to develop constructs which fit the observable clinical data, which provide a scientific theory based on the axiom of psychological determinism. . . .

The first construct is that there is an unconscious part of the self, the id, containing the instinctual forces which are rooted in biology, and molded by infantile emotional experience. These forces are aggressive, selfish, lustful, and seek immediate gratification. But their full satisfaction in each individual, were there no external or internal controls, would result in collision with the external laws and limitations of the physical world on the one hand, and with the attempts of other individuals to fulfill their instinctual strivings on the other hand. The result would be chaos. We are saved from such chaos in organized society by the inevitable operation of natural laws and by man-made restrictive rules (laws) under which unlimited freedom for each individual is sharply curtailed so that the interests of each person are protected. The aim of man-made laws is—or, at least, should be—to guarantee the maximum degree of gratification of individual needs which is consistent with the protection of the rights of others. Civilization thus sacrifices individual freedom of action to promote collective security.

The second construct of dynamic psychology is that out of the original infantile unorganized mass of instinctual wishes there develops an organized portion of the self, the ego, which is largely conscious. It co-ordinates the faculties of perception, intelligence, judgment, memory, discrimination, learning, and so on. The ego has the task of achieving what satisfactions it can of the instinctual drives of the id, while taking cognizance of the nature of the environment and its natural and man-made restrictions. The ego is the feeling, experiencing, aware portion of the personality.

The third construct is that there also develops, in early childhood, as an internalization of the restricting, frustrating, disciplining parents and their surrogates, a third portion of the psyche called the superego, or conscience, which is largely unconscious. It is an internal master to which the ego is subject, so that the ego's adjuvative task becomes one of managing the instinctual drives from within against the limita-

tions and frustrations of the outer world, while being compelled to obey also the forbidding directives of the superego.

The development and operation of each of these portions of the self, and thus of the total personality, is causally determined in accordance with the psychological laws governing the inherited endowment, biological drives, physiological and emotional experiences, and external, natural, cultural, and interpersonal pressures affecting each individual in the milieu in which he is reared. In the healthy person there is a harmonious interrelationship between the various parts of the self and with the environment, and one of the important by-products of such harmonious integration is a subjective sense of freedom. Viewed in this way, the feeling of freedom is also determined, and is possible to be experienced only to the extent that there exists within the individual a harmonious integration of his instinctual drives, his superego standards and restrictions, his ego perceptions and discriminative faculties, and the possibilities provided by the environment. Such a theoretically healthy, integrated person will then feel free, and, to some extent, will be "free." That is, his flexibility of adaptation will be greater than that of the neurotic person, and what behavior he "chooses" will conform to the laws and standards, internal and external, which he accepts, but his choices will *feel* free.

NOTE 4.

ERNST LEWY
RESPONSIBILITY, FREE WILL,
AND EGO PSYCHOLOGY*

* * *

[David] Rapaport in a personal communication [states]:

"Man has developed an anticipatory apparatus which is far more effective than any other animal's. This apparatus is very effective for outside events and fairly effective (anxiety and other affect signals) for internal events. These events play a causal role in behavior. But man himself (and every organism to some degree) is a source of causes. Man's anticipatory apparatus is a particularly effective mobilizer of man's own causal role. Man isn't freed from internal and external causes by means of his anticipatory apparatus, that is, by dint of his being

* 42 *International Journal of Psychoanalysis* 260, 267–268 (1961). Reprinted by permission.

also a source of causes. But he certainly can within limits avoid, evade, cushion, and counteract causes which would determine his behavior. Some of these causes he is less adept at avoiding or cushioning (instinctual drives)—but to the extent that he has a relatively autonomous ego, he can do even some of that. Instinctual drives are causes and motives; other causes of the same sort (neutralized to various degrees) he can cushion better. Non-motivational causes he can yet easier evade or cushion, somatic ones less so than environmental ones.—So to the degree to which he is within these limits, he is a free agent. To this degree (and to the degree he fails to use this ability) he is responsible in the broadest sense.”

In addition to the above . . . there is the question of how the acceptance of one's responsibility is achieved and transmitted. I submit that if responsibility of the individual for himself is considered traditionally and conventionally an established reality factor, this very fact acts as a sufficiently strong adaptive force to determine the individual's choice. Assuming the capacity of the ego to adapt its operations and reactions to the environment and its realities, we can expect that the ego can be purposefully influenced by reality factors. Thus, specifically the reality fact that traditionally, conventionally, and tacitly every individual is considered to be responsible for his acts by the society in which he lives, and that this is inculcated in the child through the educational and rearing process, constitutes a powerful reality factor to which the ego has to adapt itself and is capable of adapting itself. The established standard provides the environmental setting to which the adaptable ego responds. I am referring to what Erikson calls our “institutionalized attitude”. . .

* * *

An important part of the dynamics of adaptation is played, of course, in particular in the course of growing up, by the process of the formation of the superego through identification with the authority figures, their introjection and the subsequent internalization of accepted standards. . .

* * *

. . . We not only can, we also must hold man responsible, in order to establish the necessary and correct environment. To put it bluntly, I should like to re-state Voltaire's famous saying

about God with the appropriate alteration: “If free will and responsibility did not exist, they would have to be invented”. . .

* * *

b.

Benjamin N. Cardozo The Nature of the Judicial Process*

I have spoken of the forces of which judges avowedly avail to shape the form and content of their judgments. Even these forces are seldom fully in consciousness. They lie so near the surface, however, that their existence and influence are not likely to be disclaimed. But the subject is not exhausted with the recognition of their power. Deep below consciousness are other forces, the likes and the dislikes, the predilections and the prejudices, the complex of instincts and emotions and habits and convictions, which make the man, whether he be litigant or judge. . . There has been a certain lack of candor in much of the discussion of the theme, or rather perhaps in the refusal to discuss it, as if judges must lose respect and confidence by the reminder that they are subject to human limitations. I do not doubt the grandeur of the conception which lifts them into the realm of pure reason, above and beyond the sweep of perturbing and deflecting forces. Nonetheless . . . they do not stand aloof on these chill and distant heights; and we shall not help the cause of truth by acting and speaking as if they do. The great tides and currents, which engulf the rest of men, do not turn aside in their course and pass the judges by. We like to figure to ourselves the processes of justice as coldly objective and impersonal. The law, conceived of as a real existence, dwelling apart and alone, speaks, through the voices of priests and ministers, the words which they have no choice except to utter. That is an ideal of objective truth toward which every system of jurisprudence tends. It is an ideal of which great publicists and judges have spoken as of something possible to attain. “The judges of the nation,” says Montesquieu, “are only the mouths that pronounce the words of the law, inanimate beings, who can moderate neither its force nor its rigor.” So Marshall, in *Osborne v. Bank of the United States*, 9 Wheat. 738, 866: The judicial department “has no will in any case. . . Judicial power is never exercised

* New Haven: Yale University Press 167-170 (1921). Reprinted by permission.

for the purpose of giving effect to the will of the judge; always for the purpose of giving effect to the will of the legislature; or, in other words, to the will of the law." It has a lofty sound; it is well and finely said; but it can never be more than partly true. Marshall's own career is a conspicuous illustration of the fact that the ideal is beyond the reach of human faculties to attain. He gave to the constitution of the United States the impress of his own mind; and the form of our constitutional law is what it is, because he moulded it while it was still plastic and malleable in the fire of his own intense convictions. At the opposite extreme are the words of the French jurist, Saleilles, in his treatise "De la Personnalité Juridique": "One wills at the beginning the result; one finds the principle afterwards; such is the genesis of all juridical construction. Once accepted, the construction presents itself, doubtless, in the ensemble of legal doctrine, under the opposite aspect. The factors are inverted. The principle appears as an initial cause, from which one has drawn the result which is found deduced from it." I would not put the case thus broadly. So sweeping a statement exaggerates the element of free volition. It ignores the factors of determinism which cabin and confine within narrow bounds the range of unfettered choice. Nonetheless, by its very excess of emphasis, it supplies the needed corrective of an ideal of impossible objectivity. . . .

* * *

c.

Carl H. Fellner and John R. Marshall
Kidney Donors—
The Myth of Informed Consent*

* * *

[W]e undertook to study all available previous [kidney] donors to find out how they had become involved [and] how they had made their decision. . . .

* * *

Of the 20 donors interviewed, 14 were seen at five weeks to 24 months after surgery, with a mean of 11 months, and six were seen before as well as after surgery. In addition, a number of

potential donors were interviewed who were subsequently rejected as medically unsuitable. Another ten potential donors who were interviewed are currently awaiting surgery. . . .

The process of making a decision to give up a kidney for a close relative begins when the first communication about the seriousness of the recipient's illness is received. It continues when the first demand for participation in the medical selection process is made and must be sustained through the long-drawn-out medical investigation and usually through a waiting period even after the decision-making process of the renal transplantation team has been concluded, the potential donor is considered a candidate for transplantation, and has been permitted to give his consent. In addition, there appears to be a third or family system, which also tends to influence the selection of a donor but which is very difficult to demonstrate.

1. *The medical selection system.* When a transplant situation arises, all possible donor relatives of the patient are asked to come to the clinic for blood tests (ABO typing). Great care is taken at this point by the medical staff to inform the volunteer subjects that this is an exceedingly preliminary procedure and that no commitment whatsoever is involved by their appearing at this clinic, or elsewhere, to have their blood samples drawn. Those potential donors who are not ruled out on the basis of blood grouping are then asked to come to the renal clinic for a brief history-taking and complete physical examination, including routine laboratory studies.

Somewhat later, those of the possible donors who still remain are asked to return to the clinic for histocompatibility tests. The results of the mixed leucocyte culture tests (MLCT) are not known until several weeks later and may have to be repeated before they can be read conclusively. Only after this stage does it become possible for the renal transplant team to select from among the available possible donors that most suitable one. He is then asked to come to the special studies unit at the hospital for a complete work-up, careful evaluation of renal status, and so on. During this brief hospitalization he is evaluated independently by at least three of the team physicians. Only at the end of this evaluation and after intensive, repeated briefing on the risks involved and the chances for success is the potential donor asked to make a decision, and permitted, if he desires, to give

* 126 *American Journal of Psychiatry* 1245-1250 (1970). Copyright 1970, the American Psychiatric Association. Reprinted by permission.

his informed consent. A final chance to refuse any time in a dignified and comfortable manner is offered in the team's expressed willingness to supply a plausible medical excuse to the recipient and family.

2. *Donor decision.* The medical selection system as described assumes that the future donor will make his decision only at the conclusion of the medical work-up and after intensive and repeated briefing. It is assumed that the decision will occur only at the end of adequate information-gathering and weighing of the pros and cons. Actually, members of the renal transplant team were aware that most of the potential donors were ready to make a commitment earlier than that and had to be held off until the team had made its selection. It was thought that this point of commitment was reached perhaps halfway through the evaluation process.

Our findings were surprising. Not one of the donors weighed alternatives and rationally decided. Fourteen of the 20 donors and nine of the ten donors waiting for surgery stated that they had made their decision immediately when the subject of the kidney transplant was first mentioned over the telephone, "in a split-second," "instantaneously," and "right away." Five said they just went along with the tests hoping it would be someone else. They could not recall ever really having made a clear decision, yet they never considered refusing to go along either. As it became clear to each of them toward the end of the selection process that he was going to be the person most suited to be the donor, each had finally committed himself to the act. However, this decision too occurred before the sessions with the team doctors in which all the relevant information and statistics were put before these individuals and they were finally asked to decide.

Of all the subjects who made their initial decision on the telephone upon first hearing of the possibility of the kidney transplant, none had consulted his or her spouse. When questioned about this particular circumstance each explained that the spouse later on had either been neutral or reinforced the decision. To the hypothetical question of "What would you have done if your spouse had said no?" each answered, "I would have gone ahead and done it anyway." One 48-year-old woman had a good deal of trouble in making her decision. The recipient was her son and the first communication that a renal transplantation would be necessary came from the doctor who had treated her son

for some time. The immediate family consisted of the donor, her husband, and four children, two of whom were under 18. The older daughter, who might have been a potential donor, immediately refused to participate in any way. The husband was a diabetic and was therefore disqualified. The woman's own doctor advised her not to do it. However, she went along with the preliminary tests, feeling very ambivalent about them. All her tests were fine and she was finally asked to make a decision before the renal arteriograms would be taken. At that point she felt she wanted to go home for another family conference to ask her husband what she should do. This was a very frightened woman, organized along strict obsessive-compulsive lines, who said, "I get worked up over every little thing, and I have never had surgery before." In the end she did decide to donate her kidney after her family consultation, saying, "I guess I had some encouragement from my husband now."

Of all the people asked to come for the preliminary blood tests, there were about eight who did not show up. Of all those who participated in the initial screening tests, only one subject later refused to participate in further tests. None of the final potential donors availed themselves of the "last-out" opportunity, although there were one or two subjects who seemed glad when they were rejected for medical reasons after the last test (arteriogram). This leads us to believe that for all participants, and by the same token for all those who refused to participate from the beginning, decision making is an early event preceding all information-gathering and clarification offered by the renal team.

Supportive evidence for the instantaneous character of the decision making came from a rather unexpected quarter. We spoke to a resident physician whose blood had been used as a control in the MLC test. By the merest chance he had proved to be compatible with the potential kidney recipient patient. When he was informed of this finding he immediately refused without even having been asked to be a donor. He was subsequently able to tell us that this had been an immediate decision and that he had later spent much time marshalling evidence in support of this decision.

The immediacy of the decision making with regard to donorship often contrasts markedly with the usual way in which the person makes other important decisions. When questioned more closely about this contrast, all our subjects clearly expressed their opinion that

this was a rather special situation that could not be compared to ordinary decision making.

3. *The family system of donor selection.* The role the family plays in the selection of donors was very difficult to demonstrate. In retrospect, this difficulty arose perhaps from the general feeling, which we shared, that the family would tend to select a likely donor in the sense of a sacrifice or scapegoat under threat of family ostracism. We could not demonstrate such dynamics in our sample, except possibly in one case.

What we did see, once we had become aware of its possibility, was that a family would *exclude* certain members from participation. This was done most commonly at the level of the initial contact. In only one case was the donor given the first communication about the possibility of renal transplant by a member of the transplant team, and in two cases by the family physician. All the others heard about it first from a family member. Usually the communication was by telephone call, the informant telling the future donor about the seriousness of the future recipient's illness and explaining that the doctors were considering a kidney transplantation and that all close relatives would be invited in the near future to come to the clinic or the hospital for some blood samples to be taken for initial tests. Usually, the informant followed this up with a brief discussion of who among the other family members should be asked to participate, who should not, and for what reasons. The same route was subsequently used to transmit the results of tests and make further appointments and could also serve to discourage further participation.

* * *

The fact remains that all the donors and potential donors interviewed by us reported a decision-making process that was immediate and "irrational" and could not meet the requirements adopted by the American Medical Association to be accepted as an "informed consent." Actually, the medical renal transplant team did not permit these donors to volunteer until a prolonged process of repeated information (or indoctrination?) had been completed. The effectiveness of this procedure must, however, be questioned by the investigators, if for no other reason than that it did not dissuade one single volunteer.

* * *

NOTE

JEAN HAMBURGER
PROTECTION OF DONOR RIGHTS IN
RENAL TRANSPLANTATION*

What is a real volunteer? I consider this very important, for it is related to the question of "informed consent" discussed this morning. I think that four conditions should exist for a real volunteer. First, he should be fully aware of the exact dangers he is running. Second, he should have a reasonable motive for wishing to donate his kidney; that is why, at Paris and at many other centres, we have adopted the habit of considering a volunteer acceptable if he is a relative of the patient to be saved and unacceptable if he is not. There are immunological reasons also. Third, the offer should be at the free will of the volunteer; it is for the doctor and for the organization dealing with the problem to verify whether there has been pressure from the family or elsewhere, such as the promise of payment. Finally, it seems to me that mental balance must be required and that, therefore, there should be a psychological, if not a psychiatric, examination to verify that the volunteer is in a full possession of his mental faculties. This psychological examination seems to us to be mandatory, both to verify that the decision is free and to say to the volunteer that if he wishes to withdraw his offer of his kidney nobody will ever know that he himself is responsible for that decision and the doctors will assume full responsibility towards the family. The examination will also ensure whether the mental balance of the donor is fully satisfactory.

These seem to me to be reasonable requirements at present: a balance of the risks and a real volunteer. Is the wish of the donor as thus expressed always completely satisfactory? This is to me a most important point, for it seems to me capable of transcending this particular case of the kidney donor. I think that in addition the doctor should put himself in the place of the donor and carry out what might be called a "motivation check."

Since it is certain that neither a patient nor a donor will ever be completely informed, I think that it is our duty to understudy the donor by a kind of check placing of ourselves in his

* V. Fattorusso, ed.: *Biomedical Science and the Dilemma of Human Experimentation*. Paris: Council for International Organizations of Medical Sciences 44 (1967). Reprinted by permission.

situation. Now that I know the donor and his behaviour, I should morally put myself in his position and see if it is reasonable for him to take that decision, since I, the doctor, am more objectively placed for assessing the safety of the donor than if I were in his necessarily subjective circumstances.

* * *

d.

**Harold Esecover, Sidney Malitz, and
Bernard Wilkens
Clinical Profiles of Paid Normal Subjects
Volunteering for Hallucinogen Drug Studies***

* * *

Our study dealt with clinical psychiatric evaluations of 56 subjects volunteering for hallucinogen studies at the New York State Psychiatric Institute from 1956 to 1959. Our focus in this work was on motivations for volunteering, incidence and types of psychopathology, relationship between psychopathology and motivations, and personality patterns.

The sample was composed of 46 males and 10 females ranging in age from 21 to 38 with a median age of 23.4, with varying occupations but a high preponderance of students. All subjects had some college and 46 had varying degrees of post-graduate training. Volunteers were recruited by posting an announcement on the bulletin boards of a university medical school and a university undergraduate school. . . .

WANTED

Volunteers. Between 21 and 30 in good physical health for special medication studies involving temporary alterations in perceptions. Subjects should be prepared to sleep in the hospital overnight. Fee \$25.

For further information and screening interview call Dr. Malitz, N.Y. State Psychiatric Institute, LO8-4000, Ext. 96.

All volunteers received an initial 1-hour psychiatric screening interview. The interview was a semi-structured one, with sufficient latitude given so that spontaneous material could emerge. . . .

* * *

A. Motivations: Motivations for volunteering were frequently quite complex and could be seen as operating simultaneously on 2 levels.

* 117 *American Journal of Psychiatry* 910-914 (1961). Copyright 1961, the American Psychiatric Association. Reprinted by permission.

Consciously stated motivations on one level; pre-conscious and unconscious ones on another. In only certain instances did we feel that we could determine the pre-conscious and unconscious roots. We felt that the subjects' conscious motivations could generally be broken down into the following broad categories: 1. Financial need; 2. Scientific interest and curiosity; 3. Seeking new experiences (adventure); 4. Indirect seeking of psychiatric help; 5. Symptomatic relief from tension, depression or anhedonia; 6. Searching for insights into personal problems; 7. Desires for status or prestige; 8. Employing the study as a vehicle for the expression of socially unacceptable impulses; and 9. Hope of stimulating creativity through drug-induced perceptions. The following brief examples will serve to illustrate some of these categories:

Seeking relief from anhedonia: A 21-year-old single male undergraduate volunteer majoring in physics described obsessive fears of dying and of pointed instruments piercing his eyes. He was undergoing a classical analysis 5 times a week at the time of volunteering. He openly expressed his feelings of boredom and anhedonia as follows: "I'm bored by nearly everything in life. I'm looking for new forms of excitement. The only reason I don't take heroin is that it's addicting. One of the happiest days of my life was the day I took mescaline." This subject was not accepted for drug studies. He revealed in a follow-up interview that he had begun to take mescaline regularly. It seems clear that he consciously sought relief from anhedonia through means of the anticipated "pharmacogenic pleasure effect" of the drug.

* * *

Indirect seeking of psychiatric help: A 22-year-old married female with highly competitive strivings toward masculine figures volunteered for the study with the consciously stated motivation of "being interested only in the money." She had a good deal of suppressed and repressed rage toward female authority figures stemming dynamically from an unresolved conflict with a controlling, domineering mother. She developed a post-drug reaction of mild depression, anxiety, and irritability, with obsessive angry ruminations about her mother-in-law. She was seen by one of us for 5 psychotherapeutic sessions, and during the third session spontaneously stated that she was able to recognize that in volunteering she had been looking for some psychiatric help to aid her in solving her marital problems. As a result of the drug experience she felt that she

"got not only what I was looking for, but much more than I bargained for." The subject was referred for private treatment and is now receiving psychotherapy.

Seeking new experiences (adventure): A 38-year-old schizoid bachelor poignantly expressed his feelings of disappointment in his search to alleviate the isolation of his daily living as follows: "I somehow feel that I missed out on many things in my life. I was never in the service because of my deafness and I've tried to make up for this by traveling. But I've felt a further need for such experiences and the drug seemed to be able to supply this to me."

Desires for status and prestige: A 27-year-old oriental student married to a white woman had sought for identification with whites throughout his life. He attempted to deny his own racial origins and tended to think of himself as white. He felt that he had gained prestige through participating in the study because "very few people have gone through this and I am in good company—people like Aldous Huxley." Huxley was much admired by this subject.

* * *

B. *Psychopathology:* Diagnoses were made on 26 subjects. Twenty-three of these 26 subjects were evaluated as "needing psychiatric treatment." The degree of concordance between the evaluating psychiatrists in their estimations of psychopathology was quite high. One indication of the degree of psychopathology in the group was the relatively large number of volunteers exposed to psychiatric treatment. Twelve subjects either had a history of previous treatment, were in treatment, or entered treatment after volunteering. . . .

C. *Relationship between Motivation and Psychopathology:* The group of subjects with better life adaptations were motivated mainly by financial need, scientific interest and curiosity, or combinations of these. Subjects with significant psychopathology tended frequently to volunteer for reasons related to maladaptive patterns. They often perceived drug effect and the milieu of the study as having a problem-solving function. Some saw the study as a means of making contact with psychiatrists; others as fulfilling frustrated needs for excitement and adventure. Those with symptoms of anxiety, depression, or anhedonia sought magical relief from these painful feelings. Some subjects hoped to undergo transcendental experiences. Inhibited, repressed subjects fantasied being able to act out forbidden impulses. Subjects with high addic-

tive potentials looked forward to the "pharmacogenic pleasure effect" of the drug. Several of these subjects reported using mescaline regularly and deriving from it incomparable feelings of excitement and enjoyment.

* * *

Although diagnostic categories are admittedly rough estimations of psychopathology they can be exceedingly useful. On the basis of our clinical impressions the prevalence of psychopathology in the volunteer group seemed quite high. Psychiatric diagnoses were made on almost 50 percent of the group. More than one-third of the group were rated as "needing psychiatric treatment," and one-fifth of the group were or had been in psychiatric treatment. These results are similar to the incidence of psychopathology reported in Lasagna's study (48 percent) and in Pollin and Perlin's work (52 percent). . . .

* * *

NOTES

NOTE 1.

LOUIS LASAGNA AND JOHN M. VON FELSINGER
THE VOLUNTEER SUBJECT IN RESEARCH*

* * *

In the course of certain pharmacological studies on healthy young male volunteers, routine Rorschach tests and psychological interviews were obtained on 56 subjects. These young men were from 21 to 28 years of age and (with a few exceptions) were college students. All of them received one or more drugs as a part of experiments for which they received a fixed hourly stipend.

An examination of the Rorschach data and interview material revealed what seemed to be an unusually high incidence of severe psychological maladjustment (Table 1). The nosological classification is an arbitrary one, chosen to simplify the presentation of data. The "pigeonholing" of individuals into neat psychiatric categories is admittedly an oversimplification that is intended here only to indicate, in a rough way, the magnitude or nature of the psychological disturbance. There is little question that most of the subjects listed in Table 1 would qualify as deviant, regardless of the diagnostic label affixed to them by examining psychiatrists or clinical psychologists. Of the three psychotics described,

* 120 *Science* 359 (1954). Reprinted by permission.

TABLE 1
Incidence of Psychological Maladjustment
in 56 Volunteers

Psychosis	3
Psychoneurosis:	
Under treatment	1
Seeking treatment	6
Others	5
Psychopathic personality	3
Alcoholism	1
Overt homosexuality	6†
Peptic ulcer, severe	1
Stutter, severe	1

† Two of these are also represented in psychotic group above.

for example, two were hospitalized for psychiatric treatment either before or after the studies in our laboratory. One of the subjects listed as neurotic suffered from increasingly severe anxiety, for which he ultimately sought treatment in a psychiatric out-patient department. There the majority of staff members considered him to be schizophrenic. The incidence of homosexuality refers only to those volunteers freely describing overt and continuing homosexual activities and excludes any volunteers for whom evidence of homosexuality was only presumptive (for example, Rorschach responses or behavior under drugs). In all cases, *both* the Rorschach data and the interview material had to show significant deviation of personality structure and defense mechanisms from a broadly defined norm to warrant inclusion of a volunteer in the seriously maladjusted group.

The findings described thus raised the question of whether our "normal" sample was representative even of the special population subgroup from which it was drawn—that is, college students. [O]ur subjects differed from other students by reason of the very fact of volunteering for participation in experiments. . . .

* * *

An examination of the reasons for volunteering in our group is also of interest. A number of volunteers undertook to participate in experiments primarily for the monetary rewards. Many others, however, volunteered for other reasons. Some hoped to find professional advice and help or a drug that might prove "the golden key" to their personality problems. Some volunteered in a search for new experiences,

much as a potential drug addict experiments with a variety of agents in a search for "thrills" or "kicks." Finally, there were certain volunteers whose primary reason for volunteering was a search for escape or release from personal problems and drives. This latter category included (among others) those who desired temporary relief from the boredom or pressure of everyday life, those who sought sexual gratification in a relatively guilt-free environment, and those who sought to satisfy self-destructive urges.

* * *

NOTE 2.

EDMOND CAHN
DRUG EXPERIMENTS AND THE PUBLIC
CONSCIENCE*

* * *

The investigator who desires a tranquil conscience must ultimately satisfy himself that the purported consents on which he acts are understanding and real. His scientific zeal should not blind him to the fact that certain individuals seek to become subjects for neurotic or masochistic motives. When motives like these come to his attention, he need not reject the consent; he need only make certain that it is based on a reasonably stable understanding rather than a violent and momentary impulse. If we were bound to reject every act and transaction in our society that might have a neurotic incentive, not much would remain for use.

* * *

2.

The Impact of the Outer World

a.

David Rapaport The Theory of Ego Autonomy— A Generalization†

* * *

. . . I will contrast the Berkeleian view of man with the Cartesian (Descartes). In the Berkeleian view, the outside world is the crea-

*Paul Talalay, ed.: *Drugs in Our Society*. Baltimore: The Johns Hopkins Press 255, 263-264 (1964). Reprinted by permission.

† 22 *Bulletin of the Menninger Clinic* 13-32 (1958). Copyright 1958 by the Menninger Foundation. Reprinted by permission.

tion of man's imagination. In this solipsistic view, man is totally *independent* of the environment, and totally *dependent* on the forces and images residing within him: he cannot envisage an external world independent of these inner forces. In turn, he need not come to terms with the outside world: since that world is created by forces inherent in man, he is a priori in harmony with it. In the Cartesian world, on the other hand, man is born as a clean slate upon which experience writes. No forces or images exist in man except for those which arise from the impingements of the outside world. In this world, man is totally *dependent* on and in harmony with the outside world. In turn, he is totally *independent* from, i.e., autonomous from, internal forces, which in this conception do not exist.*

Observation confirms neither of these views. It shows that while man's behavior is determined by drive forces which originate in him, it is not totally at their mercy since it has a certain independence from them. We refer to this independence as *the autonomy of the ego from the id*. The most common observation which necessitated this conception was the responsiveness and relevance of behavior to external reality. But this dependence of behavior on the external world and on experience is not complete either. Man can interpose delay and thought not only between instinctual promptings and action, modifying and even indefinitely postponing drive discharge, he can likewise modify and postpone his reaction to external stimulation. This independence of behavior from external stimulation we will refer to as *the autonomy of the ego from external reality*. Since the ego is never completely independent from the id nor from external reality, we always speak about *relative autonomy*.

* * *

... I have [a] story to illuminate the autonomy of the ego from external reality. "A king returned to his capital followed by his victorious army. The band played and his horse, the army, the people, all moved in step with the rhythm. The king, amazed, contemplated the power of music. Suddenly he noticed a man who walked out of step and slowly fell behind. The king, deeply impressed, sent for the man, and told him: 'I never saw a man as strong as you are. The mu-

sic enthralled everybody except you. Where do you get the strength to resist it?' The man answered, 'I was pondering, and that gave me the strength'."

In other words, it is possible for man to maintain relative autonomy, i.e., a degree of independence, from his environment. This relative autonomy of man from his environment is the subject of the following discussion.

* * *

There is actually nothing radically new in what follows. To the medical man, it is a commonplace that nonliving matter cannot escape the impact of its environment and its reactions are strictly (or statistically) predictable, but that organisms can escape such impacts, can avoid responding to them, and, when they respond, they can do so in a variety of alternative (vicarious) ways. Man's simultaneous relative dependence on and independence from his environment is an issue well within the biological tradition. While psychoanalytic theory, in general, has had a biological cast from the beginning, this did not extend to its consideration of the environment's role in determining behavior.

Our task is to seek the answers to two questions: What are the guarantees of the ego's autonomy from the environment? How is the autonomy of the ego from the environment related to the autonomy of the ego from the id?

* * *

To approach the relationship between the two autonomies, let us examine the conditions which interfere with either or both.

Three examples will illustrate the conditions in which the ego's autonomy from the id is impaired. First, there are periods of development in which the drives are intensified and threaten this autonomy of the ego. In puberty, the intensified drives interfere with ego autonomy so extensively that the ego combats them with—among other defenses—intellectualization, which is perhaps the most powerful means of enlisting environmental reality and the apparatuses of memory and thought against the encroachments of the id. The adolescent's subjectivity, his rebellion against his environment and his seclusiveness, as well as the converse of these—for instance his striving for intellectual understanding and objectivity and the quest for all-embracing companionship—indicate the pubertal intensification of id forces and the consequent decrease of the ego's autonomy. The climacteric (both

* This sketch of Berkeley's and Descartes' views is oversimplified. Neither actually held such an extreme view. . . .

male and female) often involves a similar loss of ego autonomy.

Some recent experiments will serve as the *second* example. Hebb and his students put subjects into a sound-proof, blacked-out room, in which restraints minimized tactile and kinesthetic sensations. They made two important observations: (a) the subjects experienced autistic fantasies and a decrease of their ability to pursue ordered sequences of thought; (b) repetitive verbal information given to the subjects—against the background of the stimulus-void—attained such an impact on their minds that some of them came to experience it as “truth,” that is, this experience approached delusional intensity and persevered for several weeks. . . . Thus stimulus deprivation too is a condition which may interfere with this autonomy.

Our *third* example is the hypnotic state. A common technique of inducing hypnosis is to make the subject concentrate on something and thus in effect to reduce the intake of other external stimulation. The hypnotist further interferes with attention to external stimulation by pouring forth a steady patter. These measures pre-empt the attention cathexes available, and interfere not only with stimulus intake but also with organized, logical, reality-oriented thinking. Thus both the outside and inside sources of signals—which subserve reality orientation and support the ego’s autonomy—are blocked. The result—in hypnotizable people—is a regressive state in which the counter-cathexis barriers differentiating ego and id processes become fluid; images, ideas, and fantasies representing id contents rise to consciousness, and the sense of voluntariness disappears. In the lack of other stimulation which could serve as a comparison, pivot, or means of reality-testing, the utterances of the hypnotist attain a great impact, just like the repetitive information droned at the subject in Hebb’s room. The reduction of reality relationships to a single interpersonal relationship, in hypnosis, impairs the ego’s autonomy from the id.

Disregarding for the moment the subject’s increased susceptibility to the information given in Hebb’s room and by the hypnotist, we will consider only the interferences with the ego’s autonomy from the id in these . . . examples.

The generally held assumption that ego structures (controls, defenses, as well as the means used in reality-testing and action) are stable, and altered only by major disorders, is amply justified by the continuity of character and

behavior, as well as by the great “resistance” these structures offer to therapeutic intervention. The very concept “structure” implies a slow rate of change in comparison to processes of drive-tension accumulation and discharge. Yet Hebb’s . . . experiments suggest that these structures depend upon stimulation for their stability, or, to use Piaget’s terms, they require stimulation as nutriment for their maintenance. When such stimulus-nutriment is not available, the effectiveness of these structures in controlling id impulses may be impaired, and some of the ego’s autonomy from the id may be surrendered. The example of hypnotic induction seems to corroborate this inference, and the interference of intensified drives with ego autonomy may be considered as due to drive representations commanding attention and thus pre-empting the attention cathexes necessary for effective intake of stimulus-nutriment. The interference of passionate love and deep mourning with the ego’s autonomy and reality-testing are familiar phenomena. . . . Without assuming that ego structures (other than those of primary autonomy) need stimulus-nutriment for their autonomous effectiveness and even for their maintenance, the very process of therapy would be inconceivable.

We have long known this dependence on nutriment of certain structures, *e.g.*, those underlying the conscious superego. When a man pulls up stakes and moves far away where his past is not known, he is subject to temptations: in the course of his sea voyage, the mutt he left behind may grow into a Saint Bernard, or the painting by a local amateur which he owned may turn into a Rembrandt. The super ego is a persistent structure, but its conscious parts seem to require stimulus-nutriment. In the lack of nutriment it becomes prone to compromise and corruption, and the greater their extent, the more mercilessly does the unconscious superego exact its pound of flesh: the unconscious sense of guilt. The maintenance of conscience seems to require the continuous input of the nourishment readily provided by a stable, traditional environment in which the individual is born, grows up, and ends his life; that is, the stimulus of the presence, opinions, and memories of the “others” who have always known him and always will. We seem to choose the social bonds of marriage, friendship, *etc.*, to secure that familiar (paternal, maternal) pattern of stimulation which we need as nutriment for our various superego and ego structures) for example, (those which underlie our values and ideologies).

Now, some examples of interference with the ego's autonomy from the environment:

* * *

[T]ake the procedures lumped together under the term "brainwashing." Instead of reviewing the literature, I will discuss Orwell's *Nineteen-Eighty-Four*, in which the writer's intuition epitomizes the means used by most "brainwashing" procedures to bring the individual to the point where the ego's autonomy from the environment is surrendered. The aim of these procedures is not just to force a false *confession* of guilt, but rather to bring about a *profession* of, or a *conversion* to, a particular view and a *belief* in the "facts" pertaining to it.

In the world of *Nineteen-Eighty-Four*, the individual is robbed of his privacy, the environment invades it: whenever the individual is alone he is watched through "telescreens"; whenever he is not driven by his work, he is driven by the "telescreen," which constantly bombards him with information and with instructions which he *must* obey. The language is so simplified that it can convey only factual information and orders; it carries no implications, connotations, allusions, or individual expression. Memory is undermined: when the political alliances of the state change, the books and newspaper files are destroyed and replaced by a revised version which fits the new circumstances. Finally, the fear of unknown but horrible punishment is kept constant. The lack of unobserved privacy coupled with the steady shower of information and orders, the lack of personal expression, the changing records which attack even the continuity vouchsafed by memory, and the mortal fear of punishment, are the means by which the world of *Nineteen-Eighty-Four* robs the individual ego of its autonomy and turns the person into an automaton at the command of the environment. *Nineteen-Eighty-Four* is an overdrawn caricature of our own world and a good montage of "brainwashing" procedures. The individual rebellion which Orwell describes has its roots in a yearning for tenderness, love, and sex, which—as I suggested above—are *ultimate* guarantees of the ego's autonomy from the environment. *Nineteen-Eighty-Four* is fiction, but its implications are corroborated by the evidence available concerning "brainwashing," which indicates that the measures summarized above are potent means for impairing the ego's autonomy from the environment.

[Another] example, Bettelheim's paper "In-

dividual and Mass Behavior in Extreme Situations," will stand here for all the literature on concentration camps and on Nazi methods of mass psychology. Its study shows that in concentration camps two overlapping sets of conditions interfere with autonomy from the environment, both of which—though not discussed above—obtain to varying degrees in "brainwashing" situations also.

The first set of conditions includes extreme needfulness (hunger, cold, etc.) and danger, as well as an attack on the inmates' "identity." In extreme needfulness and danger, the drives—which are otherwise the *ultimate guarantees* of this autonomy—endow drive-satisfying objects with a power the effect of which amounts to slavery and surrender of autonomy. The attack on identity (operating through identification with the aggressor, dependence on arbitrary authority akin to the dependence of childhood, and absence of all encomia of status and other supports of identity) impairs the *proximal guarantees* of autonomy.

The second set of conditions includes curtailment of information and stimulation (though less stringent than in Hebb's room), and against the background of this stimulus-void, a steady stream of humiliating, degrading and guilt-arousing information (akin in its role to the repetitive information of the Hebb room and to the hypnotist's patter). The deprivation contributes to the surrender of autonomy both by enhancing needfulness and by providing the background for the steady and overwhelming impact of the environment.

Thus the outstanding conditions which impair the ego's autonomy from the environment are: (1) massive intrapsychic blocking of the instinctual drives which are the *ultimate guarantees* of this autonomy; (2) maximized needfulness, danger, and fear which enlist the drives (usually the *proximal guarantees* of this autonomy) to prompt surrender of autonomy; (3) lack of privacy, deprivation of stimulus-nutrient, memorial and verbal supports, all of which seem to be necessary for the maintenance of the structures (thought-structures, values, ideologies, identity) which are the *proximal guarantees* of this autonomy; (4) a steady stream of instructions and information which, in the lack of other stimulus-nutrient, attain such power that they have the ego completely at their mercy.

Just as with the guarantees of autonomy from the id, neither the *ultimate* nor the *proximal* guarantees of autonomy from the environ-

ment are absolute. Both autonomies require external and/or drive stimulation of a specific intensity and quality for maintenance and effectiveness.

* * *

[T]hese extreme instances provide good models for the relationships of the autonomies. They show that the ego's autonomy from the id may be impaired either when its necessary dependence on the environment is excessively increased, or when environmental support is excessively decreased. Likewise, the ego's autonomy from the environment may be impaired when either its necessary independence from or its necessary dependence on the id becomes excessive. Since these autonomies are always relative, their extremes are never reached. Hence, a further implication of the relativity of the autonomies is: only a relative autonomy of the ego from the id—that is, only autonomy within the optimal range—is compatible with a relative—that is, optimal—autonomy of the ego from the environment, and vice versa. This conclusion is consistent with the one reached in our discussion of the autonomy guarantees. Since reality relations guarantee autonomy from the id, excessive autonomy from the environment must impair the autonomy from the id; and since drives are the ultimate guarantees of the autonomy from the environment, and excessive autonomy from the id must impair the autonomy from the environment.

* * *

The concept of nutriment is derived from Piaget. According to him, "structures of intelligence" arise by differentiation from constitutionally given sensorimotor coordinations, but require stimulus-nutriment to do so. So far no evidence exists to clarify the relationship between Piaget's structures and those structures which psychoanalytic theory has conceptualized. But since our considerations suggest that psychoanalytic "structures" require stimulus-nutriment for their *maintenance* and *effectiveness*, the question arises: does the *development* as well as the maintenance and effectiveness of psychoanalytic "structures" require stimulus-nutriment?

[T]he concentration camp and brainwashing procedures [do not] bank primarily on the withdrawal of this elementary stimulus-nutriment, though they have used that too as an auxiliary technique. The concentration camp removes first of all the nutriment of the structures

underlying dignity, self-respect, and identity. The aim of brainwashing is to remove the nutriment for the structures which underlie beliefs, political convictions, ideology, social and personal allegiances, and ultimately identity. These differences point to what psychoanalysis has already discovered about defenses, controls, etc., namely that psychological structures form a complex hierarchy within the psychic apparatus. Moreover, these differences suggest that the structures on each hierarchical level may require a different nutriment, ranging from simple, minimally organized sensory stimulations, to those complex experiences which a society provides to maintain, in its individuals, ideological beliefs and identities compatible with that society.

* * *

[W]e must at least touch on the crucial observation that structures can persist and remain effective even when deprived of external stimulus-nutriment. What are the facts and how are they to be explained?

... Persistence in spite of deprivation is a hallmark of autonomy. Since autonomy is relative, long-range persistence despite deprivation needs further explanation. It is known that people have spent years in solitary confinement without suffering striking impairments of either of the ego-autonomies, and that people have maintained their ego-autonomy in spite of "brainwashing," though of these only a few have survived to tell the tale. There is the familiar figure of the Englishman who, totally isolated from the setting which would provide the natural nutriment for his properties, traditions, outlook and values, maintains these essentially unchanged in the solitude of the jungle or the desert. Last but not least, clinical and therapeutic observation shows that defenses (in the form of both character traits and symptoms) may survive without tangible environmental nourishment, or where the person has to "provoke" nourishment from the environment.

This survival of defense structures without external stimulus-nutriment is understood by psychoanalysis: these structures are maintained, ultimately, by internal (drive) stimulus-nutriment. Clinical evidence shows that values, ideologies, and even more complex structures (like identity) too may be maintained by drive-nutriment, to the degree to which they are part of a defensive system. The explanation of the maintenance of such higher order ego structures in instances of solitary confinement seems at first

glance equally obvious: the method of survival seems to be a deliberate application of physical and mental exercise to prevent weakening of ego autonomy and drifting into fearful or wishful daydreaming, or into mindless, empty surrender. . . .

* * *

b.

Renée C. Fox
Some Social and Cultural Factors
in American Society Conducive
to Medical Research on Human Subjects*

* * *

Clinical investigators also give special recognition to some of the persons who act as their subjects. "We celebrate our patients" was how one such investigator once described the way he and his colleagues treated their volunteer research subjects in rounds, conferences, technical medical publications, and even in releases to the lay press. Thus, in rounds and conferences in which medical investigators present their patients and their research to other physicians they often express their indebtedness and admiration for the part the patients have voluntarily played in the research:

This is Leo Angelico. . . . Leo has been assaying ACTH for us for three years now. And we've gotten some wonderful baseline studies with his help. He's been written up in many of our papers. . . .

Or, again, medical investigators speak out in letters to their patient-volunteers:

. . . You will be interested in knowing that the results from the big experiment in which you were involved are of greatest interest not only to us, but also to many scientists who work on the new steroids in Switzerland and elsewhere. . . . You are now quite a famous person. . . . The article you appeared in was a teaching paper and has proved to be of considerable value to a large number of practicing physicians.

Finally, in the prepared stories about their research activities which medical investigators sometimes release to the daily newspapers and weekly newsmagazines, and in the interviews they grant to science reporters, prestige is awarded to individual patient-volunteers:

Survives After Rare Operation: Wayne Williams is congratulated by Dr. Herbert Norton on his ability to walk after having been bedridden five years. . . . Dr. Norton said that Wayne's case was the first time in medical history that a faulty heart valve had been restored through surgery. . . .

Before the days of miracle drugs a man could not have lived more than a few weeks after surgical removal of his adrenals. . . . Last week the amphitheatre at _____ Hospital was crowded with standees as Dr. John Thomas described cases in which patients have lived as long as nine months . . . and are still going strong. . . . [One patient] Walter Cousins, 32, had been given six months to live. . . . He had the operation done months ago, responded so well that he got a job as a night orderly at the Hospital. . . .

In addition, clinical investigators often give their subjects what one physician has termed "red carpet treatment." They extend special privileges and considerations to subjects which are not accorded the "usual" hospital patient, such as free room and board in the hospital, free medical services, free supplies of new, scarce drugs, especially attractive hospital accommodations, and so on.

The manifest functions of the special personal and privileged ways in which clinical investigators treat the persons who act as their subjects, and of the ways in which they deal with them as if they were professional collaborators, are obvious.

By fully informing their subjects about the experiments in which they participate, of course, physicians are meeting the ethical and legal requirement that they obtain "the voluntary consent of the human subject," and that before they accept his "affirmative decision" they make "known to him the nature, duration and purpose of the experiment; the method and means by which it is conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiments." Reinforcing the moral reasons for which physicians give subjects a detailed explanation of the experiments in which they participate is a more pragmatic one. It is their impression that this increases their motivation to act as research subjects and makes them more cooperative about the demands and restrictions the studies impose on them. Thus, to some extent, clinical investigators provide research subjects with information about experiments in order to secure their optimal compliance.

The same thing might be said about some

* Symposium on the Study of Drugs in Man, Part IV. 1 *Clinical Pharmacology and Therapeutics* 423, 432-441 (1960). Reprinted by permission.

of the ways in which clinical investigators treat their subjects as valued colleagues and privileged friends.

In addition, there are certain more latent functions that these informal relations between medical investigators and their research subjects seem to serve. "Thank you for suffering so stoically," a research physician wrote to one of his patient-subjects after he had been discharged from the hospital. This seems to be one of the primary things the clinical investigators we observed tried to convey to the patients who acted as their subjects through the behavior described. The intimate and extra things they shared with their subjects enabled them to show their personal and professional concern over the "suffering" to which research as well as illness subjected patients. It also seemed to have given these physicians some feeling that they were compensating patients for their suffering, or at least, that they were doing something to help counter-balance it. Thus, one of the implicit functions the special ways they treated patient-subjects seems to have served for this group of clinical investigators is that it helped to relieve them of some of the anxiety and guilt they felt about subjecting their patients to the strictures and hazards of experimentation.

* * *

[W]e know that many patients serve as subjects, and that by volunteering to do so they may attain a variety of instrumental benefits. In some cases there is the possibility that new knowledge, techniques, or medicaments relevant to their maladies may result from the experiments in which they participate. Besides medical aid in this form, as we have already pointed out, patients who act as research subjects may be given free hospitalization and care, or access to otherwise rare or prohibitively expensive modes of treatment. For some patients, hospitalization as a research subject may provide a solution to a lonely or difficult home situation. The following three cases illustrate these instrumental functions:

... Margaret S., a widow of 54 ... had begun to feel weak and run-down ten or twelve years before entry [into Ward 4, the research ward of the Massachusetts General Hospital]. ... She came to Dr. Forbes at the MGH, who recognized that she had the symptom picture of classic Addison's disease. ... Dr. Forbes at once appreciated that Margaret S. would give Dr. M. M. Pechet ... an admirable chance to pursue his study of the relation between molecular configurations of steroid hormones and

their physiologic actions on people. ... Actually, the studies caused only temporary and slight inconvenience, and life in the ward itself she enjoyed, finding it preferable to her previously lonely existence in a lodging by herself.

Since 1950, this patient has been admitted every year to the Metabolic Ward [of a New England Hospital] as a volunteer ... a well-developed, well-nourished, healthy-appearing, young-looking, middle-aged male who shows no abnormalities other than paraplegia of the lower extremities and flaccid paralysis of the left arm. ... On the ward, he stays in a wheel chair during the day, and requires the help of an orderly to be put to bed at night and in his wheel chair in the morning. He is pleasant and seems to be well-adjusted. He has found a fairly satisfactory solution to his problem by serving as a permanent volunteer for metabolic studies. ...

Mr. D. suffered from ill-health from 1922 on, which was finally diagnosed as Addison's disease in 1931, when he had a series of crises. He was treated with subcutaneous adrenaline, 6 injections a day, for a few years. From 1935 on he took Eschatin [adreno-cortical extract] twice daily at a cost of \$60 a week. Mr. D. reports, "This took every cent I could lay my hands on." In 1948 he was invited to volunteer for experiments with cortisone, which was to be supplied to him free. In addition, he was to be paid all transportation costs and \$10 a day while in the hospital. After one such stay he wrote to the medical investigator: "I want to thank you and Dr. T. for having me ... for the recent tests. It was a good experience for me and the financial arrangement was most helpful, this being the first real hard cash I've been able to lay my hands on in some time. Do hope you will find an opportunity to use me again. ..."

* * *

Another important instrumental function that acting as a research subject can have is an economic one. Under certain circumstances, persons who volunteer to serve in this capacity are financially rewarded for doing so. For some ill persons and prisoners, this may be one of the few possible ways of earning some money open to them. As for the well persons and those with good standing in the eyes of society who volunteer for this role, the money payments sometimes offered to them may be a desirable or necessary supplement either to the financial resources provided by another full-time job or some temporarily unremunerative role. ...

For those persons in our society who are conscientious objectors, acting as a research subject may have still another kind of instrumental function. Under the United States Selective Service Act it is possible for a selectee to fulfill his military obligation for two years' service by con-

tributing to "the maintenance of the national health, safety, or interest" as a volunteer research subject. According to one estimate, "4000 Quakers, Mennonites, members of the Assemblies of God and Church of the Brethren, or other pacifist sects . . . choose this course each year." The Clinical Center at Bethesda, for example, has established a permanent corps of normal volunteers for medical experiments by developing contractual agreements with these "peace churches." "Young people enrolled in the church public service movements are permitted to select health research as a type of citizen duty equivalent to military service for some of the candidates."

* * *

It is primarily because of some of its value-symbolic functions that the role of volunteer research subject and those who play it are so highly regarded by medical investigators and the lay public. For in a number of ways this role seems to epitomize some of the cardinal values of American society. Ours is a society with a high regard for active, rationally based mastery of life and for any sort of achievement that blends individualism and a humanitarian sense of social responsibility. We are inclined to glorify our frontier, pioneering tradition and spirit. We have a special appreciation for the pragmatic and ethical value of science in general, and also for its particular contribution to the realization of another one of our important values, good health. In the role of volunteer research subject, these values are brought together and played out in a way that is regarded with a great deal of social approval. For, of their own volition, partly with humanitarian goals in view, research subjects endure the discomforts, uncertainties, and hazards of pioneering experiments and thus make a contribution to our rational mastery of the problems of health and social welfare.

* * *

Many patient-volunteers in this situation seem to enjoy what the psychiatrist would term "secondary gains" from this role; some establish "transference" relations with medical investigators from which they derive important emotional satisfactions. Or, as Leopold indicated, the comfort, privileges, and trust that he and his fellow-prisoners were granted as volunteers made them feel that they were "on the same side of the fence . . . partners in a common endeavor" with the Army doctors for the benefit of society,

which, in turn, gave them "more solid, lasting satisfaction from what they were doing than many of them had known in some time."

* * *

NOTES

NOTE 1.

OSCAR M. RUEBHAUSEN AND
ORVILLE G. BRIM, JR.
PRIVACY AND BEHAVIORAL RESEARCH*

* * *

[A] complicating factor in the concept of consent is the determination of whether consent has been freely given or coerced. Torture is an old and well-tried technique for extracting private information—and torture need not be physical. Mental anguish can be just as searing and difficult to endure. The prospect of release from suffering, therefore, is a powerful lever for access to the private area. Its uses for the manipulation of behavior or the probing for knowledge are not unknown to sheriffs and prosecutors, to personnel directors, school teachers, and parents—indeed, to virtually anyone who has experienced authority. Conversely, its uses are very well known by the jobless, the hungry, the homeless, the ambitious and the young. The obvious cases of physical, mental, economic, or social duress are readily identifiable; but when does a subtle inducement such as the regard of your boss or even of your peers, or some inducement, not quite so subtle, such as an extra point added to your college grade in return for participation in psychological experiments—when do these become tantamount to duress? What about the vast prestige of scientific research itself as a means of persuasion upon the unsophisticated? And when does the relative disproportion between the knowledge, sophistication and talents of the investigator and his subject make the consent of the respondent questionable, however freely and explicitly given? It is all too apparent that the distinction between consent and concealed coercion may often be difficult to establish. This is, however, the type of distinction with which our social institutions, in particular our law and our courts, have a demonstrated competence to deal.

* * *

* 65 *Columbia Law Review* 1184, 1199-1200 (1965). Reprinted by permission.

NOTE 2.

MILTON E. ROSENBAUM

THE EFFECT OF STIMULUS AND BACKGROUND
FACTORS ON THE VOLUNTEERING RESPONSE*

* * *

... The general plan of the study called for creating test situations within which invitations to participate in a psychological experiment that varied in strength were tendered to Ss after they had seen the reaction of another person to the same request, with the observed reaction also being subjected to systematic variation. Three stimulus requests were used, designed to vary along an intensity continuum in terms of their capacity to produce a volunteering response. Positive and negative backgrounds and a control condition or neutral background were introduced to determine the rate of volunteering in conjunction with each of the stimulus requests.

Hypotheses. The variations of stimulus request strength and the character of social background mentioned above lead to the following hypotheses: (a) willingness to volunteer is positively related to stimulus-request intensity, and (b) willingness to volunteer is directly related to the behavior of others who are observed responding to the same invitation.

... The study was conducted during the regular Fall semester of 1953-54 at The University of Texas. The settings were the reading rooms of two large university libraries. The Ss, numbering 135 males, were occupants of the library going about their everyday school affairs...

... Fifteen assistants participated and each served on six different testing occasions, once under each of the six experimental conditions requiring an assistant, to which they were randomly assigned. The assistants were all males recruited from undergraduate and graduate psychology courses. On each testing occasion the assistant was instructed concerning the response he was to give...

* * *

Each of the requests dealt with a need for participants in a psychological experiment, but they differed in terms of length of time implied to complete the task and the compellingness of the phrasing. The high intensity request was phrased as a plea for subjects to help complete

dissertation research. The medium intensity request was a matter of fact statement of a need for Ss for departmental research. The low intensity request was stated in a form presenting a relatively weak desire to have S participate in an experiment but discouraging him from doing so.

... Background was created by the reaction of a person invited to participate in the presence of the naive test S. By bending over between the assistant and the test S, E first approached the assistant who had been instructed as to the response he should give. Then the test S was approached and requested to participate in the experiment. The general procedure used to create each of the background conditions was as follows:

Positive background. To the invitation to participate in the experiment, the assistant responded by saying "Okay"...

* * *

Negative background. The assistant responded to the invitation by saying, "No, I'd rather not," and he turned back to his books. The E then presented the invitation to the test S...

Neutral background. The S was approached directly and tendered the invitation. He was not given the opportunity to observe the reaction of another person under this condition...

* * *

... Greatest acceptance occurred under the positive background and least under the negative background. The data necessary to evaluate the similar aspects of the present experiment are presented in Table 1.

TABLE 1

Frequencies of Acceptance and Rejection
under the Medium Intensity Stimulus-Request

Background Condition	Acceptance	Rejection
Positive	12	3
Neutral	7	8
Negative	0	15

* * *

... Both the stimulus and background variables are seen to be significant in their effect on the response elicited in the predicted direc-

* 53 *Journal of Abnormal and Social Psychology* 118-120 (1956). Reprinted by permission.

tion: the higher the intensity of the stimulus-request, the greater the willingness of the test S to volunteer. On the other hand, the more conducive the background conditions toward the act of volunteering in terms of the observed behavior of another person, the greater the willingness of the test S to volunteer. No significant interaction is indicated between the two variables. Both hypotheses therefore are supported by the results.

* * *

NOTE 3.

STUDIES WITH CHILDREN BACKED ON MEDICAL, ETHICAL GROUNDS*

* * *

[T]he obtaining of consent at Willowbrook [an institution for mentally retarded children] has not been without controversy. Dr. Jack Hammond, administrator of the institution, said the "biggest fuss" arose more than a year ago over a "complete misinterpretation . . . of an unfortunate coincidence."

The circumstances were set up by the closing of Willowbrook in late 1964 to all new admissions because of overcrowding. Parents who applied for their children to get in were sent a form letter over Dr. Hammond's signature saying that there was no space for new admissions and that their name was being put on a waiting list.

But the hepatitis program, occupying its own space in the institution, continued to admit new patients as each new study group began. "Where do you find new admissions except by canvassing the people who have applied for admission?" Dr. Hammond asked.

So a new batch of form letters went out, saying that there were a few vacancies in the hepatitis research unit if the parents cared to consider volunteering their child for that.

In some instances the second form letter apparently was received as closely as a week after the first letter arrived. "All of a sudden," Dr. Hammond recalled, "we had parents' meetings, calls from local politicians, calls from family physicians. . . all sorts of kicks."

Canvassing the parents by letter "obviously was open to misinterpretation, so we stopped it more than a year ago," Dr. Hammond said.

* * *

* 8 *Medical Tribune* 1, 23 (February 20, 1967). Copyright © 1967, Medical Tribune, Inc. Reprinted by permission.

NOTE 4.

SAUL KRUGMAN AND JOAN P. GILES VIRAL HEPATITIS—NEW LIGHT ON AN OLD DISEASE*

* * *

The study groups [at Willowbrook] have included only children whose parents gave written consent. Our method of obtaining informed consent has changed progressively. . . . At that time [1956] the information was conveyed to individual parents by letter or personal interview. More recently, we have used the group technique of obtaining consent. The following procedure has been employed: First, a psychiatric social worker discusses the project with parents during a preliminary interview. Those who are interested are invited to attend a group session at the institution to discuss the project in greater detail. These sessions are conducted by the staff responsible for the program, including the physician, supervising nurse, staff attendants, and psychiatric social workers. . . . Parents in groups of six to eight are given a tour of the facilities. The purposes, potential benefits, and potential hazards of the program are discussed with them, and they are encouraged to ask questions. Thus, all parents can hear the response to questions posed by the more articulate members of the group. After leaving this briefing session parents have an opportunity to talk with their private physicians who may call the unit for more information. Approximately two weeks after the visit, the psychiatric social worker contacts the parents for their decision. If the decision is in the affirmative, the consent is signed but parents are informed that signed consent may be withdrawn any time before the beginning of the program. . . .

NOTE 5.

EWART E. SMITH OBTAINING SUBJECTS FOR RESEARCH†

The United States Employment Service offices throughout the United States have a large continuous number of individuals entering their offices. Although we had anticipated difficulty with these subjects in filling out questionnaires developed for use with students, we have been surprised at their general literacy, and have had

* 212 *Journal of the American Medical Association* 1019, 1020 (1970). Reprinted by permission.

† 17 *American Psychologist* 577 (1962). Reprinted by permission.

no more difficulty using such instruments as the semantic differential than we have experienced with students. The employment service has been willing to select subjects for us on any variables we specify, such as age, sex, type of occupation, etc. An interviewer obtains subjects and delivers them to a room assigned to us. Subjects are always ready and waiting when we finish with a group, and we have completed a large study without the loss of a single hour or subject in two days.

The cooperation of the United States Employment Service was obtained by explaining the objectives of the research being performed, and stressing its potential value in terms of its application to national goals. It was pointed out that our military sponsor would be grateful for any cooperation received and would be informed of the help received from the United States Employment Service.

It was agreed that the subjects be paid \$1.25 an hour. This allowed the employment service to offer the unemployed something to keep them busy, and let them earn some pocket money while waiting for job leads. It might have been possible to obtain some subjects without payment, but payment insured a constant supply of subjects standing by. The employment service did not charge us for the use of their space or the interviewer. The subjects are paid in cash immediately upon completion of a session.

One of the advantages of this subject pool has been the motivation of the subjects, who are more amenable to experimental procedures than are students. They do not anticipate or attempt to deduce the "real" independent variable as overexposed student subjects frequently do. An-

other advantage is their availability for extended periods of time. It was possible to maintain experimental control at university laboratory levels.

NOTE 6.

EDMOND CAHN
THE LAWYER AS SCIENTIST AND SCOUNDREL—
REFLECTIONS ON FRANCIS BACON'S
QUADRICENTENNIAL*

* * *

One of the major malpractices of our era consists in the "engineering of consent." Sometimes this is effected simply by exploiting the condition of necessitous men, as in certain Indian states where thousands of consents to sexual sterilization have been purchased by offering a trivial bounty to the members of a destitute caste. Then again, consent may be "engineered" by the kind of psychologist who takes it for granted that his assistants and students will submit to experiments and implies a threat to advancement if they raise objections. Or the total community may "engineer" a consent, as when the president, the generals, and the newspapers call with loud fanfare for a heroic crew of astronautical volunteers to attempt some ultrahazardous exploit.

It is worth considering that the destitute Indians who accept payment for sterilization can at least know what they are consenting to; the psychological and astronautical subjects cannot. Moreover, though the astronauts are fairly certain of winning some species of glory, the lady who submits to hypnosis in the interest of science is certain of scarcely anything. . . .

* 36 *New York University Law Review* 1, 11-12 (1961). Reprinted by permission.

B. Barriers to Rational Decisionmaking

1.

Transferences

a.

Anna Freud The Doctor-Patient Relationship*

* * *

... Even if the doctor contributes a good deal to [the doctor-patient relationship] I think it is only fair to say that the patient contributes more. . . . Your patients will be ill and therefore they need a doctor. They will have bodily pains; they expect you to cure them. . . . One would expect that this is a straight-forward relationship, that the doctor . . . enters the patient's life as a new person with new qualities, that the patient reacts to him as such, that the patient values his knowledge, appreciates his attitude, and chooses him like one chooses other professional people in life. . . . But curiously enough the relationship between . . . patient and doctor does not remain the same. Elements enter it which cannot be explained by the present reality at all. We are surprised by it, we have to search for the origin. For example . . . many patients over-evaluate their doctors. . . . Their doctor is the best in the world. Their dentist is the best. Enormous expectations are raised—he will help, he will cure, he will fulfill all expectations. This gives you a warm glow of satisfaction. It's nice to be thought such a remarkable person until, a week later, the scene changes. You are no good at all—such an ignorant person has never existed. You don't fulfill the expectations. You have promised something and you can't carry it out. The patient is deeply disappointed in you, and you become dejected. Am I really as bad as that? . . . Until, when this same sequence has repeated itself a number of times, you become alerted to it and you realize this is not you at all. You are neither as good, nor as bad, neither as efficient nor as inefficient as the patient sees you. He evidently has turned you into somebody else. And this belief is strengthened by further discoveries, namely that the patient doesn't only expect you to fulfill the

contract to be cured by you, but that he expects you to like him or, if it is in analysis, even to love him, to be interested in him, to prefer him to other patients. He comes to you with details of his life, which have really nothing to do with the doctor-patient relationship on a reality basis, and you realize that now you have ceased to be what you set out to be—the person to cure this particular individual; you have become an important person in his life, somebody who is loved, hated, on whom demands are made, from whom the patient wants interest, intimacy, preference, and suddenly you feel this must be somebody quite definite from the patient's past. He treats you as if you were his parent. He obeys you as if you had authority over him, or he fights against you as if he were a rebellious child. And suddenly you find that instead of having a sensible patient before you, you have become what we call an object of his transference, namely the whole load of feeling left over from earlier years—unfulfilled, disappointed—has been unloaded onto you. You are in the center of his interest, and he expects you to play the role that you are given.

[W]hat can you do with this most disturbing doctor-patient relationship? . . .

I think that all doctors use the transferred positive relationships from the patients for their own advantage. The patient is in a state of submission, admiration, obedient to the doctor. All the better. So long as this whole trend is positive, you can use it for your own ends; you will find that your prescriptions work better, your commands are obeyed, and at least the psychological side of the patient's illness—and we know there is mostly a psychological side—will be influenced favorably. Doctors have done that always. They have done it without knowing it. It's only when this attitude becomes negative that you are in trouble. . . .

[T]o understand what is going on can be of enormous help in your profession. It will save you a lot of annoyance. It will make you very careful how to act or how to make use of the patient's personal relationship. It will do something to your self-esteem when you know that this changing picture of yourself is not your fault. It will help you to stand firm and, as in so many other walks of life, understanding the difficulties of the situation will ease them. It will ease it es-

* Unpublished manuscript, based on a lecture to students at Western Reserve Medical School (October 29, 1964). Printed by permission of the author who retains all rights.

pecially with regard to one particular point. The patient uses the doctor . . . not only to replace people of a lost past, he also uses him to represent in the outside world parts of his own person. For instance, a patient may be quite aware of the fact that either his eating habits or his drinking habits, or any other habits are injurious to his health, but he doesn't feel that he has the strength inside to combat the injurious habits. Then he will give you the role, to represent that part of himself which should control the eating and drinking. Many women who want to lose weight look for a doctor who gives them a diet, where they could diet themselves by eating less. But that is very difficult. It is easier to have the figure of the forbidding agency outside, and then either to obey or to revolt. The same is true about drinking. The same is true about people with heart trouble who cannot bring themselves to be really careful of their bodies. It's easier to have the forbidding agency outside, which in itself does not yet guarantee obedience. . . .

But even that isn't the whole story yet. I have another point to make for you. [You will discover] how badly adult and sensible people take care of their own bodies. After all, our body, our health is one of our most valuable possessions, if not the most valuable one altogether. Wouldn't you expect all your patients to take the greatest care of their bodies, never to do anything that is injurious to their health, carefully to avoid infections, damage, dangers and, if they are ill, to take the right measures immediately. Wouldn't that be eminently sensible behavior? But there are very few adults, reasonable as they may be otherwise, who show such sensible behavior. This lack of good sense in health matters will make your future work extremely difficult. It will make it all the more difficult because you will feel, "I just can't understand it. After all it's his body. Why doesn't he take better care of it? Why does he expect me to do it instead of doing it himself?" You wouldn't be at all astonished about that point, if you had the opportunity to watch the human being's relationship to his body from the very beginning. . . .

If you have the chance to observe children in their second year of life, you will make the surprising discovery that they treat their bodies as if they were not their own. Their bodies belong to their mothers which is only natural since it is not so very long ago—in the intrauterine stage—that the infant's body was actually part of the mother's. Neither in his first nor in his

second year can the infant do anything for the care of his body. There is, in the beginning, even no barrier to self-injury and the baby would draw blood from his face if the mother did not see to the cutting of his nails. What we call the pain barrier is established gradually during the first year and the child's aggression deflected with it from his own body to the world outside.

We even think that the infant begins to love and respect his own body to the degree it is loved and respected by the mother, i.e., for the mother's sake. As regards the toddler, we certainly feel that he needs more than our guardian angel to keep alive in spite of the attractions of heights, stairs, water, fire, scissors, knives, and whatever other dangerous objects he may meet. He has, at this time of life, no appreciation of danger and he will inevitably injure himself unless he is protected. Pediatricians, child analysts and other workers in the field have learned to judge the quality of mothering available to a young child by the numbers of accidents in which he has been involved.

The child's intelligence has to mature before he learns to appreciate that fire burns and water drowns, that not everything is edible, etc. What he learns last of all is submission to the rules of hygiene and obedience in medical matters. At school age even, and right up to adolescence, many children act as if it were their privilege to do the most harmful and dangerous things to their bodies, while it is the parents' duty and privilege to protect them. [You] know how difficult it is to keep a child in bed with a fever, with an infection, that the dietary rules are felt by the child as a deep offense, a deprivation, a sign of not being liked. Even the ill child would eat what is bad for him, or the child would, for its own reasons, not eat even if he were starving himself. . . .

But what about you and the doctor-patient relationship? I only tell you these stories so that you can understand where all the irrational attitudes of your adult patients towards their health and towards their bodies come from. It is true you deal with adults, but every adult who is ill, who has fever, who is in pain, or who expects an operation, returns to childhood in some way. He feels small and helpless, and due to the ease with which he transfers feelings of the past onto you, you become the parent, you own his body. It is now your duty to look after him, and it is his privilege to be naughty about it; he feels well protected by you because he feels that somehow you will see to it that he doesn't do

the wrong thing. You may get angry about it, but you will not be angry, if you remember that this adult before you is in reality a child, once more the child who has entrusted his body for safe-keeping to an adult.

This brings us to the end point and perhaps to one of the most difficult tasks of the doctor in the doctor-patient relationship. The patient, as you see from the various points I made, will do his best to push you into the place of parental authority, and he will make use of you as parental authority to the utmost. You must understand that. On the other hand, you must not be tempted to treat him as a child. You must be tolerant towards him as you would be towards a child and as respectful as you would be towards a fellow adult, because he has only gone back to childhood so far as he's ill. He also has another part of his personality which has remained intact, and that part of him will resent it deeply, if you make too much use of your authority. . . .

* * *

NOTES

NOTE 1.

PAUL SCHILDER
PSYCHOTHERAPY*

* * *

[T]he following relations between the physician and the patient are possible. We speak here primarily about the psychotherapist, but since patients go to the physician because they suffer, it is obvious that the psychotherapeutic relation is inherent in every relation between physician and patient.

(a) Physician and patient are fellow human beings. There is no fundamental difference between them. The physician merely has more knowledge in a field of experience in which the patient happens not to be so well versed. In compensation for the advice, the patient gives money to the physician as he would give it to anyone else who serves him. Relations between physician and patient are mostly not of this type.

(b) The patient wants to go to an outstanding physician. The mere fact that the patient chooses the physician gives to the latter the superiority in their relation. The patient, especially

when he comes with psychic problems, wants to find a leader in the physician. Human beings need a leader whom they admire and who takes a part of their responsibilities. In one type of leadership the leader is merely expected to have superior insight. If the patient expects such leadership, the relation between the two will be a relation of superiority and inferiority, and in their discussion common sense and reason will prevail.

(c) Since the discussion between patient and physician circles around the moral problems of life, it will sooner or later become apparent that purely from the point of view of reason, the physician is not greatly superior to the patient after all. Sooner or later the patient will have to add faith to his relation to the physician if he wants to get a sufficient amount of consolation out of this relation. The physician himself will eventually be compelled to demand faith from his patient, unless he discharges the patient in disgust as some practitioners do when they see that the patient cannot avail himself of the physician's advice. We may suppose that this elementary faith (not based upon reason) very often enters the psychotherapeutic relation without the knowledge of either patient or physician. . . . When faith enters the relation, the superior-inferior relation between physician and patient is obviously still more emphasized, but seemingly a new element has been added. The relation becomes similar to that between the adult and the child, or, better and more specifically, the relation is more like the one between parent and child. . . .

(d) From this relation to the complete surrender of the patient to the physician is only a short step. The physician does not only become a father, but he also becomes a father endowed with magic powers. . . . Since the physician is so far superior in this relation, reasoning obviously becomes unnecessary, and the physician has to direct the faith of his patient. He may become a mystical leader, or he may use the more definite technique of suggestion and hypnosis. When the faith of the patient in such a relation is blind, the physician himself is no less blind. He is called to take over a leadership by reason or faith; and according to the whole situation, he cannot know where he should lead the patient. The physician ultimately will become discontented with his role as a fellow adviser who does not know what to advise, and as a rational or mystical leader who does not know where to lead.

* * *

* New York: W. W. Norton & Co. 7-9 (1938). Reprinted by permission of W. W. Norton & Company, Inc. Copyright 1938, 1951 by W. W. Norton & Company, Inc. Copyright renewed 1965 by Lauretta Bender, M.D.

NOTE 2.

HANS JONAS
PHILOSOPHICAL REFLECTIONS ON
EXPERIMENTING WITH HUMAN SUBJECTS*

* * *

... To the question "Who is conscriptable [for experimentation]?" the spontaneous answer is: Least and last of all the sick—the most available source as they are under treatment and observation anyway. That the afflicted should not be called upon to bear additional burden and risk, that they are society's special trust and the physician's particular trust—these are elementary responses of our moral sense. Yet the very destination of medical research, the conquest of disease, requires at the crucial stage trial and verification on precisely the sufferers from the disease, and their total exemption would defeat the purpose itself. . . .

* * *

On the whole, the same principles would seem to hold here as are found to hold with "normal subjects": motivation, identification, understanding on the part of the subject. But it is clear that these conditions are peculiarly difficult to satisfy with regard to a patient. His physical state, psychic preoccupation, dependent relation to the doctor, the submissive attitude induced by treatment—everything connected with his condition and situation makes the sick person inherently less of a sovereign person than the healthy one. Spontaneity of self-offering has almost to be ruled out; consent is marred by lower resistance or captive circumstance, and so on. In fact, all the factors that make the patient, as a category, particularly accessible and welcome for experimentation at the same time compromise the quality of the responding affirmation that must morally redeem the making use of them. . . .

* * *

NOTE 3.

HENRY K. BEECHER
CONSENT IN CLINICAL EXPERIMENTATION—
MYTH AND REALITY†

* * *

Patients will, if they trust their doctor, accede to almost any request he cares to make.

* 98 *Daedalus* 219, 237–239 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

† 195 *Journal of the American Medical Association* 124 (1966). Reprinted by permission.

"My doctor would not ask anything of me not for my good." In too many cases this, too, is a myth. The experienced clinician knows that if he has a good rapport with his patients they will often knowingly submit, for the sake of "science," to inconvenience and even to discomfort, if it doesn't last very long; but, excepting the extremely rare individual, the reality is, patients will not knowingly seriously risk their health or their lives for a scientific experiment. It is ridiculous to assume otherwise. They will not do it.

* * *

NOTE 4.

AUGUST B. HOLLINGSHEAD AND
FREDERICK C. REDLICH
SOCIAL CLASS AND MENTAL ILLNESS*

* * *

A deep-seated distrust of authority figures pervades class V persons [†] from childhood to old age. Suspicion is directed toward police, clergymen, teachers, doctors, public officials, public health nurses, and social workers. A class V respondent had finished a tirade on police efficiency when he switched to doctors. He told of a neighbor's wife who had developed a side reaction from a sulfa drug prescribed by a clinic doctor:

That's a doctor for you. I wouldn't take my dog to one. To prescribe 100 pills like that for a working man's wife and not even find out if she had ever had sulfa. I can't see doctors. Maybe this one was in league with the druggist. Maybe he sells sulfa pills on the side for all I know.

Politicians are believed to operate a machine designed to exploit poor people. Non-Italians think this machine is run by Italians, "just like a gang." This statement by a person of Irish descent is typical. "The Italians stick together. The Irish don't stick together, so they can't run the machine like they used to. The machine is mostly one nationality, that is Italian." Protestants make the allegation that New Haven was run by the

* New York: John Wiley & Sons, Inc. 130–135 (1958). Copyright 1958. Reprinted by permission of John Wiley and Sons, Inc.

[†] "Occupationally, class V adults are overwhelmingly semiskilled factory hands and unskilled laborers. Educationally, most adults have not completed the elementary grades. Individuals and families are concentrated in the 'tenement' and 'cold-water flat' areas of New Haven and in semirural 'slums' in two of the suburban towns. . . ." [p. 134].

Catholics: "The Italians and the Irish got together with the Poles and ran the town for their advantage." Others claimed the machine politicians had "sold out" to the Catholic church and "the rich people."

Institutions for care of the disabled and the ill are believed to be run for money and one has to have "pull" to get into them. A family with a feeble-minded four-year-old child claimed that its efforts to have the child admitted to the state home had failed because of their lack of influence.

Hostility against official representatives of society is linked to convictions that they are being exploited. Some believe they have to live in the slums because the state is taking advantage of them. One veteran living in a three-room flat in a dilapidated tenement stated:

Like in other states, where a project is for a veteran who can buy his own home without such a hard down-payment. They have nice homes and we have to live like this. There's nothing in Connecticut—that somewhere, somehow—they can do things so that you don't have to live like this.

Another believed the city officials were taking advantage of the veterans living in an "emergency" housing project. He told how a child from the project had been drowned a few days before because a hole had been torn in the fence surrounding the area. The police had not made the responsible construction company repair the fence. He also explained how dredging in the harbor had led to sand being blown into the houses day after day. . . .

* * *

. . . Manifestations of a feeling of exploitation were encountered among families in other housing projects scattered through the area. In a low-cost state housing development, we were told that the people were not getting much for their money, but that nothing could be done about it.

What are they giving us in this project? And the people, they won't say anything because if they do what happens? They get thrown out. They (the state officials in the housing office) make life miserable for you so you have to move. You will probably have to move into something worse. What I mean is, well, people today, they won't work together for anything.

* * *

The struggle for existence is a meaningful reality to these people. Their level of skill is low, their jobs are poorly paid, and they have no savings to carry them over a crisis. Adults are re-

sentful of the way they have been treated by employers, clergymen, teachers, doctors, police, and other representatives of organized society. They express their resentments freely in the home and in other primary groups.

NOTE 5.

RALPH K. SCHWITZGEBEL
ETHICAL PROBLEMS IN EXPERIMENTATION
WITH OFFENDERS*

* * *

[T]he difficulty in adequately describing the effects of certain experiments makes it difficult for the experimenter clearly to convey relevant information to prospective subjects and therefore obtain valid consent. For example, how is it possible for a delinquent unfamiliar with Freudian theory to comprehend the concept of transference? Perhaps ultimately only the experience of transference itself may be an adequate basis for valid consent.

To avoid the situation in which subjects consent only once without an adequate understanding of the experiences produced by experimental procedures, arrangements may be made for repeatedly requesting the consent of the subjects throughout the duration of an experiment. In the case of one experiment which employs delinquents as experimental subjects over a period generally of several months, the receipts signed by the subjects upon payment are also release forms reminding them in simple language of their right to quit. In this way the subject is clearly given the opportunity to terminate his participation as he becomes increasingly familiar with the experiment. At the same time, the experimenters may be quite sure that in the absence of duress they are receiving valid, voluntary consent repeatedly affirmed.

* * *

NOTE 6.

ROBERT J. SAVARD
SERVING INVESTIGATOR, PATIENT, AND
COMMUNITY IN RESEARCH STUDIES†

* * *

As many authorities have pointed out, consent is not a one-time process. The patient retains the right to reconsider his original consent

* 38 *American Journal of Orthopsychiatry* 738, 744 (1968). Copyright 1968, the American Orthopsychiatric Association, Inc. Reprinted by permission.

† 169 *Annals of the New York Academy of Sciences* 428, 433 (1970). Reprinted by permission.

at any time. But reconsideration and thoughts of withdrawal are painful experiences for most people. In the research situation, many subjects become, in effect, members of the team. Withdrawal may represent the cutting off of very meaningful allegiances. In some cases, when chronic illness is involved, patients may feel so guilty about their inadequate and parasitic-like existence, that to expiate a sense of guilt they may allow the continuation of procedures past what could be considered a reasonable point.

* * *

b.

Renée C. Fox
A Sociological Perspective on
Organ Transplantation and Hemodialysis*

* * *

... Clinical investigations typically are responsible for the care of many gravely ill patients, moving rapidly toward what seems likely to be their imminent deaths because their conditions are those that elude the knowledge and skills of medicine at a given historical juncture. Frequently, such a patient and the members of his family are desperately and uncritically enthusiastic about a new experimental treatment that they know the research physician might make available, and they prevail upon him to do so. As Dr. Norman Shumway, a cardiac surgeon prominent in the field of heart transplantation, explains: "When you get a very sick patient . . . to the doctor, it may be a clinical trial, but to that patient, it is very definitely therapy. When you get such a case, it is very difficult to withhold something that can be attempted." The believing hope of such a patient that an experimental measure will prove to be life-saving therapy is not only a consequence of his otherwise hopeless medical situation. In American society, it is also frequently an expression of his positive commitment to medical science and faith in the day-to-day progress it is making to stem back and "conquer" disease. This is a set of attitudes shared by many other members of the population, both sick and well. With this as a background, a strong transference relationship to the research physician may lead such a patient to see him as the charismatic personification of the dramatic, supercompetent, but thoroughly human capacities of medical science and technology

to save, if not cure, him. The research physician not only has these patient-induced emotional pressures upon him to try experimental means, but also his own professional motivation to do what he can to help a dying patient. . . .

* * *

[T]o our knowledge all kidney transplant centers intensively interview donor-candidates as part of an evaluative medical work-up. It has become a generalized norm among transplantation teams that if they discover a potential donor to be what they consider "psychologically unsuited or incorrectly motivated . . . a medical reason will be found to exclude him, the usual one being that he has not proved to be compatible with the proposed recipient." Too much ambivalence, fear, anxiety, resentment, or reluctance on the part of the donor regarding the gift he has offered are among the attitudes that might psychologically disqualify him. The rationale given for this procedure of stating that a donor is physically rather than psychologically incompatible is that it will protect him against self-condemnation and "blame" by the recipient and relatives. In medical practice as a whole, it is not uncommon for physicians deliberately to withhold information from patients or their families on the grounds that it would cause them excessive psychological pain or harm. But physicians rarely tell patients and family members calculated nontruths. The fact that such a convention has grown up in connection with kidney transplantation is an important indicator of how grave physicians feel the individual, interpersonal, and familial consequences would be if they revealed that the prospective donor was not acceptably motivated to give his kidney.

* * *

NOTE

PHILIP BLAIBERG
 LOOKING AT MY HEART

* * *

... December 3 . . . was the day the world learned that 45-year-old Professor Christiaan N. Barnard, head of a specially trained and selected team, had transplanted a new heart, taken from a car accident victim, Denise Darvall, into Louis Washkansky, a sufferer like myself.

* 169 *Annals of the New York Academy of Sciences* 406, 413-415 (1970). Reprinted by permission.

* New York: Stein and Day 56-57, 65-66, 69, 70 (1968). Copyright © 1968 by Dr. Philip Blaiberg. Reprinted by permission.

I was feeling particularly ill and despondent at the time, but when I heard the momentous news over the radio at the lunch hour I called [my wife] Eileen. She hurried to the bedroom to find me wildly excited.

"Did you hear the news?" I asked her.

"No, what news?" she said.

"A man," I said, "has been given a new heart. Right here in Cape Town, in the Groote Schuur Hospital. His name is Louis Washkansky. Isn't that terrific?" At first, I thought, the implications of the operation did not seem to register with her.

Let her take up the story of the events of that day:

"I thought Phil's remark interesting, but somehow I could not comprehend exactly what had happened. Though I knew he was desperately ill, I had no thought that he could also be given a new heart and he certainly didn't mention it. But he remained excited and said he hoped Louis Washkansky would pull through. He just could not stop talking about it.

"By four o'clock, however, he was so ill that I was more anxious than usual. I had never telephoned Professor Schrire directly before, but I believed a call was warranted now. He walked in while I was talking to his wife. He took the receiver from her and inquired what was the matter. I replied that Phil was very ill indeed. He asked whether I had not received his message—that he had told our family doctor Phil was being considered for a second heart transplant. It appeared later that our doctor had telephoned several times but he had missed me.

"Anyhow, Professor Schrire repeated that Phil was next on the list. I was astounded. . . ."

* * *

The day after my admission to Ward D 1, I was lying in bed with eyes closed, feeling drowsy and thoroughly miserable when I sensed someone at the head of my bed. I opened my eyes and saw a man. He was tall, young, good-looking with features that reminded me a lot of General Jan Christian Smuts in his later years. His hands were beautiful; the hands of the born surgeon.

"Don't you know me?" he asked.

"No," I said with little interest, "I don't."

"I'm Professor Chris Barnard," he said.

"I'm sorry, Professor," I replied, "but I didn't recognize you. I have never seen you in person, and you look so different from your photographs in the Press."

He spoke earnestly. "Dr. Blaiberg, how do

you feel about the prospect of a heart transplant operation? You probably know, don't you, that I am prepared to do you next?"

"The sooner the better," I said fervently, "and I promise you my full cooperation at all times."

Though our conversation was brief and he stayed only a few minutes, I was immediately impressed with the stature of the man and his air of buoyant optimism. He inspired me with the greatest confidence, an invaluable asset in the relations between a surgeon and his patient.

I felt somewhat better. Here was a man to whom I would willingly entrust my life. I came to know him well in the weeks and months that followed. He is a vital, determined, somewhat mercurial, personality, utterly dedicated to his profession.

* * *

On the morning of December 21, 1967, I was surprised to see my wife walk into my ward at about 9:30. Her visits had always been in the afternoons because of her morning job.

"Aren't you working today?" I asked.

"No," she said. "I just felt I wanted to see you."

"The nurses have told me that Professor Barnard is also coming to see me this morning," I said.

It seemed strange and unusual, but I did not give the matter further thought. I accepted Eileen's explanation and believed Professor Barnard's visit would be mere routine. Soon afterward he walked in. Eileen rose to excuse herself.

"No, don't go," Professor Barnard said to her. "I want to speak to you together." I looked more closely at him. He was haggard and drawn as though he had not slept all night. He no longer resembled the handsome Smuts, to whom I had compared him, but more a martyred Christ. I felt a twinge of pity for him when I noticed the pain in his face and eyes. Something, I was sure, had happened to dampen the gaiety and boundless optimism I had seen before.

* * *

Professor Barnard spoke in low tones. "I feel like a pilot who has just crashed," he said. "Now I want you, Dr. Blaiberg, to help me by taking up another plane as soon as possible to get back my confidence."

Still I did not know what he was driving at. "Professor," I said, puzzled, "why are you tell-

ing me this? You know I am prepared to undergo a heart transplant operation at any time you wish."

"But don't you know that Louis Washkansky is dead?" he asked. "He died this morning, of pneumonia."

It dawned on me why Eileen and Professor Barnard had paid me this unexpected visit. Now I knew the reason for his distress and agitation.

"Professor Barnard," I said at once, "I want to go through with it now more than ever—not only for my sake but for you and your team who put so much into your effort to save Louis Washkansky."

* * *

"Don't worry," he said a little more cheerfully now, "everything is going to be fine."

* * *

2.

Countertransferences

a. O. Spurgeon English and Gerald H. J. Pearson Common Neuroses of Children and Adults*

* * *

[I]t must not be overlooked that the transference process is one that works both ways. It is impossible for the physician not to have some attitude toward the patient, and this is called *countertransference*. The good psychotherapist, however, is able and willing to conceal any feelings he may have beyond desire to help the patient. Overt pity, sympathy, criticism, intolerance, affection, etc., are best kept out of the attitude of the psychotherapist. His role is to skillfully and tactfully mirror the patient's emotions and conflicts in such a way that the patient will see their origin and the futility of their endless repetition. The good psychotherapist must necessarily keep out of the therapeutic relationship any personal prejudices he may have upon arbitrary social questions such as divorce, contraception, religious belief. His attitude may be inquiring but impartial. He may discuss current opinions upon these topics but refrain from injecting his own, even though the patient asks

for it. He must be understanding of human weaknesses and fears, but firm in demanding as much adult behavior as the patient can give to his daily living.

* * *

b.

Anna Freud The Doctor-Patient Relationship*

* * *

According to our experience, there are three different ways which urge a young person to choose the medical career. One, and a very good one, is curiosity. The wish to know, as you are probably familiar with, arises very early in the human individual. Already at the age of two, three and four, certainly later also in the school ages, you can distinguish the curious children from those who have no special interest in the mysteries, in the riddles of their surroundings. But the curious ones want to know everything. Parents and teachers are plagued by the continual "why" of the young child—a "why" that they are not always to counter with the proper answer. And very often when parents and teachers do their best to answer the child as fully as they can, the "why" continues, because it springs from rather deep sources. The child wants to know everything about his own body, about his own sex, about the workings of the different parts of himself, of other people's bodies, of the difference between the sexes, of how one becomes a father and a mother, how children are born, what intercourse is about, and from this field curiosity widens to the world as a whole, to the whole world of adults. If curiosity is blocked by the attitude of the adult world, the child may become stunted, apparently incurious and uninterested, and a bad learner. Sometimes not answering the child's questions has the opposite effect. "They don't tell me but I will find out," which means the child becomes more curious. There is somewhere in the child an insatiable wish to know, which stands him in very good stead in later life. One of the ways in which this wish reveals itself rather early, at nursery school age already, is "doctor play." Doctor play goes on between little girls and boys, by preference in secret, because it doesn't always respect the

* Unpublished manuscript based on a lecture to students at Western Reserve Medical School (October 29, 1964). Printed by permission of the author who retains all rights.

* New York: W. W. Norton & Co. 302-303 (1937). Reprinted by permission.

bounds set by the adult world, but it combines curiosity about the other child's body with the wish to interfere with that body. Both wishes can be only fully satisfied in later life—if they stay alive somewhere—and lead the child into medicine. So much for curiosity.

But also at these early ages you can find something else. In every nursery school, the nursery school teacher is prepared that in some corner of the room, or of the garden if there is one, a hospital will be established, and this hospital will be usually for insects, frogs or lizards or any other small animals that can be found. And these small animals will be tended carefully in boxes, fed and looked after and, as the child says, cured. Sometimes, especially when it is an insect, legs will be pulled off beforehand so that a patient is produced, and the patient is cured afterwards. Which means that the child's wish to help and to cure is still very close to the wish to hurt and to maim. The younger the child, the stronger his wish to hurt. The older and more socially adapted he becomes, the more this aggressive wish can be submerged under a strong urge to help. Both wishes can lead the growing individual straight into medicine. Naturally, no need for the doctor anymore to provide his own patients by harming them. Fate does that for him. He only needs to cure them. But the wish to deal with those who are hurt, in pain, maimed has to be there, and probably always underlies, even though hidden in the unconscious, the wish to cure and to help.

There's a third source—a very respectable one, too—for the wish to become a doctor. I remember very vividly when I was a child, myself, of being impressed by those fairy tales usually placed somewhere in the middle ages, where an unusually trained or gifted medical man took up straightforwardly the battle with death, and proved that he could conquer death at any time and save his patients. Death was his enemy. He was the savior and the hero. And this image of the medical profession being heroes strong enough and wise enough to conquer death or at least to put off and postpone death is certainly an idea which is attractive to many people. I know if I had become a doctor, it would have been very attractive to me. In your medical training I know that this interest in death as an enemy has been deflected in part to the interest in birth—birth which provides you with your patients.

I think we have every right to expect that these three sources of interest in medicine pro-

duce three very different types of doctors. The one who is led to medicine by curiosity quite evidently becomes the researcher—the one who wants to know more and more, who is never satisfied with the knowledge that is handed on to him, who wants to add to it and hand on more. The second one quite evidently is the helper, much appreciated by his patients. The third, I suppose, is the autocrat because his is the wish for power. The patients, I believe, react very differently to the three types. By rights they should welcome the researcher, because he is the one who will bring new knowledge into the field, will be able to cure illnesses which have not been cured before, and will offer them the best of medicine. But instead of welcoming that attitude in the doctor, you will hear the patients complain. If you are one of the researchers later on, the patients will probably say you are inhuman—you are not interested in them, you are interested in their illness. They can't make real contact with you, because you overlook them and look at the body and the illness instead. And I suppose you will rightly feel that it is really very ungrateful of the patients. But if you become one of the helpers, the patients will appreciate you. They will appreciate it even if your knowledge of medicine should be minimal compared to the researcher, which is a danger. The one who wants to fight death brings a rather dangerous attitude to the doctor-patient relationship. Patients know it very well, that he's only interested in them if they respond well to treatment. These doctors love the patients who get well, and who thereby give obvious signs of their power and knowledge, and they resent deeply those patients who don't respond to their treatment. And this is an attitude to guard against on your side. It is not the patient's fault, if you cannot cure him.

* * *

C.

Carl H. Fellner and Shalom H. Schwartz
Altruism in Disrepute*

* * *

[W]e have become increasingly aware of another variable that seems to affect donor selection, mostly in a negative sense: the distrust and suspicion with which the medical profession regards the volunteer donor and his motiva-

* 284 *New England Journal of Medicine* 282-285 (1971). Reprinted by permission.

tion. This distrust and suspicion reaches major proportions in the genetically unrelated donor, often unacquainted with the recipient, who wants to volunteer.

Sadler et al. recently reported that of 54 world transplant centers that responded to their questionnaire, half disapproved of using the living unrelated kidney donor, and 20 per cent have used such donors themselves. [T]he replies contained "much evidence of distrust and suspicion toward the motivation of such donors and a definite repugnance concerning their use". . . .

Not only is the altruism of potential donors held suspect owing to estimates of their current psychological status, but it is feared that actual donation will produce further disturbance. Thus, Hamburger asserts that "very few types of medical interventions are as capable of disturbing the innermost core of the personality of the protagonists". . . . Finally, by the choice of vocabulary in his guidelines for the transplant physician, Hamburger implies that the would-be altruistic donation may be akin to a criminal rather than an ethical act: "The major problem is the question as to how far the physician has the right to become the accomplice of a person who wishes to take a risk with his or her own life. . . ."

Despite the widespread medical bias against the unrelated living transplant donor, 85 people answered a plea for a kidney to be used in a transplant in Cleveland in 1963. Does this response indicate that the medical profession is out of step with public opinion in considering unrelated transplant donation to be unreasonable? Does such willingness to be a donor reflect psychopathology, or could it reflect healthy altruism derived from genuine moral concern? . . .

Written questionnaires were completed by 116 adults in a Midwestern city of 175,000 population while they waited in bus, train and airplane terminals and in laundromats. A cover sheet provided information about the purpose, results, donors used and costs involved in heart, kidney, liver and bone-marrow transplants. . . .

* * *

How willing are people actually to donate a kidney to a stranger? If a substantial proportion of the public would seriously consider becoming a kidney donor, doctors would have less reason to suspect the potential volunteers they encounter. Belief in the normality of volunteering is supported by the fact that only 46 per cent of our respondents thought there was less than an

even chance that they would donate one of their kidneys to a stranger in need, with only 24 per cent definitely ruling this out. . . .

* * *

Is the public . . . as greatly concerned as the medical profession with the possibility that transplants are unethical and psychologically disturbing? Responses . . . suggest that this is not so. Fewer than one in five respondents thought that each of [the] ethical or psychologic objections, which were presented as "reasons that doctors and other serious critics have given for considering reductions in transplant activity," had a great deal of merit. In the light of the assumption that sensitivity to psychologic and perhaps to ethical analyses of behavior increases with education, the negative correlations between schooling and acceptance of these items as meritorious objections is especially revealing. It is the well educated in particular who dismiss the objections that members of the medical profession have raised.

* * *

It might be objected that answers to questions in this research . . . are hypothetical, and do not reflect accurately how members of the public would feel and what they would do when faced with a real request to donate. The one reported study in which such a request has been made suggests that the survey results may not overestimate the public's favorable attitude toward involvement in transplant activities. Schwartz has found, in an experimental study, that 83 per cent of a sample of 144 blood donors actually agreed to have their blood tested for compatibility with a stranger, with the understanding that there was at least a 50-50 chance that they would be willing to donate bone marrow if they were found compatible.

What additional reasons can be offered for the distrust and suspicion with which the medical profession regards the volunteer donor? Certainly, the reluctance to inflict irreversible damage on a healthy person can account for much of it. Every member of a surgical team that has participated in the removal of a healthy donor organ will testify to that. The point has even been made that the operation on the donor is not a medical procedure at all since it is not making a sick person well but a well person sick.

But there appear to be other, more irrational reasons on which available research bears. First of all, the spontaneous, often immediate

character of the related donor's decision is interpreted as "emotional" or "impulsive," and therefore symptomatic of psychopathology. . . .

Secondly, the role of other family members in donor selection is a priori suspect by physicians; "undue pressure" and "scapegoating" are readily assumed. . . .

A final argument against the use of live donors, the assumption that the donor cannot possibly derive any benefit from giving up an organ, completely ignores the very real increase in self-esteem and feelings of worth that result from donorship. Time and again, donors have asserted that they have no regret, that they would do it all over again, and that each derived a sense of worthwhile accomplishment from helping to save a life. And it has been shown that these positive changes in self-feeling persist irrespective of the vagaries of the donated organ and the fate of the recipient.

Regardless of the merits of the many arguments that we have discussed, the fact remains that almost uniformly the genetically unrelated, live kidney donor, and quite often also the related live donor, are excluded from donation. The almost mandatory psychiatric examination of donors in transplant centers that still use live kidney donors is most often but another expression of the same medical bias. There have been several medical conferences on the ethical and legal aspects of organ transplantation, but they have failed to pay attention to this medical bias. We believe the time has come for the medical profession to reconsider where it stands in this issue.

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d.

**H. Harrison Sadler, Leslie Davison,
Charles Carroll, and Samuel L. Kountz
The Living, Genetically Unrelated,
Kidney Donor***

* * *

This survey began in late 1967 with the purpose of helping to form a local policy regarding the use of living, unrelated donors for kidney transplantation. We were aware of five general objections to using the living, unrelated donor as an organ source: (1) The prevailing statistical conclusion: "The results are no better than the cadaver series." (2) The psychological verdict:

* Pietro Castelnovo-Tedesco, ed.: *Psychiatric Aspects of Organ Transplantation. 3 Seminars in Psychiatry* 86-88, 92-93, 98-99 (1971). Reprinted by permission of Grune & Stratton, Inc.

"He's crazy." (3) The ethics of medicine: "*Primum non nocere* (in regard to the donor)." (4) The legal implication: "Someday he will harass the recipient or the hospital." (5) The attitude of physicians: "He offends the human conscience."

* * *

We carried out a detailed, prospective, psychiatric study of the donors (8 in number) who were operated on after December 1967, and a retrospective study of those (10 in number) who had been operated on prior to this date. . . . All the donor candidates were interviewed for at least 10 hours and one for over 50 hours. To date we remain in touch with all of these patients and, with their permission, monitor them through friends, relatives and various agencies.

* * *

In the data from the donors who had experienced the transplant operation, certain universal findings appeared in every protocol: (1) No matter how they heard of the need for a kidney, their declaration to give in response to this plea was almost immediate. For example, 15 donors reported their readiness to give a kidney in less than 12 hours. (2) All were supported in their donation by their families and later by friends, although initially these supporters reported that such an act seemed "crazy." (3) None of the donors reported feeling coerced by physicians. (4) The operation itself, the hospital stay and subsequent outpatient visits were uneventful. (5) After the operation each donor reported a deep feeling of increased self-esteem (i.e., that he had done something wholesome and natural) with no indication of regret. (6) The donors reported no depression which needed special attention, nor have there been any subsequent complications, either psychological or physiological, related to the transplantation. Our data indicate that each donor lives a well-balanced life at his own level.

* * *

Typical . . . is the 46-year-old wife of a successful civil engineer. She lives an active personal and social life in an upper-middle class suburban community. Her four children range in age from 14 to 7; the two middle children, a brother and a sister, were adopted following a newspaper appeal by an adoption agency. Prior to her marriage at age 35, she had been a successful executive secretary in a large insurance company.

* * *

She had no interest in kidney disease or transplantation until by chance she read in the paper that in a nearby community a 46-year-old man with two adopted children, the ages of her own, could "have his life saved if donors with O negative blood would come forth and offer their organs." She excitedly "knew" she would volunteer: "His children are the same ages as mine. What if mine needed a father? . . . How often are you given the chance on a silver platter to save a man's life?" She immediately shared her thoughts with her whole family, discussed all of the pros and cons, extracted their cooperation, and made the experience "ours." Six hours later she called the recipient. (She chose not to meet him actually until after the operation.)

In the three-month intervening period prior to the operation, she and her entire family remained firm and energetically devoted to the work-up and study. Her children shared each phase with their school friends. She took an impish delight in "letting the secret out" and enjoyed the feedback of awe, praise, and adoration.

The operation, the hospital stay, and the postoperative course were without any serious complications. She visited the recipient on the fourth postoperative day, and they fell spontaneously into each other's arms. They have remained distant friends ever since. She continues to work for the local Kidney Foundation and as a community volunteer. Her reflections immediately after recovery were: "I feel so full of love and now know that such a feeling is humanly possible. I really have gotten so much more than I have given. I know now that it is possible that such love is a potential of the human being and that it has no other need for reward than the giving itself."

Although not all of our donors have shown this dramatic growth, we can find no examples of anyone having been injured by the experience. An example of a less integrated individual, who by our current psychological standards would not now be chosen, is a 28-year-old, former nurse who presented herself in 1966. She had read about the need for a kidney in the newspaper and was strangely moved to offer her own organ with the reason that, "It might make my own life better." She described "deeper feelings" that the recipient, as depicted in the paper, seemed a most worthy person, and there was evidence of a strange feeling of identification. She was not moved, however, to make an actual declaration until a second newspaper appeal impressed her even more: "Why don't

people want to help others?" She thought about this declaration for 2 more weeks and then called the recipient's local physician, who introduced her to the recipient's family. She then decided to go ahead.

Prior to her appearance as a donor, she had a four-year history of addiction to amphetamines and methadone, had experienced a broken marriage and was a member of Alcoholics Anonymous. She had attempted burglary and had received a suspension of her nurse's certification because of antisocial behavior, which included being in jail. She was isolated from her family and was living an almost nomadic life.

Following the transplant there was a striking display of increased self-esteem and an increase in her actual ability to relate to people in the hospital, in the community, at AA meetings, and with her family: "The transplant has broadened my whole interest in working with people. It makes me forget the bad things of my past." In those years the publicity was great, and she had received over 50 letters of praise as well as visits from unknown people. With the many offers that came to her, she reported feeling "a new start." Two months following the transplant, the organ failed and the recipient died. The donor rapidly reverted to her former antisocial pattern and later was hospitalized at a state mental institution. Her reflections were "Why should someone like me live and someone as fine as that die?"

In the interim (4 years) she has not taken alcohol or drugs and, since her discharge from the hospital, has been living a controlled life. She is now a welfare recipient and occasionally babysits or cooks for those who need her. There is no evidence that the transplant episode injured her. She now tells us she feels it was a crisis experience from which she benefited, and the fact that she made this donation has been one wholesome experience in her life. She is gradually attempting a rehabilitation program.

* * *

In spite of these findings and the data supporting them, most physicians who discussed this paper at a scientific meeting, and many transplant surgeons, in responding to the prepublication article, have continued to maintain that "no matter what you show, these people must be abnormal—to do such a thing." They indicate that psychological tests and interviews may fail to reveal the presence of psychopathology. They offer as evidence for this agreement the

donor's "social role." For example, for those donors with young children (10 out of 18) to jeopardize their own health by giving a kidney was an indication of "a defective sense of parental responsibility." Furthermore they declare that "if these people derived emotional gain from the experience, they must have been acting out of highly subjective neurotic motives."

Our prospective analysis of the eight donors has included free associative interviews, dream analysis, exploratory long-term psychological investigations (some continuing for 2½ years), Rorschach and Thematic Apperception projective test analyses, and a continual monitoring of their lives. These studies have revealed ample evidence for the presence of primitive masochistic trends, reaction formation against early sadism, homosexual conflict, pregnancy symbolism, penis envy in women, etc.—all the primitive and elemental forces present in mankind. However, the human mind is not a fixed and static organization, but is by its very nature capable of palpable self-awareness and possesses the capacity for synthesis and growth. Therefore, the question to be asked is not "Are these primitive factors present?", but rather, "To what degree are they present?" "Do they preempt behavior and thereby the decision to donate?" "Will the surgical procedures weaken the mind's ability to grow?"

* * *

To the question, "Have any donors been harmed, especially if they had obvious psychological problems?" the answer is "No, none of the 18 donors have been harmed." In our retrospective study, we found three candidates who would not be accepted by today's standards. Two have been diagnosed as chronic alcoholics and one has an antisocial character disorder. All three had given their "informed consent." The two alcoholics are 6-years postoperative and the one antisocial character 4-years. We found that they were not injured psychologically, socially, or physiologically. Whereas their underlying psychiatric condition has not improved, neither has there been evidence of decompensation. . . .

Perhaps the greatest discrepancy found in this study revolves around two poles: a voluntary, altruistic, and personally rewarding act of donating a kidney to an unrelated person is viewed by most physicians as impulsive, suspect, and repugnant—although the public does not share their view. It seems that these physicians base their clinical judgments on their own "view of human nature." Guided by the tone of

the letters from the various transplant centers, we interpret this viewpoint as follows: if one experiments with human beings for therapeutic reasons, one needs convincing evidence that the experiment will be successful. In as much as the evidence is not at hand, this is scientific reason not to use them as donors. There is also the unacknowledged problem that an added responsibility exists because the donor becomes another patient as a result of the surgery. The surgeon must then assume care for donor as well as recipient. The physician's own anxiety as a result of these problems gives rise to defensive statements and the tendency to legitimize.

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NOTES

NOTE 1.

WILLIAM B. BEAN
A TESTAMENT OF DUTY—
SOME STRICTURES ON MORAL RESPONSIBILITIES
IN CLINICAL RESEARCH*

* * *

Clinical investigators rarely meditate upon the wide cleavage which separates clinician from investigator in their split personality. As physicians, their prime concern is intimate, personal responsibility in caring for sick people. As investigators they are goaded by divine discontent and impelled by curiosity as well as ambition for renown. Such stimulus sometimes suppresses the physician altogether. The different views are seen well in the subtle but great change which occurs when a house officer becomes a research fellow. Unless wisdom and compassion are neatly blended, the friction between the excited investigator bent on research and the resident with his mind set on care for the patient may produce fire as well as acrid smoke.

* * *

Of more danger and concern is the custom now current that clinical investigators come to positions of academic responsibility by apprenticeship in laboratory science rather than by the thornier path as practitioners of the art who become wise clinicians. And the danger is not in the matter of teaching, which may be done well or poorly without exact correlation with training, but that the most praiseworthy zeal for knowledge may lead the man whose technical background overshadows his caring for the pa-

* 39 *Journal of Laboratory and Clinical Medicine* 3, 4-5 (1952). Reprinted by permission.

tient into a disregard for the subject of his researches. Thus, potentially dangerous experiments may be done without the subjects' knowledge or express permission. Whether it be thoughtlessness or heartlessness, such practice is a measure of the moral obliquity which exists in some high places of research today. Fortunately, it is not widely current, but it does exist. At a time when ethical standards are high, or religion elevates moral tone, this situation would have other correctives. They are not effective today. Moral necrosis is sinister in its pervasive insinuations, and all who are concerned with clinical research, that is, experiments on themselves and their fellow man, must face the implications. The recent degradation of physicians in Nazi Germany exemplifies the decline and fall of a group whose moral obligations went by default in a single generation. The house would not have fallen had not many timbers been rotten. Descent into the gas chamber by doctors of infamy had its beginning in disregard for the patient. Never forget that the difference between an experiment on human beings without clear understanding and freely granted permission, and the determination of the M.L.D. [minimum lethal dose] in man is one of degree, not of kind. . . .

* * *

NOTE 2.

DEPARTMENT OF PSYCHIATRY—
UNIVERSITY OF PENNSYLVANIA
STATEMENT OF PRINCIPLES COVERING
THE USE OF VOLUNTEER SUBJECTS IN
PSYCHIATRIC RESEARCH*

* * *

. . . The investigator, using normal human subjects, must be aware of his dual responsibility to the subject participant as well as to the scientific community. Thus, whenever possible, the purposes of the research, the procedures to be followed, and the possible risks involved must be explained to the subject; the investigator is to make certain that the subject understands the explanation. When such an explanation might bias the results, as in much psychological research, such an account may be postponed. In so doing, the investigator assumes an even greater responsibility. The subject's participation is predicated on his faith in the investigator and the institution that no harm shall befall. The investigator must be careful to pre-

serve this faith. Unless it would be deleterious to the research effort, every effort should be made to indicate to the subject, at least after the experiment, something of the purpose and aims of the research. . . .

* * *

NOTE 3.

FROM A CORRESPONDENT
PSYCHIATRY*

* * *

. . . Desire to alleviate suffering was, in Dr. Szent-Gyorgyi's view, of small value in research—such a person should be advised to work for a charity. "Research wants egotists, damn egotists, who seek their own pleasure and satisfaction, but find it in solving the puzzles of nature." Material success, however, also played a very small part, and most significant researchers and artists died poor. Mere knowledge did not interest him, it was *new* knowledge he sought, and he often felt ashamed of his general ignorance compared with his colleagues; but really such learning as this would only serve to weigh him down and he preferred to see things without much sophistication.

* * *

NOTE 4.

LORD PLATT
MEDICAL SCIENCE—MASTER OR SERVANT?†

* * *

Patients, often hideously called the "clinical material" of teaching and research, have been drawn so far as possible from the lower social classes (everyone well brought up knows that the lower social classes have no emotional needs or feelings), and were, and still are, interrogated either in an almost open outpatient department in the presence of numerous students or recumbent in a hospital bed in an open ward; conditions chosen with unerring insight to ensure that the psychological factors in disease, even if present, cannot obtrude and disturb the proper pursuit of scientific medicine. But to make assurance doubly sure, the ward round is conducted as a ritual, the chief followed by his numerous attendants.

The advent of the professional medical departments, which should have brought with

* 1 *The Lancet* 1394 (1961). Reprinted by permission.

† 4 *British Medical Journal* 439, 442 (1967). Reprinted by permission.

* Memorandum to Faculty (1965). Reprinted by permission.

it new attitudes towards patients consistent with the new understanding of interpersonal relations, has in some instances merely reinforced the defences by a more refined and narrow choice of the "clinical material" . . . by the development of grand rounds to replace the ritual visits of former years. I have seen a patient wheeled in and demonstrated to a large meeting and wheeled out again without a single word being said to her—not even a word of thanks. . . .

* * *

NOTE 5.

MOORE v. WEBB
345 S.W.2D 239, 242 (Mo. 1961)

* * *

Dr. Webb testified he had no recollection of talking to plaintiff about what teeth were to be extracted or discussing the X-rays, with her. . . . Further testimony of Dr. Webb is quoted as follows:

Q: Isn't that pretty much up to the patients what they would do with reference to a partial plate, if they wanted a partial plate? A: No sir.

Q: Couldn't they have that if they wanted that? A: That all depends. I don't think so. I think you should strive to do for the patient what is the best thing over a long period of time for the patient. We tried to abide by that.

Q: Isn't that up to the patient? A: No, I don't think it should be. If they go to a doctor they should discuss it. He should decide. The patient should agree that that is what is to be done and should be done.

Q: Isn't this up to the patient? If I want to pay \$800.00 for a partial, I hope the dear Lord lets me keep my teeth. If I want to keep these teeth, can't I do it? A: You don't know whether they are causing you trouble.

Q: That is up to me, isn't it? A: Not if you come to see me it wouldn't be."

* * *

NOTE 6.

FRANCIS D. MOORE
THERAPEUTIC INNOVATION—
ETHICAL BOUNDARIES IN THE INITIAL CLINICAL
TRIALS OF NEW DRUGS AND SURGICAL
PROCEDURES*

* * *

[T]he principle of informed consent has two special limitations. The first unique feature

of informed consent in therapeutic innovation is that the patient actively seeks the untried therapy with an earnest plea to become the willing subject. To those who have never dealt with such desperate patients, it may come as a surprise to witness the enthusiasm with which the patient with late cancer or the family of children with severe heart disease approach an entirely new and untried procedure. This willingness is especially notable if the family knows or suspects, with or without suggestions by the doctor, that the new procedure is the only source of hope for survival. The cancer patient himself seeks out the new drug or the new treatment; people of education and considerable scientific sophistication become blinded and will transgress the boundaries of the simplest common sense not only in accepting new drugs, but in seeking quackery in the hope of a cure. The posture of "informed consent" in therapeutic innovation is, therefore, not a matter of trying safely and sanely to explain to a volunteer what is going to be done, but rather the much more difficult task of explaining alternatives to a worried patient who wishes, above all else, to have the experiment carried out on him.

* * *

An intrinsic feature of consent lies in the presentation of sound alternatives to the patient. If I were to identify any one feature of the doctor-patient relationship that is most frequently colored by unconscious subjective factors on the part of the doctor, it is this question of clinical alternatives. One or two examples will illustrate. A colostomy or ileostomy is a form of diversion of the gastrointestinal tract made so that the fecal contents are emptied onto the abdominal skin. Here the discharge is received in some sort of a bag or receptacle that the patient empties from time to time. While unpleasant and unhygienic, most intelligent persons accept this as the price that they pay for the treatment of severe disease—usually malignancy. The more intelligent the patient and the more fastidious his care of his own physical person, the less difficulty he has with colostomy or ileostomy, since he takes special time each day to care for himself in a way that is acceptable to his own high standards. On many occasions I have borne witness to conversations between physicians and patients in which the picture painted of this colostomy or ileostomy was entirely the product of a physician's imagination, based on the fear that he himself might one day have to have such a procedure. A patient suffering from ulcerative co-

* 98 *Daedalus* 502, 509–511 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

litis or cancer of the rectum who is given an offensive or frightening verbal description of colostomy or ileostomy would be so biased in his approach to the operation that he may actually refuse a procedure that offers him the greatest likelihood of survival. By contrast, the over-enthusiastic description of the state of well-being which may result from the surgical treatment of ruptured intervertebral disc, bursitis of the elbow, or hypertrophy of the prostate (considering only three of many examples) will sometimes result in a patient entering into an operation for benign disease, not life-threatening, with an optimism born of the surgeon's tone of voice rather than a realistic estimate of his own response to the projected treatment.

* * *

NOTE 7.

MULLOY v. HOP SANG
[1935] 1 W.W.R. 714 (ALTA. APP. DIV.)

JACKSON, D.C.J.—The plaintiff's claim is for professional fees for an operation involving the amputation of the defendant's hand which was badly injured in a motor-car accident. The accident took place near the town of Cardston and the defendant was taken to the hospital there. The plaintiff, a physician and surgeon duly qualified to practice, was called to the hospital and the defendant, being a stranger and unacquainted with the plaintiff, asked him to fix up his hand but not to cut it off as he wanted to have it looked after in Lethbridge, his home city. Later on in the operating room the defendant repeated his request that he did not want his hand cut off. The doctor, being more concerned in relieving the suffering of the patient, replied that he would be governed by the conditions found when the anaesthetic had been administered. The defendant said nothing. As the hand was covered by an old piece of cloth and it was necessary to administer an anaesthetic before doing anything, the doctor was not in a position to advise what should be done. On examination he decided an operation was necessary and the hand was amputated. Dr. Mulloy said the wounds indicated an operation as the condition of the hand was such that delay would mean blood poisoning with no possibility of saving it. In this he was supported by the two other attending physicians. I am, however, not satisfied that the defendant could not have been rushed to Lethbridge where he evidently wished to consult with a physician whom he knew and relied

on. Dr. Mulloy took it for granted when the defendant, a Chinaman without much education in English and probably not of any more than average mentality, did not reply or make any objection to his statement that he would be governed by conditions as he found them, that he had full power to go ahead and perform an operation if found necessary. On the other hand, the defendant did not, in my opinion, understand what the doctor meant, and he would most likely have refused to allow the operation if he did. Further, he did not consider it necessary to reply as he had already given explicit instructions.

Under these circumstances I think the plaintiff should have made full explanation and should have endeavoured to get the defendant to consent to an operation, if necessary. . . .

3.

Regression

Edmund C. Payne, Jr. Teaching Medical Psychotherapy in Special Clinical Settings*

* * *

The concept of regression is useful in explaining many of the otherwise puzzling attitudes that a patient shows in response to illness. By regression we mean the replacement of more complexly organized and more recently acquired aspects of the functioning of personality by more primitive and chronologically earlier modes of functioning. Human personality develops by changing and integrating simple forms of behavior into more highly organized patterns that possess a broader capacity for adaptation. . . . Many of the earlier patterns, however, persist in modified form in a hierarchically ordered relation to the more highly developed and usually controlling systems. In the face of stress, whether caused by internal conflict or by external danger or frustration, a person may give up the more mature aims and ways of functioning and again seek gratification and attempt to cope with his problems in ways more in accordance with these earlier patterns. A simple example of regression is seen in the toddler who

* Norman E. Zinberg, ed.: *Psychiatry and Medical Practice in a General Hospital*. New York: International Universities Press, Inc. 135, 143-144 (1964). Copyright 1964, International Universities Press. Reprinted by permission.

is gaining increasing independence and self-reliance, but who periodically turns back to his mother's lap for comfort and security when the world is temporarily too much for him. When a person falls ill, some degree of regression invariably occurs, induced by a number of factors. Illness interferes with bodily functions that are necessary for the maintenance of important aspects of the personality. The patient who comes to the hospital loses freedom of movement, is deprived of his clothes, and must literally put himself into the hands of other people and depend on them to care for many of the needs that he normally attends to himself. His passive dependent needs are increased, his usual patterns of adjustment are disrupted, and he often suffers intense conflict. Illness is a threat to the integrity of his body and to his life, and consequently generates feelings of anxiety. Since he may be unable to cope with these dangers himself, his anxiety is usually accompanied by a feeling of helplessness. Thus he is forced to rely on the physician for security in ways that resemble his dependence on his parents when he was a child. All of these factors encourage regression. When regression occurs, conflicts that

were important in childhood but that may have subsequently become latent tend to regain their intensity, and the old defenses that were associated with those conflicts may be mobilized again. In many cases these unconsciously determined defensive reactions are not appropriate to reality, to the requirements of dealing with the present illness and of adapting to the necessary medical procedures; in some cases they may be diametrically opposed. The regressive process not only adds a burden of irrational anxiety to the difficulties created by the illness, but may also distort the patient's relationship with his physician. Under the pressure of regression, the patient frequently attributes to the physician characteristics that really belonged to people who were important in an earlier period of his life. In some patients this attribution will increase their confidence and trust in the doctor and thus augment the doctor's effectiveness in providing support and allaying anxiety. In other patients it may produce a negative reaction that can prove both baffling and frustrating to the physician.

* * *

C.

Barriers to Comprehension

1.

Failures of Communication

a.

Corn v. French **71 Nev. 280, 289 P.2d 173 (1955)**

BADT, JUSTICE.

Plaintiff sued defendant for the unauthorized and unnecessary amputation of her right breast, alleging that the operation was contrary to her desire and consent and without making an appropriate diagnosis to ascertain presence of malignancy therein, it appearing from a post-operation pathological analysis that there was no malignancy. After the plaintiff had completed the presentation of her evidence, the court granted a motion for involuntary dismissal on the ground that upon the facts and the law the plaintiff had failed to prove a sufficient case for the jury. . . .

Plaintiff testified that on August 12, 1950

she had an appointment with defendant at the latter's office at Boulder City, Clark County, Nevada: ". . . We talked about the condition of my breast; that there were danger signals; and he examined me and it was my understanding that he would make a test of a lump under my breast to see if it was cancerous. . . . He didn't make X-rays or blood tests or anything like that, whatever tests you make. He did examine me with his hands, looked at my breast and examined me with his hands. . . . I asked him if he could make a test to see whether or not it was cancerous and he said he could and that he would. . . . [He] called the hospital later when I was dressed, and he said he was going to make sure that they would have a room reserved for us, myself and another patient he had in mind. . . . At that time that he was talking on the telephone, to the hospital, he was talking about preparing a tray. And he said 'for the removal of a right breast.' And I said 'If that's my breast you are talking about, you are not going to remove it.' He said 'I have no intentions

of removing your breast. I wouldn't think of doing so without first making a test.' He said 'It takes the same instruments to make a test as it does to remove one.' I subsequently entered the hospital. . . . At that time I signed a consent." She then identified a document as the one which she had signed and which reads as follows: "I hereby give my consent to James B. French, M.D., to perform an operation for mastectomy and hemorrhoidectomy upon myself, and to do whatever may be deemed necessary in his judgment." It was witnessed by her husband and a hospital nurse. She testified further: "Up to that time that I signed that document I had never heard the word mastectomy that I know of. I did not know the term. . . . On the evening of the 14th I saw Dr. French at the hospital. One of the sisters in the hospital and Junelle Sherwood were also present. . . . I asked [the doctor] again to make sure that he understood he was just to make a test of the breast, and the hemorrhoidectomy. His answer was that he had no intentions of doing anything different; he was to make a test of the breast only. I remember that I just kept repeating it, and talking about it, and I did say to him that if he did go ahead and remove the breast that it could not be put back on, but if he didn't take it off, then we could make the test and it need not be taken off."

After the removal of her breast she testified to a subsequent conversation with Dr. French at the hospital and she understood him to say that she had had cancer but that he had removed it: that he had got it early and got every bit of it. "I said 'Are you sure you got it all' and he said 'yes,' and I said 'How long would it have been before it started to spread?' He said 'That I can't say, maybe two days, maybe a week.' He said it hadn't started to spread." She testified to a later conversation with the doctor at his office in Boulder City concerning some lumps on her ribs. "And I went to see if the cancer was spreading and he said that it could not be, because I didn't have cancer in the first place. That was the first time I was aware of the fact that the breast did not have cancer."

* * *

Plaintiff's theory of this issue is, first, that when she signed the written consent to the operation she had never heard and did not know the meaning of the word mastectomy, and, secondly, that in any event she clearly and unmistakably made known to the defendant that he was just to make a test of the breast and that his answers

showed that he completely understood such instructions; that the witness Junelle Sherwood substantially corroborated her testimony; that the jury had the right to believe this testimony and to determine that the operation was unauthorized. The trial court's reaction to this contention, when made in opposition to the motion to dismiss was as follows: "Now, if any person after signing that sort of consent, which is general in its terms as well as specific, could repudiate it after an operation, there wouldn't be any doctor in the country that would be safe from suits of this sort. She, whether or not she understood the meaning of it, by her action in giving a general consent, is estopped from denying that she gave her consent to the very operation that was performed." Plaintiff's contention however is not that she had a right to repudiate her consent but that, even assuming that she signed the written consent with full knowledge of its meaning, she was not precluded from canceling or withdrawing it before the operation. Such right is not seriously denied by defendant. . . .

* * *

[W]e are not called upon to determine whether or not defendant, in removing plaintiff's breast as the result of his original provisional diagnosis and without any pathological examination, failed to use ordinary care and diligence, but rather whether the evidence presented was sufficient to have justified a finding, or a necessary inference from the facts, to such effect, by a jury.

For over two generations pathologists and other medical men have been writing treatises on the pathological analysis of tissues for the diagnosis of cancer, and general practitioners have been sending their patients with symptoms of the disease to specialists. "What everybody knows the court must know." And this knowledge might well permit a jury to peer beneath the cloak of protection thrown about the defendant by the testimony that his diagnosis and treatment were in accordance with the standards of the profession in his community. . . .

. . . Dr. Hemmington, called by the plaintiff, but characterized by the trial court as a hostile witness, did come forward with an "explanation" that the ordinary diagnostic procedure of biopsy was not followed because there was no local pathologist in the county. This might well serve to explain why no biopsy was secured during the operation proper, preliminary to the

mastectomy. It would not explain absence of a preliminary or independent pathological examination. There was no evidence that an emergency existed and no explanation as to why a specimen could not have been sent to an outside pathologist or the patient referred to another city for treatment where these services were available, or why she was not at least advised that defendant intended to make a diagnosis without the assistance of a biopsy or pathological examination, or why she was not advised of Clark County's lack of such facilities and the availability to her of these facilities in some other city that could be readily reached by air transportation within the course of a couple of hours. At this stage in the proceedings (before the defendant had made a presentation of his defense) the absence of such explanation is readily understandable. We may not, however, anticipate that it would eventually have been given or that if given it would unquestionably have served to satisfy the jury.

[W]e are convinced . . . that . . . the use of (or the failure to make use of) the pathological analysis of the tissue, in a proper case, for the purpose of diagnosis [can be taken into consideration by a jury] in its own common knowledge and experience and without the assistance of expert testimony—the knowledge, concisely expressed, that “[m]icroscopic diagnosis is the *sine qua non* of neoplastic disease. It is the only means of absolutely establishing the true nature of the disease.”

For the reasons given, we conclude that the order granting the motion for involuntary dismissal was error, and that the judgment must be reversed and the case remanded for a new trial.

b.

Wilson v. Scott
412 S.W. 2d 299 (Tex. 1967)

POPE, JUSTICE.

* * *

Plaintiff, Frank E. Scott, sued Dr. Anthony Wilson for failure to make reasonable disclosure of risks incident to a stapedectomy operation. He alleged that his right to refuse the operation upon his left ear was violated because the pre-operative warning was not sufficiently full for him to exercise an informed consent, and the operation was unsuccessful. The trial court rendered judgment for Dr. Wilson. . . .

* * *

In 1962 Scott consulted Dr. Wilson who correctly diagnosed the cause of the hearing defect as a bony growth on the stapes bone which inhibited its vibration and dulled Scott's hearing. He recommended a stapedectomy with a vein graft. The operation is relatively new and is regarded as a delicate and complex one. . . . Dr. Wilson is highly trained and has received special instruction in the performance of stapedectomy surgery. He had performed similar ear operations, but Scott's operation was his first stapedectomy with vein graft. . . .

* * *

Scott testified that Dr. Wilson, in discussing the probable results, told him about statistical experiences in terms of “we,” from which he inferred that Dr. Wilson had performed this specific operation previously. Although he had performed related operations, Dr. Wilson's former experience with this specific procedure had been confined to experimental operations upon cadavers under the instruction of the originators of the procedure and the best available instructors.

* * *

. . . Neither Dr. Wilson nor any other witness testified about a medical standard for disclosure to a patient about the surgeon's experience with a specific operation. . . .

* * *

SMITH, JUSTICE [dissenting].

Scott alleged that the doctor was guilty of fraud in representing that he was thoroughly experienced in performing a stapedectomy and that a “stapedectomy with vein graft and polyethylene prosthesis was a safe and proven operation when in fact it was an experimental operation condemned by some of the most prominent experts and authorities. Had Scott been informed of this fact, he would not have submitted to the operation.” Scott's third theory of recovery was that “[a]lthough Scott had specifically inquired of Dr. Wilson prior to the operation whether there was danger of disability, Dr. Wilson stated that there was none other than the normal risk of taking anesthetics and possibly some slight loss of taste. In truth and in fact the risk of nerve deafness, tinnitus, vertigo, dizziness and other nervous disorders were well-known to Dr. Wilson, and the operation was still in the experimental stage. Dr. Wilson's failure or refusal to advise and inform Scott of such

facts made it impossible for Scott to know and understand the nature of the operation or to give a knowledgeable consent to such operation. Had Scott been informed of such facts, he would not have consented to said operation. *Such operation constituted an assault and battery.*" [Emphasis added.]

* * *

. . . This is a case of first impression in Texas, but I find no case decided in other jurisdictions that holds a doctor is under a duty to state in precise words that there probably would be 1 percent who would sustain a complete loss of hearing as a result of the stapedectomy. Nor do I find any cases which sustain Scott's apparent theory that to be an informed consent the doctor is required to relate all of the dangers associated with the operation, such as 1 percent of patients sustain a complete loss of hearing, or that tinnitus, vertigo, dizziness and other nervous disorders probably would follow the operation.

Whether or not a physician or surgeon is under a duty to warn a patient of the possibility of a *specific* adverse result of a proposed treatment or operation depends upon *the circumstances of the particular case, and of the general practice with respect to such cases followed by the medical profession in the locality.* The custom of the medical profession to warn must be established by expert medical testimony.

It is not the duty of a physician in this type of case to relate specific adverse results that might obtain after surgery. The physician's duty to disclose is limited to those disclosures which a reasonable medical practitioner would make under the same or similar circumstances.

c.

Steele v. Woods
327 S.W.2d 187 (Mo. 1959)

JUSTIN RUARK, SPECIAL JUDGE.

This is a malpractice case. Plaintiff sought and obtained damages because of gangrene and resulting crippling by the loss of her toes and part of her feet following a varicose vein operation. . . .

. . . Defendant contended that plaintiff's gangrene and subsequent disability resulted from her refusal to submit to certain postoperative treatment which is referred to as a paravertebral block. At the close of the evidence the defendant was permitted to amend his answer by charging

contributory negligence on the part of the plaintiff (among other things) in failing or refusing to have such paravertebral block when it became apparently necessary following the operation. Plaintiff abandoned her theory of negligence in failure to give preoperative tests and submitted her case to the jury upon the theory that, following the operation, plaintiff suffered an impairment of circulation, that a paravertebral nerve block was necessary, that defendant negligently failed to advise the plaintiff of the need for such paravertebral block and that it was not performed. The defendant caused the jury to be instructed on the theory that plaintiff refused to have the nerve block suggested by the defendant and thereby contributed to her own disability. Thus the sole issue which went to the jury was (a) whether the defendant advised a paravertebral nerve block and (b) whether the plaintiff refused to permit it. The plaintiff received a jury verdict for \$40,000. Thereafter the court sustained the defendant's motion for judgment after verdict and also sustained defendant's motion for new trial. . . . Plaintiff has appealed.

* * *

Practically all the medical opinion, including that of the defendant himself, is to the effect that plaintiff's gangrenous condition was the result of a failure or incompetence of the inner circulation; that this was caused by spasms of the blood vessels, and that this in turn was caused by the action of automatic sympathetic nerves which constrict the vessels. Such spasms are not a usual occurrence and are not necessarily to be anticipated. They sometimes result from the trauma or shock of the operation. These spasms can be allayed by the performance of a sympathectomy (cutting of the nerves which control the constricting muscles or sheaths) or a paravertebral block, which consists of injecting the nerves with novocain or other anesthetic agent. The latter is the more conservative treatment, since its result is only a temporary anesthetization and consequent relaxation of the nerves involved. . . . Defendant's witness Graham . . . further testified that the doctor has a duty to tell the patient what treatment is necessary, and that, if necessary treatment was refused, he as a skillful and prudent physician would inform the patient that he was going to make it plain to his colleagues and to the patient's family that the proffered treatment had been refused.

In reference to the paravertebral block the plaintiff testified:

Q: Did you ever have any conversation with Dr. Woods about giving you one of those? A: Not to my knowledge.

* * *

Q: Well, you were conscious at all of those times the doctor asked to have a paravertebral block, were you not? A: I don't remember him ever asking me about a block, sir.

* * *

Q: Didn't Dr. Woods explain to you that a paravertebral block would release the spasm around your arteries in your legs and increase your blood circulation? A: No, sir, he didn't.

* * *

The defendant testified that for the first two or three days the patient seemingly progressed all right except that she was complaining of more pain than the usual vein patient complains of, "and it wasn't until a little later on that these areas of discoloration showed up . . . and subsequently broke down;" that as this complication arose he felt that there had been a spasm and that a paravertebral block was necessary; that he desired to do this and "I discussed it, tried to explain it to her, on two or three occasions. . . . We were in rather desperate straits, and she didn't want it done". . . .

* * *

[T]he refusal of treatment, after reasonable explanation as to its necessity, by an adult patient who is in possession of her faculties and capable of exercising free judgment in agreeing or refusing, is a complete defense of the doctor who is accused of negligence in not giving the treatment. But whether the treatment was so offered and so refused is a question of fact for the jury.

And this brings us to the hub of the question: was there probative evidence that the paravertebral block was offered and refused? Appellant says that the testimony of plaintiff is an assertion that it was not. Respondent contends that her testimony only indicates a lack of memory as to whether or not the block was offered.

* * *

. . . We are of the opinion that . . . the doctor never discussed a paravertebral block with her at any time or interval when she was so sufficiently in possession of her mental faculties that it reached into her consciousness and understanding, when she knew and understood what he was talking about. [A]dvise to a pa-

tient unable to comprehend it is no advice at all. The patient who is charged with contributory negligence is to be charged in the light of what she should have known, and it is the duty of her physician to see that she is fully advised and informed as to the treatment which is necessary. And if the patient is incompetent or incapable of understanding but urgently requires the necessary treatment proffered and the doctor knows or should know of this condition, the duty of the physician to advise the treatment does not necessarily end. Depending upon the circumstances of the case, the seriousness of the need, and the urgency of the situation, perhaps the time or interval of the patient's mental incapacity, the circumstances may require and make it his duty to communicate with and advise the husband or other members of the family who are available and competent to advise with or speak for the patient or take other steps to bring understanding of the need home to the plaintiff. In this case the defendant said that he did not talk with the husband about plaintiff's condition and the need for a paravertebral block, although the husband testified that he was at the hospital almost every day.

* * *

So here we have the proposition from the standpoint of plaintiff's evidence. The treatment was needed; a jury could find that a reasonably careful physician should have advised it. The physician did not advise it at a time when the patient was capable of understanding, remembering, and heeding that advice. This we think is sufficient negative to make a jury issue on the affirmative defense of contributory negligence. But the question is, is it sufficient to make the plaintiff's case in chief? Under this testimony there is an "open end," an *alternative* possibility that the doctor may have (as the plaintiff's hospital records say he did) advised the operation to the patient, who was then incompetent. The doctor would not necessarily and automatically become liable upon the bare fact he had an incompetent patient who refused his treatment, but his duty to advise and treat might extend and require him to make further effort to communicate with the patient at a more propitious time or to communicate with the husband or someone in position of authority, as the circumstances demanded and the opportunity permitted. Is this, the duty which may have arisen under this alternative possibility, sufficiently within the pleadings or issues which were tried as to support the submissibility? This alternative

proposition, which really arose with the development of the evidence, is ignored by both the parties here, because they both contend for and tug at the nether ends, i.e., the block was advised and refused—the block was not advised and refused. However, it is such proposition which causes us the most concern. If it is the injection of an entirely new and different violation of duty which was not pleaded or tried by consent, then it was beyond the issues which could have been submitted to the jury. But if the question of duty to take further effort at communication with the patient or to communicate necessity of treatment to some competent person (if available) in position of authority to speak for or advise the incompetent is really a part of the basic duty to communicate the necessity of the treatment, as a matter of fact a part of the treatment itself, then it is not beyond the scope of the issues which the parties tried. We think it was so in this case. Quite obviously the plaintiff was attempting to inquire during the trial of this case concerning such extended or continuing duty in this respect, so it was not foreign to her theory, and we think it is but a natural extension of the issue, which defendant himself contended for and willingly tried, i.e., that the needed treatment was by him advised. We conclude that plaintiff made a submissible case.

* * *

The judgment is reversed in respect to the sustention of the motion for judgment and affirmed in respect to the granting of a new trial, and the cause is remanded for further proceedings.

d.

Haggerty v. McCarthy
344 Mass. 136, 181 N.E.2d 562 (1962)

CUTTER, JUSTICE.

Count 1 of the declaration in an action of tort alleged that the defendant, a surgeon, failed to remove the plaintiff's appendix completely during an operation, on May 1, 1949, was doubtful whether he had done so, and negligently failed to inform the plaintiff of his doubts, with the consequence that the plaintiff later "provided an inaccurate . . . medical history to . . . [a] physician whom he subsequently consulted regarding . . . abdominal pains, and accordingly was unnecessarily subjected to a series of . . . operations commencing . . . about January 23, 1957 . . . to his damage." Count 2 recited essentially the same averments with the

addition of allegations that the surgeon "represented . . . that the operation had been a complete success, the appendix completely removed and the danger of further appendicitis attacks removed; [and] that the plaintiff relied on . . . [the surgeon's] failure to . . . inform him as to his doubt," to the plaintiff's damage.

* * *

The operation on May 1, 1949, lasted about two hours. The surgeon in notes described the operation as follows: "Right Rectus incision. No free fluid in abdomen. Small intestine distended. Cecum tied down. *Appendix finally found Retrocecal* and at the bottom of a mushy area. *The appendix was covered with adhesions, was very small and was tied down.* . . . [T]he tissues were very friable and the clamps tore off and there was brisk bleeding for a few minutes. Vessels reclamped and tied. *Appendix removed to what appeared to be the base, but there were such dense adhesions that it was impossible to be certain and the raw oozing area at the bottom of the space was considerable.* A piece of oxycel gauze was placed at the bottom of wound over the ooze. It was dry on closing. Abdomen closed in layers with great difficulty because of [s]pasm and [t]ightness which was finally overcome with [c]ther and curare. Patient left O[perating] R[oom] in good condition" (emphasis as it appears in record). Following the operation, the surgeon informed the plaintiff that the operation had been long because "it had taken a long time to find the appendix." The surgeon "made no further report to [the plaintiff] then or later about the operation or the appendix."

The plaintiff was discharged from the hospital approximately ten days after the operation. He "had no abdominal operations or . . . pain . . . until on or about January 14, 1957," nearly eight years later. As a result of symptoms then developing, he consulted Dr. Meyer, a general practitioner in Schenectady, where the plaintiff then resided. Dr. Meyer testified that the plaintiff's symptoms "were consistent with several abdominal disorders, but were particularly suggestive of appendicitis." He, however, noted the "rectus scar, and [the plaintiff] reported . . . that his appendix had been removed . . . in 1949." As a consequence Dr. Meyer omitted certain "standard medical tests in cases of suspected appendicitis, and diagnosed [the] illness as gastroenteritis or 'intestinal grippe.'"

The pain continued during the following week increasing to acute on January 23. Dr.

Breault, a surgeon, was consulted. He "operated on [the plaintiff] locating a large abscess . . . of infectious pus, together with considerable local peritonitis, caused by a ruptured appendix. . . . He also stated "that the abscess would not have formed, and the operation to drain it would not have been necessary, if the appendicitis condition had been discovered and the diseased appendix removed before it had ruptured."

* * *

. . . There was evidence, in addition to what has already been summarized, that, following the operation, the plaintiff asked the surgeon why the operation had taken so long and that the surgeon (who "made no further report to [the plaintiff] then or later about the operation or the appendix") replied "that it had taken a long time to find the appendix." There is no evidence of any affirmative misrepresentation . . . or any statement of fact, without disclosure of other known facts which might affect that statement. . . . Any contention that there was deceit must rest upon the surgeon's failure to comply with some duty to disclose his doubts. . . . We think that whether there was a duty to disclose depends upon whether there was, in the circumstances, conduct which would have been noncompliance with the special duty . . . created by the doctor-patient relationship. . . .

. . . A verdict for the surgeon was properly directed on each count. . . .

SPiegel JUSTICE, with whom SPALDING and WHITMORE, JJ., concur (dissenting).

* * *

[I]t should be borne in mind that it is the patient who is taking the risk, not the surgeon, nor a group of surgeons in the particular locality where the operation takes place. If an appendix requires removal it would seem to be a corollary that the failure to remove the complete organ might result in subsequent difficulties.

This is not a case of a dread illness. There is not the slightest suggestion that the psychological condition of the patient was such that the surgeon was justified in withholding the fact that he was uncertain as to whether he had removed the complete appendix. The failure to disclose this fact was not in the interest of the plaintiff. As to information revealed in diagnosis it has been said that "no medical privilege should be recognized to withhold the diagnosis in ordinary cases where the usual patient would feel entitled to have the information as a basis for charting his course and there being no apparent grounds for

supposing that a disclosure of the truth would engender in the patient reactions dangerous to his health or life." Smith, *Therapeutic Privilege to Withhold Specific Diagnosis from Patient Sick with Serious or Fatal Illness*, 19 *Tenn.L.Rev.* 349, 350-351. It is readily understandable why a surgeon may withhold information from a patient afflicted with cancer. However, we are not confronted with that type of situation in an operation for the removal of an appendix. Even if the possibility of the need for further medical treatment is quite remote, I can think of no sound reason for not disclosing the information to the patient. . . .

* * *

Under the circumstances of this case, I do not believe that evidence of the prevailing medical practice in the neighborhood was necessary to show that the defendant had a duty to disclose to the plaintiff his doubts as to the complete removal of the appendix. Even if there had been evidence that the practice was to maintain silence under these circumstances, this court should not be foreclosed from imposing a duty to disclose. "Courts must in the end say what is required; there are precautions so imperative that even their universal disregard will not excuse their omission." *L. Hand, J., in The T. J. Hooper*, 2 *Cir.*, 60 *F. 2d* 737, 740.

* * *

c.

Kraus v. Spielberg
37 Misc. 2d 519, 236 N.Y.S.2d 143
(Sup.Ct. 1962)

BENJAMIN BRENNER, JUSTICE.

The defendant is a treating doctor accused of erroneously informing the plaintiff that her arrested pulmonary tubercular condition had become active and that tuberculosis germs were in her stomach. In effect, plaintiff says that this misinformation and resultant therapy have caused her to suffer from a tuberculosis phobia. . . .

There is little reason to doubt the plaintiff's testimony that, while she is a highly nervous individual and was always apprehensive about her long-standing disease, she has become exceedingly conscious of the possibility of the spread of the tuberculosis germ to her intestines and that her doctor's statements and treatment have caused her real distress. A verdict was nevertheless directed for the defendant in the light of the overwhelming evidence that the diagnosis of active tuberculosis disclosed by him to the plaintiff

and his administration of effective chemotherapy were medically warranted and constituted no deviation from standard medical practice. . . .

The doctor's statement to the plaintiff that the "germs may have reached her intestines," though not then medically verified, also presented no fact question for the jury. This, too, being a statement of the well-known fact that the germ could affect the entire body, did not constitute a departure from standard medical practice or present a jury question to determine lack of care or an error of judgment, for, regardless of whether the disease was active or inactive, or whether it had invaded intestinal tissue or not, the administration of the drugs was plainly curative. On all the evidence, the statement clearly was a requisite medical technique to induce plaintiff, then suffering from stomach pains, to undergo the treatment and indeed, though she may have been badly frightened, plaintiff may be alive today because of the very chemotherapy thus administered to her.

. . . No case has been brought to my attention which holds a doctor liable for causing fright and a psychic injury brought on by a statement in the course of his diagnosis or treatment.

The reappearance of positive tubercular sputa, based on recognized tests, convinced the defendant doctor that the inactive tubercular condition had become active once more. As plaintiff was suffering from unexplained gastric pains and was again actively tubercular, he informed her, in the light of those findings and the history of her illness, of the possibility that the tuberculosis germs may have invaded the intestines and that this was an added reason why she must embark upon chemotherapy at once. He may have been mistaken and possibly he should have awaited added clinical signs and medical proof but certain it is that if he was in error, it was an understandable error, if not an error of judgment. In any case, he did not report the information to his patient capriciously or without medical foundation nor was his prescription of chemotherapy palpably an improper prescription for her condition or harmful to her, even if the tuberculosis germ had not invaded the intestines.

Doctors are sometimes held legally responsible for their failure to alert patients to the existence of disease. . . . Had this defendant failed to fully alert plaintiff he could conceivably have been subjected to censure and suit and thus, on plaintiff's reasoning, there is jeopardy both for making the disclosure and for withholding it.

Were doctors to be made conscious of the possibility of suit for honestly explaining their diagnoses to patients for purpose of swift cure they would, with so hazardous a cloud hanging over them, tend to avoid doing so. What sort of medicine would we then achieve? The practice of medicine would then become a secretive practice with doctors uncommunicative to patients, delaying therapy and withholding information for fear that frightened patients might turn upon them. Indeed, professionals in other fields would also find advice to clients most hazardous if fright were caused thereby. Think of the plight of a lawyer sued by a frightened cardiac client when informed of the poor prospects of a lawsuit or of the size of a proposed fee which could be exceeded by the client's recovery against the lawyer for fright.

[R]eason and common sense demand that in the interest of public health and safety a doctor who stands in a special relationship to his patient, even if his diagnosis be not fully verified, shall be free to inform his patient of the presence of disease if he needs to alert her to it or to induce her to embark upon safe and healing therapy. It therefore seems to me that a psychic injury suit, based upon fright from medical advice by a diagnosing doctor, should be confined to gross negligence and is not warranted if the information is well founded, not capricious and does not induce harmful therapy.

The claims of the plaintiff that the doctor erroneously interpreted the x-rays as evidence of cavity rather than of bronchiectasis and that he made a change of his diagnosis to "minimal inactivity," even if true, have no bearing on the issues and in any event are not proximately related to the psychic or other injury resulting from the chemotherapy. Upon the law and the facts the defendant is entitled to the direction of a verdict in his favor.

NOTES

NOTE 1.

PRESTON J. BURNHAM MEDICAL EXPERIMENTATION ON HUMANS*

Having read the News and Comment headed "Human experimentation: New York verdict affirms patient's rights," I believe I under-

* 152 *Science* 448-450 (1966). Copyright 1966 by the American Association for the Advancement of Science. Reprinted by permission.

stand the situation well enough to attempt to help lay committees develop a series of forms for obtaining patients' informed consent. I am working now on forms . . . for our standard operations. . . .

* * *

Consent Form for Hernia Patients:

I, _____, being about to be subjected to a surgical operation said to be for repair of what my doctor thinks is a hernia (rupture or loss of belly stuff—intestines—out of the belly through a hole in the muscles), do hereby give said doctor permission to cut into me and do duly swear that I am giving my informed consent, based upon the following information:

Operative procedure is as follows: The doctor first cuts through the skin by a four-inch gash in the lower abdomen. He then slashes through the other things—fascia (a tough layer over the muscles) and layers of muscle—until he sees the cord (tube that brings the sperm from testicle to outside) with all its arteries and veins. The doctor then tears the hernia (thin sac of bowels and things) from the cord and ties off the sac with a string. He then pushes the testicle back into the scrotum and sews everything together, trying not to sew up the big arteries and veins that nourish the leg.

Possible complications are as follows:

- 1) Large artery may be cut and I may bleed to death.
- 2) Large vein may be cut and I may bleed to death.
- 3) Tube from testicle may be cut. I will then be sterile on that side.
- 4) Artery or veins to testicles may be cut—same result.
- 5) Opening around cord in muscles may be made too tight.
- 6) Clot may develop in these veins which will loosen when I get out of bed and hit my lungs, killing me.
- 7) Clot may develop in one or both legs which may cripple me, lead to loss of one or both legs, go to my lungs, or make my veins no good for life.
- 8) I may develop a horrible infection that may kill me.
- 9) The hernia may come back again after it has been operated on.
- 10) I may die from general anesthesia.
- 11) I may be paralyzed if spinal anesthesia is used.

12) If ether is used, it could explode inside me.

13) I may slip in hospital bathroom.

14) I may be run over going to the hospital.

15) The hospital may burn down.

I understand: the anatomy of the body, the pathology of the development of hernia, the surgical technique that will be used to repair the hernia, the physiology of wound healing, the dietetic chemistry of the foods that I must eat to cause healing, the chemistry of body repair, and the course which my physician will take in treating any of the complications that can occur as a sequel of repairing an otherwise simple hernia.

Patient

Lawyer for Patient

Lawyer for Doctor

Lawyer for Hospital

Lawyer for Anesthesiologist

Mother-in-Law

Notary Public

NOTE 2.

FRANCIS D. MOORE BIOLOGIC AND MEDICAL STUDIES IN HUMAN VOLUNTEER SUBJECTS—ETHICS AND SAFEGUARDS*

In approaching the study of normal man, medicolegal precautions must be taken. In our experience these have [included]:

* * *

A signed and witnessed *permission slip* that is completely realistic in all its details. It is not enough for the volunteer to say that he is willing to undergo study. He must specifically say that he is willing to undergo a period of seven days of semi-starvation, with four injections, sixteen blood samples . . . or whatever the details must be. We have also taken special pains to tell our subjects, often in rather discouraging terms,

* Symposium on the Study of Drugs in Man, Part II. 1 *Clinical Pharmacology and Therapeutics* 149, 153 (1960). Reprinted by permission.

the actual details of our studies so that the reality would be a pleasant rather than an unpleasant surprise.

* * *

f.

Bradford H. Gray **Some Vagaries of Consent***

Although the informed consent of human research subjects has been a key concept and an important topic in clinical investigation, little empirical research bearing on the discussion has been reported. This is a preliminary report of some findings which emerged from interviews with actual research subjects. It is limited to a discussion of some ways informed consent can fail to occur even where currently accepted procedures are followed. The material discussed here is based on interviews with 51 subjects who participated in a single investigation conducted by a medical school faculty member (assisted by a postdoctoral fellow). The subjects were patients hospitalized in a large, research-oriented, teaching hospital. During a 6-month period in 1970-71, all English-speaking subjects were interviewed, although the project was started before and continued beyond the interviewing period.

The subjects were women having their labor induced in a double-blind drug study. One drug was the standard one used for this purpose; the other was an experimental drug in which the investigators were interested. There were no known risks with either drug, although the experimental drug was still of Phase I FDA status, and one of the purposes of the study was to evaluate its risks as well as its effectiveness. Fetal monitoring, customarily employed only when problems with birth are anticipated, was used on the subjects in the project; this resulted in some discomfort but had the advantage of quick detection of certain kinds of fetal problems. The research also called for the drawing of several blood samples. In a related study, the subjects were also asked to consent to having their babies observed by a pediatrician interested in the effects of the procedure on the newborn. Another important aspect of the research situation was the presence of two nurses who were part of the study team and whose duties were confined to the study. Subjects received a high degree of

pre-delivery care from very competent and experienced nurses who always cared for only that one subject.

The usual procedure (with a few exceptions) was for the woman's doctor to arrange for participation in the study a few days ahead of time. Almost one-third of the subjects had private physicians; the remainder were patients of the house staff. Patients were instructed by their doctors to come to the hospital at 7:00 A.M. on a given day for the induction to take place. There was great variation in how much subjects knew about the project before admission; only 19 to 50 reporting knew before admission that they were going to take part in research. However, after admission a standard procedure was followed in obtaining consent. When she reached the labor room, the subject would sign the consent form given to her by one of the research nurses, and, after other preparations by the nurses, one of the investigators would start the intravenous infusion of one of the drugs. Shortly thereafter, with the permission of the principal investigator, I conducted a short interview with the subject; a more extensive interview was done later, usually in the next two days. The interviews, which were recorded and transcribed, covered a series of topics centering around the decision to become involved in the study.

A widespread lack of informed consent was found among the subjects. The lack of informed consent was of three types, the first two perhaps differing only in degree. First, 20 subjects (of 51) were not aware that they were experimental subjects until their participation in the study was well underway. Most of these subjects learned of the existence of the study during the interviews done for my research. Second, many more subjects (the exact number awaits further analysis), while aware of the research, had significant gaps in their understanding of the project and consented on a more or less uninformed basis. These included women who had no knowledge of whether there were alternatives to participation, women who did not know that two drugs were involved, women who did not know of the double-blind nature of the study (it was not part of the research design to withhold this information), and women who were not aware of the fetal monitoring procedures and extra blood samples required by the research. Others were not aware beforehand that their consent to have the baby observed would be sought by a separate researcher.

* This is a preliminary report (1971) on data collected for the author's doctoral thesis. Printed by permission of the author who retains all rights.

The third way in which informed consent failed to occur had to do with pressure to participate. Several subjects reported that they would have preferred not to participate but felt they had no choice. Of these, two stated that pressure from their physician had been the overriding factor. In these instances, the physician involved was a private physician, and the two complied, even though they did not want to, because they felt that refusal would jeopardize their relationship with him. Both of these subjects felt later (after delivery) that it had been best for them, but both still felt that they should have been given more information about the study and their doctor's reasons for wanting them to take part, and that they should have been given more of a choice. Some other subjects felt constrained by circumstances which will be described below.

A number of different factors can be identified as contributing to the widespread lack of awareness of the research and the lack of knowledge found even where awareness was present. Since this is written at a preliminary stage in the analysis, this discussion will be limited to factors that became apparent during the interviews with the subjects. Other factors will no doubt emerge during data analysis when variables such as level of education of subjects and the presence of a private physician are systematically examined.

Lack of Explanation

Although a few subjects were well informed about the study, many subjects received the consent form with little or no prior or accompanying explanation. In some cases where an explanation was given, its purpose was not made clear, and it was not sufficiently precise; thus, for example, many subjects who knew that a "new drug" was involved in their induction did not understand that they were taking part in research. These subjects had obviously received some information but not an explanation that communicated the necessary information. A number of interrelated factors were behind the lack of an adequate explanation received by many subjects.

First, no one person was assigned responsibility for communicating the necessary information to the subject. Since subjects came from several sources, and responsibility for patients was shared by the researchers and each subject's physician (house staff or private), gaps in disclosure occurred which were not necessarily intended by anybody.

The principal investigator reported that he had held a meeting with residents at the begin-

ning of the research and had asked them to inform prospective subjects before sending them in to be induced in the study; yet about two-thirds of subjects from the clinic indicated that they knew nothing about the research *qua* research until they were handed the consent form in the labor room (if they even realized then). With regard to private physicians, the principal investigator said that he felt it was not his place to suggest to them how to inform their patients. These physicians did not always choose to do so at all, although in some cases they gave detailed explanations to their patients. As to the two investigators themselves, at the time of their usual first contact with a subject, she was already in the labor room, with preliminary preparations completed, a signed consent form nearby, awaiting the start of the drug infusion to bring her baby. A natural assumption for the investigator encountering such a scene would be that the patient had already been informed. Even if such an assumption were not made, it would hardly have seemed appropriate to begin an explanation of the research at this point.

All of this meant that often the subject received no information about the research from a physician. Or if she was given information, it was not recognized for what it was.

The two research nurses seemed to have taken the responsibility for getting consent forms signed almost by default, partially because they had the first actual research contact with the subjects after their admission. The principal investigator reported that convenience was the main reason why the nurses performed this task, and that he had not given them any special instructions because they had long experience (both over 10 years) as research nurses. It was not clear how much responsibility the nurses felt they had for *informing* the subject although they clearly took responsibility for getting a signature on the consent form; it is also not clear whether the nurses were aware that many subjects knew little or nothing about the project prior to admission.

In any event, an explanation did not necessarily accompany the consent form in the labor room. This was indicated by several subjects who reported that they were given the form with instructions to "read this and sign it" or "sign this and we can get started," and was reflected in the large number of subjects who were not aware of what they had signed. The nurses were not at all reluctant to discuss the research with subjects during the long day they would spend together;

in fact, many subjects later commented enthusiastically on how much they had learned from the nurses and how much they felt a part of the whole procedure. However, several things worked against detailed explanations by the nurses (unless questioned by the subjects) at the time the consent form was presented.

First, they had no clear responsibility to give such an explanation. Second, getting the subject's signature on the consent form was only one of many tasks and procedures that had to be carried out prior to the starting of the drug infusion by one of the investigators. The more drawn out these tasks, the longer would be their day since the nurses stayed until after delivery (up to 14 hours among the subjects interviewed) or until the end of labor (the drug infusion stopped after 10 hours, but labor could continue for some time, even for those who failed to deliver). So, strong incentives to be brisk were present. Third, the nurses' job was to assist the investigators in innumerable ways, and causing difficulty with subjects would have been inconsistent with this role. Certainly they did not want to be responsible for causing a subject to refuse to participate after being admitted to the hospital. An occasional subject became upset in the labor room upon learning of the study itself or about particular details of the study, and this could be awkward and difficult to handle, so there was ample incentive to keep everything under control.

A primary method of maintaining this control was to treat everything as being routine in nature. Thus, certain words, particularly "research" and "experiment" were avoided. One of the nurses warned me against using these terms with the subjects for fear of arousing their anxieties and raising questions in their mind. The experimental drug when referred to was called a "new drug" by professionals, subjects, and this researcher. One had the feeling that the situation was very delicate and one had to be very circumspect in making references to the research. The delicacy was handled by avoiding possibly emotionally charged words in favor of terms which neither aroused the subject nor, in many cases, informed her.

Also contributing to the success of the "routinization" efforts were the fact that the research consent form was the second of two consent forms signed by the subject (the first one being truly routine), and the outward similarity of the research to a normal induction, particularly at the beginning. The procedure that subjects were

undergoing did not differ markedly from what they had expected.

This suggests that the danger of leaving subjects uninformed is heightened when an investigator gives his responsibility to a subordinate. Because of the nature of superordinate-subordinate relationships, the tendency is for the subordinate to perform the visible task (getting a signed form) at the expense of the less tangible task of giving the subject a complete explanation. This is particularly true where the subordinate fears that full disclosure might jeopardize the chances of "getting the consent" by alarming the subject.

Deficiencies in the Consent Form

The consent form itself was another reason why *informed* consent did not take place in many cases. It was incomplete in that the blood samples were not mentioned. Also it made no reference to alternatives; thus, it was not clear even to most aware subjects what their alternative was, i.e., whether labor could have been induced in another way. The consent form also did not mention the planned 6-hour observation (with blood test and X-ray) of the baby; this was usually presented to the woman for her consent during her labor. Although a separate investigator was involved in that study, this was a serious omission since many of the women going into labor expressed more concern about the health of their baby than anything else.

The word "research" does not appear on the consent form although the term "study" is used. The form itself—standard at the institution—is headed "Patient Consent Form for Participation in a Clinical Investigation Project." The term "clinical investigation" may not carry the negative connotations that are perhaps associated with the terms "experiment," and "research," but it also may not communicate much to many patients, particularly since patients of relatively low educational levels are often used in such investigations. The experimental drug is initially referred to on the form as a "new drug," but the form goes on to designate it as "experimental" at one point. This was the form's strongest indication that it was not a routine form, but the clue was not picked up by 20 subjects.

Circumstantial Factors

The circumstances under which the form was presented to subjects are another set of factors which worked against *informed* consent. Preliminary figures indicate that at least 31 sub-

jects did not know they were to be in research at the time of their admission. Of these, 20 never did find out until they were actively participating by receiving the drug, although all signed the consent form in the labor room. A number of circumstantial factors working together are involved in explaining this.

Patients came in at 7:00 A.M. prepared to be induced and prepared to sign whatever forms were necessary for this. Most had other children for whom arrangements had been made. Under these circumstances, they were in a poor position to give careful attention to anything other than the job ahead of them. Several said that they "hadn't felt like" reading the forms they were given. The inadequacies of the consent form, and the facts that it was one of two forms to be signed and was presented as routine have already been discussed.

A further consequence of the form's being presented under these circumstances was that this often took the husband out of the decision-making process, because hospital procedure had the husband at the admissions desk completing forms while preparations were being done in the labor room. Usually, by the time a husband was able to join his wife in the labor room, the form had been signed and she was receiving the drug. One woman who did refuse to sign until her husband arrived in the labor room said that she had felt very uncomfortable doing so, because everything around her had ground to a halt and she sensed impatience.

Role Relationships and Status Differences

The final main category of factors interfering with *informed* consent is perhaps less specific to this particular study than the others previously discussed. Some subjects among those who were aware that they were taking part in research stated that they agreed to do so because this is how the doctors wanted it done and the doctors knew what was best for them. This suggests that, to put it in sociological terms, they were not aware that they had been asked to assume a role other than the patient role.

Although there are important differences in the requirements of the role of patient and the role of subject, there is widespread lack of knowledge about the unique requirements of the subject's role—particularly that a decision-making responsibility is involved. Thus, some women did not understand that a decision was being asked of them—that consent rather than compliance was being asked—when the consent form

was handed to them; many were not aware of what information was relevant to such a decision; and most seemed unaware that the researchers had strong interests in the *research*—interests that had little to do with subjects' welfare although, in this instance, seemingly not in conflict with subjects' welfare. That is, some subjects' assumption that they were asked to participate because the doctor thought it was best for them was not necessarily the case. For example, there were elective inductions among the subjects.

Even though research is involved, prospective subjects coming into the hospital often move into the familiar role of patient when they come into contact with doctors and nurses. The tendency to react to the researcher as therapist, and only as therapist, is to the detriment of the consent process, for as patients many people are accustomed to leaving all decisions in the therapist's hands.

Related to this are the barriers raised by the wide status differential that exists between the researchers and low-status patients, particularly from the clinic. Such status differences may help account for the tendency toward acquiescence and a reluctance to raise questions found in many subjects, even if they were aware of their own lack of understanding. In the absence of any cues that consent was being asked and questions were appropriate, low-status subjects may have felt that they lacked the standing to raise questions, particularly on the professionals' home ground.

2.

Failures of Understanding

a.

Francis D. Moore

Letter to Jay Katz—September 2, 1964*

* * *

You ask if there ever is a situation in which "explanation of potential hazards or discomforts" is not enough. Let me give you an example.

Some years ago an individual from this country went to Nigeria to try out a new measles vaccine on a lot of small children.

Now exactly how are you going to explain to a black African jungle mother the fact that measles vaccine occasionally produces encephalitis but that more important than that it might

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sensitize the child for the rest of his life to some other protein in the vaccine? We now know that any sort of an immune response excites cross-reactions. For example if a person develops a heightened immune reaction to some specific antigen such as typhoid he will be found to have other higher titers against non-specific antigens at the same time. In fact there is a suspicion that some of the so-called auto-immune diseases are aroused by exposure of the reticuloendothelial system to completely different antigens.

The possibility therefore arises that measles vaccines applied to thousands and thousands of children might excite in some of them such diseases as thyroiditis and ulcerative colitis.

Can you imagine trying to explain that to a jungle mother? I doubt as a matter of fact that you can make much sense out of the foregoing because it is a bit out of your field as a learned man.

We therefore have a problem of ethics and morality which has nothing whatsoever to do with "seeking permission."

One of the greatest assets of a good doctor is the ability to look the patient in the eye and have that patient go along with him on a hazardous course of treatment. This is something that a surgeon experiences everyday as he asks a patient to put his life in the surgeon's trusted hands for some operation or other.

This same quality is exhibited by a medical experimenter when he looks at a patient and says that he thinks everything is all right.

However there is a difference and that is that in the case of the medical experimenter he would not be doing the experiment at all if he was actually sure that he knew all the answers. So there we are.

NOTES

NOTE 1.

DAVID L. RIMOIN, THOMAS J. MERIMEE,
DAVID RABINOWITZ, L. L. CAVALLI-SPORZA,
AND VICTOR A. MCKUSICK

PERIPHERAL SUBRESPONSIVENESS TO HUMAN
GROWTH HORMONE IN THE AFRICAN PYGMIES*

The cause of the African pygmies' short stature has long been a subject of speculation. Because of their resemblance to persons with isolated growth-hormone deficiency (sexual ateliotic dwarfs), an expedition was made to the Central African Republic to assess the pygmies' abil-

ity to secrete human growth hormone (HGH). This study clearly demonstrated that the pygmies attain normal plasma concentrations of immunoreactive HGH after insulin-induced hypoglycemia and arginine infusion. Nevertheless, a number of clinical and metabolic similarities were observed between the pygmies and patients with isolated HGH deficiency. Two possible mechanisms were postulated to explain these paradoxical findings: the pygmies might secrete an altered HGH molecule that was functionally inert but antigenically intact; or they might secrete normal HGH to which their peripheral tissues were unresponsive.

In an attempt to distinguish between these two possible mechanisms, another expedition to Central Africa was made to assess the pygmies' ability to respond to exogenous HGH. . . .

* * *

Two expeditions were made to the M'Baiki Region of the Central African Republic, where a group of Babinga pygmies, living in typical pygmy camps, was studied. On the first trip, HGH secretion was assessed in 22 pygmies (15 males and seven females) who were subjected to insulin-induced hypoglycemia . . . or arginine infusion . . . or both. . . .

On the second expedition, 19 Babinga pygmies (13 males and six females) were studied before and after the administration of HGH. Eight pygmies received an acute intravenous infusion of HGH (4 mg over 20 minutes), as did five white control subjects of normal stature and eight ateliotics. Oral glucose tolerance tests (50 gm of glucose) were performed on 11 pygmies before and after the intra-muscular administration of 5 mg of HGH for five days. Arginine infusions (0.25 gm per pound of body weight) were given to six of these pygmies before and after this intramuscular HGH regimen. Similar studies were performed on four controls of normal stature and five ateliotic dwarfs before and after five days of intramuscular HGH administration (5 mg per day). All subjects studied were post-adolescent.

* * *

The mean fasting plasma HGH concentration of the pygmies . . . did not differ greatly from that of the controls. . . . After the infusion of 0.1 unit of insulin per kilogram of body weight, plasma HGH levels rose to a mean peak concentration of 29.6 ± 0.35 ng per milliliter in the pygmies, a value not markedly different from that attained by the controls (25.6 ± 3.9 ng per

* 281 *New England Journal of Medicine* 138:1384 (1969). Reprinted by permission.

milliliter). Unlike the controls, however, in whom the plasma glucose concentrations returned to baseline values by 90 minutes, the pygmies had an exaggerated hypoglycemic response. Both the pygmies and the ateliotic dwarfs had severe hypoglycemic symptoms after insulin and maintained low blood glucose concentrations for over 90 minutes.

* * *

NOTE 2.

DANIEL P. ASNES
CONSENT FOR STUDIES ON PYGMIES*

... I wonder what sort of explanation of the research the subjects were given. Were they aware of the feelings they might experience after receiving insulin? The problem of maintaining high ethical standards in the recruiting of experimental subjects is difficult enough in our own culture. It seems to be even more difficult in a culture that might not have a conception of "medical research" and the tacit acceptance of its value.

* * *

NOTE 3.

DAVID L. RIMOIN
CONSENT FOR STUDIES ON PYGMIES†

I can assure Dr. Asnes that with the use of Bantu interpreters, we obtained full consent from the pygmies after a detailed explanation of the procedures. Indeed, when pygmy subjects were required to return for second and third procedures, not one refused after his first experience.

NOTE 4.

T. A. LAMBO
ASPECTS OF CLINICAL RESEARCH IN
DEVELOPING COUNTRIES‡

... We have found in some areas of Africa that we have not only to consider or to weigh the balance between therapy and the risks to human life, but also to consider the philosophy of the dignity and rights of human beings. Not long ago, a comatose patient was picked up in the

street; while he was still unconscious, he was given a blood transfusion. A few weeks later I was called to see him on one of the wards where he was having a very severe psychotic breakdown, because he had been rejected by his own tribe for having received blood from another tribe. The patient said to me that it would be better for him to die than to remain alive; this raised another set of problems, another dilemma. Again, not long ago, we had another problem, a tribe in Nigeria taking a case to court because one of the physicians had taken postmortem material from an old man who died and they felt that this should have been explained to them. To a person of Western culture this may seem absurd, but it involves the question of ancestor worship, which is a culture-bound phenomenon in many of the African tribes: it has been prescribed by tradition that the old man should arrive upstairs with all his organs in the right place, and this was not the case. So that you see that there are many problems which in fact do not involve directly the question of risk to human life, but which may imply cultural differences, ethical differences which are of very deep emotional significance to individuals in a particular society. ...

NOTE 5.

J. HIERNAX
ETHICAL PROBLEMS IN
ANTHROPOBIOLOGICAL RESEARCH*

* * *

Whatever the individual risk in this research, the consent of the subject is required. In a large number of populations where the hygiene and nutrition are very deficient and where the most urgent need for research exists—those on which the efforts of the International Biological Programme will be concentrated—the great majority of the people are illiterate and the cultural set-up requires the prior informed consent of the leaders of the community, whether the administrative—including the medical—leaders, the political leaders, or the customary leaders, but especially the customary religious leaders. The consent of the individuals often depends on these people, who in any case are the best placed to understand the value of the research for the community and to tell the people so in terms that they can follow (for often the investigator does not speak the language of the subjects he

* 282 *New England Journal of Medicine* 634 (1970). Reprinted by permission.

† 282 *New England Journal of Medicine* 634 (1970). Reprinted by permission.

‡ V. Fattorusso, ed.: *Biomedical Science and the Dilemma of Human Experimentation*. Paris: Council for International Organizations of Medical Sciences 63, 66–67 (1967). Reprinted by permission.

* V. Fattorusso, ed.: *Biomedical Science and the Dilemma of Human Experimentation*. Paris: Council for International Organizations of Medical Sciences 70 (1967). Reprinted by permission.

is going to examine). The prior agreement of these leaders will meet both the ethical requirements and the efficiency requirements of the research and integrate it in the cultural values of the community. . . .

* * *

NOTE 6.

MARGARET MEAD
RESEARCH WITH HUMAN BEINGS—A
MODEL DERIVED FROM ANTHROPOLOGICAL
FIELD PRACTICE*

* * *

The problem of communicating to a primitive people what will be done with the information that they have helped develop is of a different order. They may have no conception of printing or of what the publication of details about their social forms and individual behavior may mean. Consent in such cases would be even more ridiculous than it has been shown to be in the case of complicated experiments in our own society. Furthermore, it is not only their own current reputations that are at a risk they cannot estimate, but today, as primitive peoples are rapidly entering the modern world, it is the dignity and sensitivity of their descendants that must be considered. The situation is somewhat comparable to consent given by parents for the use of films made of their children in a modern country, without any real ability to predict how the children will feel about such continuing exposure to the public eye. Here, in the case of primitive peoples, of children, or of any individuals who are not in a position to evaluate the effects of publication, a heavy responsibility falls upon the research worker. . . .

* * *

b.

Mitchell v. Robinson **334 S.W.2d 11 (Mo. 1960)**

BARRETT, COMMISSIONER.

William Mitchell has been awarded \$15,000 damages against the Doctors Robinson and their associates, particularly Dr. Jack DeMott, for malpractice, and the essentially meritorious problem is whether upon the record there is any evidence to support the jury's finding of negligence.

. . . Mitchell had "a rather severe emotional

illness," process schizophrenia, but he was not mentally incompetent; his illness was characterized by serious depression and rather severe anxiety, complicated by alcoholism. It is not necessary at this point to detail his case history and symptoms; it was the opinion of the doctors that he should have "combined electroshock and insulin subcoma therapy." The general purpose of electroshock treatment is to build up the patient's "defense and controls and self-confidence" while insulin relieves "basic anxiety" and "disturbance of the mood." The desired physical reaction and intended purpose of electroshock is to induce convulsive seizures of forty to fifty seconds duration. The desired physical reaction of insulin shock is the induction of unconsciousness, a "subcoma" state, but it is neither intended nor desired, as it is with electroshock, that the patient suffer a convulsion. One of the unpredictable results of insulin shock, however, is an unpreventable convulsion and one of the hazards of convulsions, whether from insulin or electroshock, is fractured vertebrae, fractured legs and various other injuries.

[W]ith his seventh insulin treatment of 40 units, he had "a hard generalized convulsion," a grand mal seizure, which resulted in a compression fracture of the fifth, sixth and seventh dorsal vertebrae. It is to recover damages for these specific injuries that Mitchell instituted this action.

* * *

This . . . brings us to the really meritorious question of whether in the circumstances of this case, the illness and treatment involved, the doctors were under a duty to inform the plaintiff that one of the hazards of insulin treatment is the fracture of bones not involved in either the illness or the treatment. That the hazard exists is beyond question; Dr. G. Wilse Robinson, Jr., said that fractured bones, serious paralysis of limbs, irreversible coma and even death were hazards incident to shock therapy and further that there are no completely reliable or successful precautions. In their amended answer the defendants "state that the fracture of bones is a danger and risk that is inherent in insulin shock therapy, and that compression fractures of the spine, and fractures of the limbs can and frequently do occur when said insulin shock therapy is properly administered." The plaintiff's principal claim here is that "There was evidence of a negligent failure to disclose to plaintiff the hazards of insulin treatment," and, of course, evidence that plaintiff would not have consented to the treatment had he known of the dangers. . . .

* 98 *Daedalus* 361, 364 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

[T]he serious hazards being admitted, the problem is whether in the circumstances of this record the doctors were under a duty to inform their patient of the hazards of the treatment, leaving to the patient the option of living with his illness or of taking the treatment and accepting its hazards.

* * *

. . . Dr. DeMott and Dr. Robinson insist that they did warn Mitchell of the dangers and risks of the treatment in great detail, including the possibilities of fractures from either intended or unintended convulsive seizures. Upon this precise point the burden of the doctors' argument is that "Mitchell's contrary testimony is not substantial and competent to sustain his verdict in view of Dr. DeMott's testimony that in the mental and emotional state that Mitchell was in at the time of the conferences, he could not possibly have an accurate memory of the conferences after the passage of a number of years." And while on this subject it is just as well to note that Mitchell testified that he did indeed remember the conferences and he said that Drs. Robinson and DeMott recommended the electroshock and insulin therapies, that he personally had no knowledge of the possibilities of fractures from insulin, that they explained the "process" to him "but there was nothing in his conversation to me that indicated any risk or disability as a result of the insulin treatment or any risk of disability at all." He categorically denied that either of the doctors advised him of the possibility of bone injuries or death from the treatments. He said that he asked Dr. DeMott if there was any danger and "His answer was that the treatments had only a temporary effect, a confusion that would last only a matter of an hour or so. He didn't say there would be any lasting effect at all"—in fact the doctor replied, "no danger."

* * *

In the particular circumstances of this record, considering the nature of Mitchell's illness and this rather new and radical procedure with its rather high incidence of serious and permanent injuries not connected with the illness, the doctors owed their patient in possession of his faculties the duty to inform him generally of the possible serious collateral hazards; and in the detailed circumstances there was a submissible fact issue of whether the doctors were negligent in failing to inform him of the dangers of shock therapy.

. . . Even though there was a submissible case, solely upon the indicated hypothesis, it is not possible to affirm the judgment plaintiff has obtained. The principal instruction is indeed a very sketchy submission of his basic theory and right of recovery and that theory is submitted conjunctively with extraneous matter and another hypothesis upon which he was not entitled to recover . . . one that required expert medical testimony. . . . For these indicated reasons the judgment is reversed and the cause remanded.

NOTE

GRANNUM V. BERARD

70 WASH.2D 304, 307, 422 P.2D 812, 814 (1967)

HUNTER, JUDGE:

* * *

The mental capacity necessary to consent to a surgical operation is a question of fact to be determined from the circumstances of each individual case. In *Peterson v. Eritsland*, 69 Wash. 2d 588, 419 P.2d 332 (1966), we stated:

The mental competency or capacity of an individual to execute an agreement, when challenged, presents a factual issue to be determined by the trier of the fact, with the test being whether the person in question, at the time of executing the contract, possessed sufficient mind or reason to enable him to understand the nature, the terms and the effect of the transaction. . . .

It is well settled that the law will presume sanity rather than insanity, competency rather than incompetency; it will presume that every man is sane and fully competent until satisfactory proof to the contrary is presented. . . . In Washington we have held that the standard of proof required to overcome this presumption, in civil cases, is that of clear, cogent and convincing evidence. . . .

C.

Hans Jonas

Philosophical Reflections on Experimenting with Human Subjects*

* * *

To whom should the appeal [to participate in the research project] be addressed? The natural issuer of the call is also the first natural ad-

* 98 *Daedalus* 219, 234-237 (1969). Reprinted by permission of *Daedalus*. Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

dresser: the physician-researcher himself and the scientific confraternity at large. With such a coincidence—indeed, the noble tradition with which the whole business of human experimentation started—almost all of the associated legal, ethical, and metaphysical problems vanish. If it is full, autonomous identification of the subject with the purpose that is required for the dignifying of his serving as a subject—here it is; if strongest motivation—here it is; if fullest understanding—here it is; if freest decision—here it is; if greatest integration with the person's total, chosen pursuit—here it is. . . .

* * *

If the properties we adduced as the particular qualifications of the members of the scientific fraternity itself are taken as general criteria of selection, then one should look for additional subjects where a maximum of identification, understanding, and spontaneity can be expected—that is, among the most highly motivated, the most highly educated, and the least “captive” members of the community. From this naturally scarce resource, a descending order of permissibility leads to greater abundance and ease of supply, whose use should become proportionately more hesitant as the exculpatory criteria are relaxed. An inversion of normal “market” behavior is demanded here—namely, to accept the lowest quotation last (and excused only by the greatest pressure of need), to pay the highest price first.

As such a rule of selection is bound to be rather hard on the number-hungry research industry, it will be asked: Why all the fuss? . . . What is wrong with making a person an experimental subject is not so much that we make him thereby a means (which happens in social contexts of all kinds), as that we make him a thing—a passive thing merely to be acted on, and passive not even for real action, but for token action whose token object he is. His being is reduced to that of a mere token or “sample.” This is different from even the most exploitative situations of social life; there the business is real, not fictitious. . . . The soldier's case . . . is instructive: Subject to most unilateral discipline, forced to risk mutilation and death, conscripted without, perhaps against, his will—he is still conscripted with his capacities to act, to hold his own or fail in situations, to meet real challenges for real stakes. Though a mere “number” to the High Command, he is not a token and not a thing. (Imagine what he would say if it turned out that the war was a game staged to sample observations on his endurance, courage, or cowardice.)

These compensations of personhood are denied to the subject of experimentation, who is acted upon for an extraneous end without being engaged in a real relation where he would be the counterpoint to the other or to circumstance. Mere “consent” (mostly amounting to no more than permission) does not right this reification. The “wrong” of it can only be made “right” by such authentic identification with the cause that it is the subject's as well as the researcher's cause—whereby his role in its service is not just permitted by him, but *willed*. That sovereign will of his which embraces the end as his own restores his personhood to the otherwise depersonalizing context. To be valid it must be autonomous and informed. The latter condition can, outside the research community, only be fulfilled by degrees; but the higher the degree of the understanding regarding the purpose and the technique, the more valid becomes the endorsement of the will. A margin of mere trust inevitably remains. Ultimately, the appeal for volunteers should seek this free and generous endorsement, the appropriation of the research purpose into the person's own scheme of ends. Thus, the appeal is in truth addressed to the one, mysterious, and sacred source of any such generosity of the will—“devotion,” whose forms and objects of commitment are various and may invest different motivations in different individuals. The following, for instance, may be responsive to the “call” we are discussing: compassion with human suffering, zeal for humanity, reverence for the Golden Rule, enthusiasm for progress, homage to the cause of knowledge, even longing for sacrificial justification (do not call that “masochism,” please). On all these, I say, it is defensible and right to draw when the research objective is worthy enough. . . .

We have laid down what must seem to be a forbidding rule. Having faith in the transcendent potential of man, I do not fear that the “source” will ever fail a society that does not destroy it—and only such a one is worthy of the blessings of progress. But “elitistic” the rule is (as is the enterprise of progress itself), and elites are by nature small. The combined attribute of motivation and information, plus the absence of external pressures, tends to be socially so circumscribed that strict adherence to the rule might numerically starve the research process. This is why I spoke of a descending order of permissibility, which is itself permissive, but where the realization that it is a *descending* order is not without pragmatic import. Departing from the august norm, the appeal must needs shift from

idealism to docility, from high-mindedness to compliance, from judgment to trust. Consent spreads over the whole spectrum. I will not go into the casuistics of this penumbral area. I merely indicate the principle of the order of preference: The poorer in knowledge, motivation, and freedom of decision (and that, alas, means the more readily available in terms of numbers and possible manipulation), the more sparingly and indeed reluctantly should the reservoir be used, and the more compelling must therefore become the countervailing justification.

Let us note that this is the opposite of a social utility standard, the reverse of the order by "availability and expendability": The most valuable and scarcest, the least expendable elements of the social organism, are to be the first candidates for risk and sacrifice. It is the standard of *noblesse oblige*; and with all its counterutility and seeming "wastefulness," we feel a rightness about it and perhaps even a higher "utility," for the soul of the community lives by this spirit. It is also the opposite of what the day-to-day interests of research clamor for, and for the scientific community to honor it will mean that it will have to fight a strong temptation to go by routine to the readiest sources of supply—the suggestible, ignorant, the dependent, the "captive" in various senses. I do not believe that heightened resistance here must cripple research, which cannot be permitted; but it may slow it down by the smaller numbers fed into experimentation in consequence. This price—a possibly slower rate of progress—may have to be paid for the preservation of the most precious capital of higher communal life.

d.

**John Griffiths and Richard E. Ayres
A Postscript to the Miranda Project—
Interrogation of Draft Protestors***

* * *

During the week beginning Monday, October 23, agents of the Federal Bureau of Investigation questioned about 21 undergraduate and graduate students, faculty, and staff of Yale who had earlier turned in their draft cards. . . .

* * *

On Monday morning, October 23, shortly after 9 o'clock, Dean Johnson of the Divinity

* 77 *Yale Law Journal* 300-319 (1967). Reprinted by permission of the Yale Law Journal Company and Fred B. Rothman & Company.

School learned that FBI agents intended to question Divinity School students who had turned in their cards. The interrogations began immediately thereafter. That day five Divinity School students and the Assistant to the University Chaplain were interrogated. Word spread quickly, and several persons telephoned the Law School for legal advice immediately before or after being questioned. A number of us at the Law School concluded almost at once that something should be done to inform those about to be interviewed of their rights and to help them obtain a lawyer if they felt the need. . . . Notices giving warning of the FBI's presence and emphasizing the right to silence were posted all over the campus. A meeting was organized for that evening. . . .

Of the 21 people . . . seven were members of the Yale faculty or staff, 11 were graduate or professional students, and only three were undergraduates. The oldest was 36 and the youngest 19; their average age was 25. A substantial minority of them were old enough, or enough encumbered with family obligations, to be virtually draft exempt. One had actually received an honorable discharge from the Army, along with a letter of commendation from his commanding officer. Ten held advanced degrees, and several held more than one.

* * *

The interrogations followed a standard format. Two agents arrived at the suspect's home, office or dormitory room. In eight cases their visit was unheralded; in six cases, they had telephoned beforehand; and in seven cases their impending visit was presaged by an earlier unsuccessful attempt. They confirmed the suspect's name, identified themselves, and asked to speak to the suspect alone. Two suspects insisted on having their wives or friends present; the agents successfully discouraged two others who expressed such an interest.

Unless cut off at the outset, the agents came quickly to the point. One asked the questions, while the other recorded the answers with pen and paper. When a statement was taken, the agent asked the student to sign it and to initial any changes he made in the wording. . . .

* * *

The *Journal's* study of the impact of *Miranda* in New Haven concluded that warnings, even when given clearly and distinctly and without any attempt to discourage the suspect from exercising them, are an inadequate means to as-

sure that he can make an informed decision whether to answer questions. The observations which led to that conclusion may have derived in part from the trauma of arrest, the "inherently coercive" stationhouse atmosphere, and the apparent inability of many ordinary criminal suspects to understand, or even to read, a printed warning. The suspects in this study—all of them well-educated and highly intelligent, and questioned in their homes or offices without an arrest—enabled us to test the *Miranda Project's* conclusion in a situation where those other factors were not present. Under these favorable circumstances, it appears that the waiver forms effectively conveyed the limited message that one could remain silent or could ask to see an attorney. Of the five suspects interrogated on Monday, before the meeting at which rights were explained, all but one said they had learned of at least some part of their *Miranda* rights from the form the agents gave them. Most of the suspects interrogated, before and after the Monday meeting, told us that reading the form reassured them in their assertion of their rights.

However, despite the effectiveness of the forms in conveying the literal meaning of the *Miranda* advice, most of the suspects interrogated on Monday signed the waiver form, and all gave written statements to the agents. All of these told us that in the light of the explanation of rights afforded after their interrogation by the Monday night meeting, they regretted having answered the agents' questions. It should be emphasized that this regret was entirely based upon a greater understanding of the role of interrogation in the criminal process, the possible uses of admissions in a trial, and the extra-judicial uses of admissions: none of them regretted making the statement simply because, having had some legal advice, they later concluded they might be able to "beat the rap" except for their admissions under interrogation. In other words we have here a fairly pure case of admissions made simply because of a lack of *understanding* of the nature and function of the constitutional rights at stake, and of later regret based wholly upon increased understanding, not of a change of heart.

* * *

The Monday meeting afforded those who were interrogated thereafter a substantial degree of understanding of the nature and significance of their rights. It corrected a number of misconceptions they had about the interrogation process. The effect of the meeting was dramatic. While

all those interrogated before the meeting made more or less full incriminating statements to the agents, no suspect interrogated after the meeting did so. . . .

* * *

The question why suspects talk to interrogators is one which has evoked many different answers in the controversy over the *Miranda* decision. . . .

* * *

With the suspects interrogated by the FBI, we had a chance, very shortly after they had been questioned, to ask a group of articulate people their reasons for talking to the agents. It would be unrealistic to generalize widely from such a small and atypical group, of course. Still, the reasons they gave for their decisions to answer some or all of the agents' questions may suggest factors important in other contexts as well.

One of the prime reasons why the suspects questioned Monday answered the questions of the agents was that they did not appreciate the reasons for remaining silent. Because, as we have observed above, they lacked knowledge of the legal context of the decisions they faced, they could not make an informed choice whether to exercise their rights, even though they were more or less aware of the literal meaning of the statements on the waiver form. One suspect, presented with the form by the agents, said to them, "I really don't know what I should do in a situation like this because I've never been in a situation such as this—I really don't know". . . .

* * *

One of the major factors preventing intelligent exercise of rights in the typical interrogation is the fact, as the *Miranda Project* expressed it, that the suspect "is in a crisis-laden situation." . . .

* * *

Nervousness alone, however, probably did not prevent any of those questioned after Monday from carrying through whatever resolve they had taken. What nervousness did do, we think, was to interfere with the capacity of suspects, including those interrogated after the Monday meeting, to exercise their powers of judgment in conducting themselves deliberately during their interrogations. . . . This problem was more serious for the pre-Monday-meeting group, where nervousness combined with ignorance and sur-

prise to produce waivers of rights that were not "intelligently" made.

Most of the little that suspects said to the FBI after Monday probably flowed from their desire to appear courteous and not to offend. The most striking lesson we learned from interviewing the suspects after their interrogation is the point, obvious once noticed, that interrogation is a social situation, and suspects respond according to the normal rules of social interaction in such a situation. For middle-class suspects like ours, it seems that one of the fundamental rules is that one not be unnecessarily rude. . . .

* * *

The failure of the agents to overcome the determination of the few post-Monday suspects who did not answer *any* questions was determined by these suspects' ability to seize and maintain the offensive. In most of the interrogations, the agents assumed the offensive from the outset and imposed their format upon the encounter. They would begin asking questions, and, in the social situation we have described above, a question demands an answer (*Miranda* states legal, not social, rules). The suspect is thus in a position of having to *decide* whether to answer each question. In making each such decision, he is subject to all of the stresses and incapacities we have dealt with above, and above all to the disability of ignorance and the pressure of politeness. . . .

* * *

Our interviews reinforce the conclusions of the *Miranda Project* that the psychological interaction between the interrogator and the suspect in an interrogation is extremely subtle, and the interrogator has most of the advantages. Even when we explained their rights to silence and counsel to a group of very bright and extremely willful people, they felt pressed to answer at least some of the questions put to them by the agents. Absent such a preparatory infusion, the experience of the suspects questioned on Monday confirms the *Project's* finding that the *Miranda* warnings are almost wholly ineffective, and this obtains even when the suspect is intelligent, and the interrogation is polite, non-custodial, and at the suspect's home.

We conclude, therefore, that if the high purposes of *Miranda* are to be effected, the warnings alone are insufficient even in the extremely favorable situation we have discussed. For full achievement of *Miranda's* values, a suspect needs

even more than a sympathetic explanation before his interrogation—he needs a sympathetic advocate during the interrogation. Only in this way will most suspects be able to assert a measure of control over the situation, overcome inevitable nervousness, and avoid the impact of perceived (but irrelevant) social rules operating in a situation structured and manipulated by a professional interrogator.

NOTES

NOTE 1.

HENRY K. BEECHER
EXPERIMENTATION IN MAN*

* * *

. . . At one time Pfeiffer held the view that one should ". . . never use anyone except a volunteer who is at least at the level of a graduate student and who has investigated for himself the nature and possible dangers of the drug or procedure involved." Many would not agree with this last view. For some types of investigation, especially when subjective factors are involved, it is essential to have subjects who know nothing about the expected results and have no vested interest in the outcome. . . . Pfeiffer states his present view: "My quotation from 1951 must certainly be modified as of this date since we are using prisoners at the Atlanta Penitentiary who are not graduate students! We do screen our prisoners for psychiatric difficulties by having them complete a Rorschach examination, IQ assay and MMPI tests. We also go over their psychiatric history very carefully. My statement of 1951 represents the ideal situation rather than the practical situation."

* * *

NOTE 2.

SIR AUSTIN B. HILL
MEDICAL ETHICS AND CONTROLLED TRIALS†

* * *

. . . Surely it is often quite impossible to tell ill-educated and sick persons the pros and cons of a new and unknown treatment versus the orthodox and known? And, in fact, of course one does not know the pros and cons. The situation

* Springfield, Ill.: Charles C. Thomas 16-17 (1959). Reprinted by courtesy of Charles C. Thomas, Publisher, Springfield, Ill.

† 1 *British Medical Journal* 1043, 1046 (1963). Reprinted by permission.

implicit in the controlled trial is that one has two (or more) possible treatments and that one is wholly, or to a very large extent, ignorant of their relative values (and dangers). Can you describe that situation to a patient so that he does not lose confidence in you—the essence of the doctor/patient relationship—and in such a way that he fully understands and can therefore give an *understanding* consent to his inclusion in a trial? In my opinion nothing less is of value. Just to ask the patient does he mind if you try some new tablets on him does nothing, I suggest, to meet the problem. That is merely paying lip-service to it. If the patient cannot really grasp the whole situation, or without upsetting his faith in your judgment cannot be made to grasp it, then in my opinion the ethical decision still lies with the doctor, whether or not it is proper to exhibit, or withhold, a treatment. He cannot divest himself of it simply by means of an illusory or uncomprehending consent.

* * *

NOTE 3.

G. LONG, R. D. DRIPPS, AND H. L. PRICE
MEASUREMENT OF ANTI-ARRHYTHMIC
POTENCY OF DRUGS IN MAN—
EFFECTS OF DEHYDROBENZPERIDOL *

Among the various pharmacologic agents used in the operating room, perhaps none is more difficult to evaluate than an anti-arrhythmic drug. Species differences render animal data suspect. . . .

The belief arose—largely from the results of giving . . . large doses of epinephrine to animals—that any attempt to provoke arrhythmias during anesthesia in man would be hazardous. Yet the alternative—that of trying to study “spontaneous arrhythmias”—is probably doomed to failure because of their evanescent nature.

It occurred to us that there was no a priori reason to fear the effect of an intravenous infusion of epinephrine which was just adequate to provoke an arrhythmia. Using a calibrated constant-rate infusion pump and continuous observation of the ECG, we developed a method which we believed to be objective, accurate and safe for determining the “arrhythmic threshold” in any subject under specified conditions. . . .

* * *

Nine normal female patients scheduled for

* 28 *Anesthesiology* 318–319 (1967). Reprinted by permission.

elective operation were studied; they ranged in age from 29 to 51 years. . . . [The problem of obtaining valid consent always exists in an experiment performed on human beings. Despite the fact that all of our subjects were interviewed before the study and the procedure explained, we believe that an informed consent cannot be obtained for a study of this type, because of the impossibility of transmitting to a patient both the relevant information and the background needed to analyze and evaluate such information. Instead, we have accepted the role of guarantor of the patient's rights and safety. . . .]

* * *

The method of determining the threshold for production of ventricular arrhythmias was as follows. An initial injection at a rate of 4 g./minute was first tried. If this did not produce an arrhythmia within 5 minutes, the infusion was terminated and restarted at a higher rate following a pause of 5 to 10 minutes. In general, rates were increased in increments of 50 per cent until an arrhythmia was observed. In every case determination of the arrhythmic threshold was repeated at least once in order to ascertain that the value was reproducible.

NOTE 4.

LORD PLATT
MEDICAL SCIENCE—MASTER OR SERVANT? *

* * *

To use the new aids which science has now put at his command the doctor does not have to know the scientific principles from which they have developed; and as science advances and becomes more complex it becomes increasingly impossible for him to do so. This should be accepted by medical educators without guilt or shame. The modern physician does not have to learn the engineering and physical principles on which an x-ray machine is constructed or the chemical nature of the emulsions used on the film in order to interpret an x-ray picture. (Even the interpretation is usually done for him.) He does not have to be a physicist to read an electrocardiogram. Almost none of the physicians who daily prescribe the tetracycline group of drugs knows anything about their chemical structure; or cares. . . .

* * *

* 4 *British Medical Journal* 439, 443 (1967). Reprinted by permission.

NOTE 5.

ERICH FROMM
ESCAPE FROM FREEDOM*

* * *

... With regard to all basic questions of individual and social life, with regard to psychological, economic, political, and moral problems, a great sector of our culture has just one function—to befog the issues. One kind of smokescreen is the assertion that the problems are too complicated for the average individual to grasp. On the

* New York: Holt, Rinehart and Winston, Inc. 249-250 (1941). Reprinted by permission.

contrary it would seem that many of the basic issues of individual and social life are very simple, so simple, in fact, that everyone should be expected to understand them. To let them appear to be so enormously complicated that only a "specialist" can understand them, and he only in his own limited field, actually—and often intentionally—tends to discourage people from trusting their own capacity to think about those problems that really matter. The individual feels helplessly caught in a chaotic mass of data and with pathetic patience waits until the specialists have found out what to do and where to go.

* * *

CHAPTER TEN

What Limitations Should Be Imposed on Informed Consent?

In this chapter we focus on the restraints which the professions and society place on informed consent to “protect” the subject’s and society’s “best interests.” Such constraints are invoked by investigators in order to shield the subject, usually also a patient, from “unpleasant” knowledge and “unwise” choices or by lawmakers in order to shield society from troublesome choices, like euthanasia, considered offensive to the “moral sense” of the community.

Though encroachments on self-determination are traditionally viewed with disquiet, law has, without careful scrutiny, recognized, or at least acquiesced in, broadly defined limitations on informed consent. We seek to search out the conscious and unconscious assumptions about man which underlie these limitations and to compare them with observations about patient-subjects’ actual behavior and desires. Materials are presented which illustrate the dilemma that arises from the conflict between the requirement of informed consent and the value of hope and blind faith in safeguarding patient-subjects’ health or life. The chapter closes with a discussion of the grounds on which society either overrides a subject’s choice to participate in a risky procedure or alternatively requires him to take part without his consent.

In studying these materials, reevaluate the answers already given to the questions posed in Chapters Eight and Nine. In addition, also consider:

1. To what extent should the status of being sick and dying extend or limit the right to self-determination or the capacity to give informed consent?

2. Who should have the authority to give consent for subjects whose "best interests" preclude their having knowledge about a research project?
3. To what extent should what kind of harm or benefit to subjects or society affect the decision to experiment without consent?

A.

In the Subject's Interests

1.

Safeguarding "Health"

a.

How Much Should the Patient-Subject Know?

[i]

L. J. Henderson

*Physician and Patient as a Social System**

* * *

[I]t is meaningless to speak of telling the truth, the whole truth, and nothing but the truth, to a patient. It is meaningless because it is impossible;—a sheer impossibility. Since this assertion is likely to be subjected to both objective and subjective criticism, it will be well that I should try to explain it. I know of no other way to explain it than by means of an example. Let us scrutinize this example, so far as we may be able, objectively, putting aside all our habits of moralistic thought that we acquired in early years and that arise from the theological and metaphysical traditions of our civilization.

Consider the statement, "This is a carcinoma." Let us assume in the first place that the statement has been made by a skilful and experienced pathologist, that he has found a typical carcinoma—in short, that the diagnosis is as certain as it ever can be. Let us also put aside the consideration that no two carcinomas are alike, that no two patients are alike, and that, at one extreme, death may be rapid and painful or, at another extreme, there may be but a small prospect of death from cancer. In short, let us assume, putting aside all such considerations, that the statement has nearly the same validity as the assertions contained in the nautical almanac. If we now look at things, not from the standpoint of philosophers, moralists, or lawyers, but from the standpoint of biologists, we may regard the statement as a stimulus applied to the patient.

This stimulus will produce a response and the response, together with the mechanism that is involved in its production, is an extremely complex one, at least in those cases where a not too vague cognition of the meaning of the four words is involved in the process. For instance, there are likely to be circulatory and respiratory changes accompanying many complex changes in the central and peripheral nervous system. With the cognition there is a correlated fear. There will probably be concern for the economic interests of others, for example, of wife and children. All these intricate processes constitute the response to the stimulus made up of the four words, "This is a carcinoma," in case the statement is addressed by the physician to the patient, and it is obviously impossible to produce in the patient cognition without the accompanying affective phenomena and without concern for the economic interests. I suggest, in view of these obvious facts, that, if you recognize the duty of telling the truth to the patient, you range yourself outside the class of biologists, with lawyers, and philosophers. The idea that the truth, the whole truth and nothing but the truth can be conveyed to the patient is an example of false abstraction, of that fallacy called by Whitehead, "the fallacy of misplaced concreteness." It results from neglecting factors that cannot be excluded from the concrete situation and that have an effect that cannot be neglected. Another fallacy also is involved, the belief that it is not too difficult to know the truth; but of this I shall not speak further.

I beg that you will not suppose that I am recommending, for this reason, that you should always lie to your patients. Such a conclusion from what I have said would correspond roughly to a class of fallacies that I have already referred to above. Since telling the truth is impossible, there can be no sharp distinction between what is true and what is false. But surely that does not relieve the physician of his moral responsibility. On the contrary, the difficulties that arise from

* 212 *New England Journal of Medicine* 819, 822, 823 (1935). Reprinted by permission.

the immense complexity of the phenomena do not diminish, but rather increase, the moral responsibility of the physician, and one of my objects has been to describe the facts through which the nature of that moral responsibility is determined.

Far older than the precept, "the truth, the whole truth, and nothing but the truth," is another that originates within our profession, that has always been the guide of the best physicians, and, if I may venture a prophecy, will always remain so: So far as possible, do no harm. You can do harm by the process that is quaintly called telling the truth. You can do harm by lying. In your relations with your patients you will inevitably do much harm, and this will be by no means confined to your strictly medical blunders. It will arise also from what you say and what you fail to say. But try to do as little harm as possible, not only in treatment with drugs, or with the knife, but also in treatment with words, with the expression of your sentiments and emotions. Try at all times to act upon the patient so as to modify his sentiments to his own advantage, and remember that, to this end, nothing is more effective than arousing in him the belief that you are concerned whole-heartedly and exclusively for his welfare.

* * *

NOTES

NOTE 1.

HUBERT WINSTON SMITH
THERAPEUTIC PRIVILEGE TO WITHHOLD
SPECIFIC DIAGNOSIS FROM PATIENT SICK
WITH SERIOUS OR FATAL ILLNESS*

* * *

Anglo-American law starts with the premise of thoroughgoing self-determination; it follows that each man is considered to be master of his own body, and he may, if he be of sound mind, expressly prohibit the performance of life-saving surgery. A doctor might well believe that an operation is medically desirable or necessary but the law does not permit him to substitute his own judgment for that of the patient by any form of artifice or deception. . . .

[I]n general, no medical privilege should be recognized to withhold the diagnosis in ordinary cases where the usual patient would feel entitled

to have the information as a basis for charting his course and there being no apparent grounds for supposing that a disclosure of the truth would engender in the patient reactions dangerous to his health or life. If a broad, absolute privilege were granted to the physician to withhold medical information on allegedly therapeutic grounds, this would afford a perfect shield to cover the negligence of many who were unable to reach a timely or accurate diagnosis of the true illness. The physician could always say that he knew the diagnosis but withheld it for fear of worsening the patient's condition. Secondly, it would be dangerous in the extreme to say that a physician is entitled, either by misrepresentation or concealment, to gain the patient's consent to particular forms of treatment on the theory that "the doctor knows best" and it would only make the patient a sicker man to hear the risks.

[T]he physician should be recognized to have a therapeutic privilege to withhold part or all of the facts regarding a dread illness, when he has reason to believe that communicating them freely to the patient will involve risks of causing his death or serious impairment of his health without any countervailing gain. It is suggested that this should be in the nature of an imperfect privilege, to be passed upon by the presiding judge in the light of evidence adduced in the particular case. . . .

[T]he question was raised, to some degree, however, in the early Massachusetts case of *Twombly and wife v. Leach*, an action on the case against a physician for alleged malpractice in treating a felon of the thumb and consequent lymphangitis which plaintiff's wife developed after accidentally inflicting a penetrating wound upon herself with a paring knife. It appeared that defendant treated her for a considerable time without disclosing the diagnosis. On the trial of the case, the court refused to permit defendant to ask several expert witnesses: "whether or not it is good medical treatment in some cases to withhold from the patient the extent of the disease and her actual condition?" The jury returned a verdict in plaintiff's favor in the trial court, but on appeal defendant's exceptions were sustained and a new trial was granted on the ground, among others, that "upon the question whether it be good medical practice to withhold from a patient in a particular emergency, or under given or supposed circumstances, a knowledge of the extent and danger of his disease, the testimony of educated and experienced medical practitioners is material and peculiarly appropriate."

* 19 *Tennessee Law Review* 349, 350-352 (1946). Reprinted by permission.

The one sovereign question by which one may fairly test the obligation of the physician is this: considering the nature of the particular physician-patient relationship, or of the employment, would the withholding of the specific diagnosis defeat the patient's just expectations or would this, under all the circumstances, really contribute to a successful performance of the physician's mission in the case?

* * *

NOTE 2.

HUNT V. BRADSHAW
242 N.C. 517, 88 S.E.2d 762 (1955)

* * *

On July 18, 1950, the plaintiff, an able-bodied man, was working in his auto repair shop near Kingsport, Tenn., when a small piece of steel, about $3/8" \times 2/8" \times 2/8"$, with sharp edges, broke off from the end of an automobile axle under a sledge hammer blow and penetrated plaintiff's body, entering the left front side of his neck just above his collar bone. He was examined by Dr. Howkins and later by Dr. Reed. There was bleeding from the entrance wound for about 15 or 20 minutes, but afterwards very little pain, no fever, and no apparent adverse effect from the accident. However, Dr. Reed had x-ray photographs made. He recommended that plaintiff consult the defendant, Dr. Bradshaw, and follow his advice as to an operation for removal of the missile.

On July 31, 1950, plaintiff consulted Dr. Bradshaw, who had five x-ray pictures made of plaintiff's upper chest. The pictures were taken from the front, back and side. On one or two the foreign body showed indistinctly. When asked for his advice after the examination, Dr. Bradshaw stated that he thought the metal was going down, that it might get into his heart, and he strongly recommended it be removed. "I asked him about the operation, if it was a very serious one, and he said it wasn't nothing to it, it was very simple."

The defendant performed the operation on the morning of August 2, 1950. Plaintiff testified: "When I woke up, I was trying to work my hand, and I couldn't use my fingers at all; I had never experienced that feeling before. At the present time (1955) I can't use my left hand at all. I can't use those fingers no way at all". . . .

At the conclusion of the plaintiff's evidence, the defendant's motion for judgment as of non-

suit was allowed, judgment entered accordingly, and the plaintiff excepted and appealed.

HIGGINS, JUSTICE.

* * *

The plaintiff's evidence is sufficient to support a finding the operation was of a very serious nature. Dr. Bradshaw, after examination, advised the plaintiff the missile might move and get to the heart, and recommended the operation. That a sharp-edged piece of steel does migrate is borne out by plaintiff's expert evidence, especially by Dr. Jeffreys. Upon Dr. Bradshaw's advice the operation was decided upon. It is understandable the surgeon wanted to reassure the patient so that he would not go to the operating room unduly apprehensive. Failure to explain the risk involved, therefore, may be considered a mistake on the part of the surgeon, but under the facts cannot be deemed such want of ordinary care as to import liability.

* * *

Of course, it seems hard to the patient in apparent good health that he should be advised to undergo an operation, and upon regaining consciousness finds that he has lost the use of an arm for the remainder of his life. Infallibility in human beings is not attainable. The law recognizes, and we think properly so, that the surgeon's hand, with its skill and training, is, after all, a human hand, guided by a human brain in a procedure in which the margin between safety and danger sometimes measures little more than the thickness of a sheet of paper.

The plaintiff's case fails because of lack of expert testimony that the defendant failed, either to exercise due care in the operation, or to use his best judgment in advising it. . . .

The judgment of nonsuit entered in the Superior Court is Affirmed.

[ii]

Ferrara v. Galluchio
5 N.Y.2d 16, 152 N.E.2d 249 (1958)

CONWAY, CHIEF JUDGE.

Plaintiff wife, who was suffering from bursitis in the right shoulder, received a series of X-ray treatments from defendants, doctors specializing in X-ray therapy. . . . At the conclusion of the sixth treatment she still had a pain in her right shoulder and one of the defendants sug-

gested that if the pain continued she should come back for a seventh treatment. The pain persisted and three days later she returned and the seventh treatment was administered. Subsequent thereto, the shoulder began to itch, turned pink, then red, and blisters formed. These blisters ruptured and the skin peeled, leaving the raw flesh of the shoulder exposed. Scabs formed and lasted several months, a few as long as five or six months and one lasted several years. . . . This condition was diagnosed as chronic radiodermatitis which was caused by the X-ray therapy. While the blisters were still present the plaintiff went back to the defendants and showed them the condition of her shoulder. They gave her a prescription for some salve which she procured and used.

On December 3, 1951, approximately two years after the treatments, the plaintiff was referred by her attorney to a dermatologist for examination. After taking a history and making an examination the dermatologist prescribed a substance used in the treatment of radiodermatitis, and advised the plaintiff to have her shoulder checked every six months inasmuch as the area of the burn might become cancerous.

The instant action for malpractice was predicated upon (the theory) that the total number of Roentgens (1,400) applied to the plaintiff was excessive. . . . Plaintiff also introduced, on the issue of mental anguish, the testimony of a neuro-psychiatrist to the effect that she was suffering from a severe cancerophobia, that is, the phobic apprehension that she would ultimately develop cancer in the site of the radiation burn. The witness further testified that she might have permanent symptoms of anxiety.

* * *

The dermatologist apparently thought it essential as part of his treatment and as a protective measure for plaintiff to advise her to have her shoulder checked every six months because of the possibility of cancer. Under our law the risk of such advice and its effects on the plaintiff must be borne by the wrongdoers who started the chain of circumstances without which the cancerophobia would not have developed.

This case is somewhat novel, of course, in that it appears to be the first case in which a recovery has been allowed against the original wrongdoer for purely mental suffering arising from information the plaintiff received from a doctor to whom she went for treatment of the original injury. We have concluded, however,

that under the circumstances of the case such recovery was justified.

* * *

FROESSEL, JUDGE (dissenting).

* * *

Whatever argument may be made to the contrary, we do not feel, on balance and as a matter of public policy, that damages based upon mental anguish, engendered by a physician's statement as to a *possible* development of another ailment, are warranted under such a rule. Physicians commonly inform patients of conceivable complications which may arise from an injury, and we do not believe that so ready a road to the multiplication of damages ensuing from physical injury should be opened to plaintiffs. The unfortunate result of the rule announced by this decision, albeit disclaimed, is that a doctor's mere statement as to a possibility is a steppingstone to an increased recovery should the patient simply claim to be concerned enough to suffer worry by reason thereof. In other words, recovery would depend upon the subjective mind of the litigating plaintiff and speculation by the physician, without even the safeguard of an opinion by the latter based on reasonable certainty.

* * *

[iii]

Bolam v. Friern Hospital Committee
[1957] 2 All E. R. 118

McNair, J. [to the jury]:

* * *

Let us examine those three points. Bear in mind that your task is to say whether, in failing to take the action which it is said Dr. Allfrey should have taken, he has fallen below a standard of practice recognised as proper by a competent reasonable body of opinion. First let me deal with the question of warning. There are two questions that you have to consider. First—does good medical practice require that a warning should be given to a patient before he is submitted to electro-convulsive therapy? Secondly—if a warning had been given, what difference would it have made? Are you satisfied that the plaintiff would have said: "You tell me what the risks are. I won't take those risks. I prefer not to have the treatment."

The plaintiff relies, on this aspect of the

case, on the evidence of Dr. Randall who, you may think, was a most distinguished psychiatrist, well-qualified to express an opinion. He said regarding his practice as to giving a warning:

Having assessed the patient, it is then put to him that he might benefit from electro-convulsive therapy—some people call it electro-shock therapy, but from the point of view of the patient that is not material because the patient is never aware either that he has a shock or a convulsion. Our practice at St. Thomas's Hospital, and my practice at Charing Cross Hospital is to provide the patient with a consent form.

Dr. Randall was asked whether he would warn the patient of the risks involved. He answered:

Yes, I would indeed; in fact, we do. I make a practice always of saying to the patient that, using the technique of relaxation, he would be given an injection which would put him to sleep; that he would then be given another injection which would have the effect of paralysing all his muscles so that he could not move. I explain to the patient that if he were not given a relaxant drug his body would make some strong movements.

Dr. Randall was asked about the warning:

Q: If you feel very sincerely as a doctor that it is the only hope of relieving this illness, would you think it wise to discourage the patient by describing to him the possible risk of serious fractures? A: I suppose that one has to form some opinion whether the patient is likely to be influenced by it. Depressed patients are often deluded about their bodily health, and nothing will alter their attitude. Taking that distortion of judgment into account, it is probable that to tell a patient that a risk of fracture exists will not materially alter his attitude to treatment, or his attitude to his illness.

If it is right that to tell a patient of the risk of fracture will not materially alter his attitude to treatment or his attitude to his illness, you may ask yourselves: Is there really any great value in giving this warning? In dealing with consent forms, Dr. Randall says that these forms are provided so that the patient may be aware of the nature of the treatment, and also because it is the practice of the boards of governors of hospitals to provide them in case litigation ensues. Then Dr. Randall's evidence continued:

Q: Does it help the patient in any way to be told all the risks which are involved in electro-convulsive therapy? A: In the outcome I think that it does, because the patient takes the decision whether or not to have a treatment which might affect his

whole future, and at that point he has the chance of deciding whether he will do it or whether he will not do it.

Q: Would you quarrel with a point of view as being wholly unsound if it was held that it was not beneficial to the patient to hear about that sort of thing? A: I can believe that there would be circumstances in which it could be considered that it would not be beneficial to tell a patient of possible dangers and mishaps, subject to what I have already said.

Then I put questions to him:

Q: Do you think that other competent people might take a contrary view to the one which you have expressed? A: I think so, my Lord; yes, they might.

Q: Other competent people might think that it is better not to give any warning at all? A: I think that that is going a little further than I could go generally, but I think that other people might consider it better not to give any warning at all.

Counsel for the plaintiff quite rightly relies on answers which Dr. Randall gave on reexamination:

Q: Do you think it ever right to give no warning of the risk to a person who can understand the warning? A: I think that it is not right to give no warning of the risks to a patient who can understand the import of the warning.

That is the high-water mark of the case for the plaintiff in favour of the view that it was negligent, in the sense which I have used, not to give a warning.

Against that, you have to consider the evidence given by the defendants, first, by Dr. de Bastarrechea, who says:

I don't warn as to technique. I don't think it desirable to do so. If the patient asks me about the risks, I say that there is a very slight risk to life, less than in any surgical operation. Risk of fracture 1 in 10,000. If they don't ask me anything, I don't say anything about the risk.

Dr. de Bastarrechea also said that in his view there was some danger in emphasising to a patient who ex hypothesi is mentally ill any dangers which in the doctor's view were minimal, because, if he does so, the patient may deprive himself by refusal of a remedy which is the only available hopeful remedy open to him. In cross-examination Dr. de Bastarrechea agreed that when an operation is decided on, the patient should be carefully examined, but not that he should be warned of all the risks involved. He agreed that a man should be given the opportu-

nity of deciding whether to take the risk, but it should be left to him to put questions; he should be told that there were some slight risks, but not told of the risks of catastrophe.

* * *

That is, in very summary form, the evidence on this point that you have to consider: and, having considered it, you have to make up your minds whether it has been proved to your satisfaction that when the defendants adopted the practice that they did (namely, the practice of saying very little and waiting for questions from the patient), they were falling below a proper standard of competent professional opinion on this question of whether or not it is right to warn. Members of the jury, though it is a matter entirely for you, you may well think that when a doctor is dealing with a mentally sick man and has a strong belief that his only hope of cure is submission to electro-convulsive therapy, the doctor cannot be criticised if he does not stress the dangers, which he believes to be minimal, which are involved in that treatment.

The second point on the question of giving a warning is this: Suppose you come to the conclusion that proper practice requires some warning to be given. If a warning had been given, would it have made any difference? Only the plaintiff can answer that question, and he was never asked it. . . .

* * *

. . . The question what the plaintiff would have done if he had been told that there was a one in ten thousand risk was never put. Surely, members of the jury, it is mere speculation on your part to decide what the answer would have been, and you might well take the view that unless the plaintiff has satisfied you that he would not have taken the treatment if he had been warned, there is really nothing in this point.

* * *

NOTE

PHYSICIAN'S DUTY TO WARN*

* * *

. . . The duty to warn should be based not on the doctors' practice but on the patients'

* 75 *Harvard Law Review* 1445, 1447-1448 (1962). Copyright 1962 by the Harvard Law Review Association. Reprinted by permission.

needs; that is, the inquiry should be whether a reasonable man in the doctor's position and with his knowledge of the patient would have been justified in concluding with substantial certainty that the patient, if informed of this risk, would not have withdrawn his consent. [T]he patient of average sophistication is already aware of certain dangers inherent in any surgical treatment; he may be presumed to have considered these in giving his consent, even though he has not been specifically reminded of them. The duty narrows then, in the average case, to disclosure of dangers peculiar to the treatment proposed and of which it is likely that the patient is unaware. The doctor should have little difficulty in choosing from these the risks that are sufficiently serious and likely to occur as to be essential to an intelligent decision by his patient.

Circumstances will occasionally arise, however, in which the disclosure of risks should be limited or withheld for therapeutic reasons—that is, where the patient's emotional condition is such that full disclosure would seriously complicate or hinder treatment. In other cases, the patient might justifiably be considered incapable of coping with knowledge of potential dangers and likely to distort them in such a way that rational decision would be impossible. In either of these cases, a privilege to withhold or to limit disclosure would seem justified, though it would seem desirable to require the physician to make full disclosure to a relative when possible. Disclosure, it may be noted, cannot be withheld or limited merely because the patient might, on learning of the risks, rationally decline treatment. The right to decline is the very right being protected. . . .

[Jury found defendants not negligent.]

* * *

[iv]

Irving L. Janis

*Psychological Stress—Psychoanalytic and Behavioral Studies of Surgical Patients**

* * *

To obtain observational data . . . the author has conducted systematic studies of hospitalized patients who were required to have surgical operations. . . .

A major goal of the research was to arrive at propositions that are likely to be broadly ap-

* New York: John Wiley & Sons, Inc. 8, 352-353, 367-371 (1958). Copyright 1958, Irving L. Janis. Reprinted by permission.

plicable to most people in contemporary society and that will pertain to behavior in a wide variety of danger situations. Accordingly, the main variables investigated in the surgery studies were selected on the basis of *uniformities* noted in the extensive observational reports currently available on how people in many different national and cultural subgroups tend to react to severe physical dangers—tornadoes, floods, industrial accidents, air raids, criminal assaults, concentration camp tortures, epidemics, acute illness, etc. . . .

* * *

The theoretical concepts and hypotheses which have evolved . . . have a number of important implications for the role of warnings, information about impending events, and other types of communications which can influence the adequacy of a person's psychological preparation for stressful life experiences. The case study evidence . . . suggests that the arousal of some degree of anticipatory fear may be one of the necessary conditions for developing inner defenses of the type that can function effectively when the external dangers materialize. In many of the individual case studies we have examined, the patient had received very little information about the suffering that he would undergo and, in some cases, this lack of information seems to have been a major factor in determining the relative absence of anticipatory fear. One surmises that most people ignore problematical dangers of the future unless they receive specific warnings or predictions from respected authorities. The unpleasant task of mental rehearsal, which appears to be essential for developing effective danger-contingent reassurances, is apt to be shirked, even when a person knows that he is going to be exposed to some form of suffering or deprivation.

If a person is given appropriate preparatory communications before being exposed to potentially traumatizing stimuli, his chances of behaving in a disorganized way and of suffering from prolonged desensitization effects may be greatly decreased. . . .

* * *

[A]n essential difference between the moderate and low anticipatory fear groups lies in the sphere of stress tolerance. Perhaps one reason for the difference is that the patients with moderate anticipatory fear, having greater motiva-

tion to seek information and to mentally rehearse the coming events, are in a better position to ignore a host of potentially distressing perceptions which they are able to explain away as being in the "normal course of events". . . .

The pathogenic consequences of warding off anticipatory fear by means of blanket immunity defenses . . . are not limited merely to the direct effects of being unprepared to cope with clear-cut danger stimuli but also include the indirect effects of lower tolerance for ambiguous threat stimuli. This theoretical notion carries some specific implications for psychological preparation for stress. In order to be maximally effective, preparatory communications should presumably have the goal of giving as complete a cognitive framework as possible for appraising the potentially frightening and disturbing perceptions that the person might actually experience, so as to prevent the type of surprise and ambiguity that generates unproductive, energy-consuming reactions of hypervigilance. Provided that the material is not presented in a lurid or threatening manner, and is accompanied by impressive reassuring comments, specific forecasts about future stressful experiences can probably influence most persons to engage in an imaginative mental rehearsal of the type that promotes the development of effective danger-contingent reassurances.

* * *

Probably the most effective preparatory communications would be those which give a detailed factual account of the *outstanding perceptual experiences that are most likely to occur*, concentrating especially on the vague and ambiguous events that are most likely to be misinterpreted. Communications of this type are currently being given, presumably with some success, to prepare pregnant women for the stresses of childbirth. For surgical patients, however, it is much more difficult to predict in advance the outstanding crises that may arise (e.g., unusual organic complications may drastically interfere with the normal course of recovery). Nevertheless, the patient could be told in advance about all those pains, discomforts, and unpleasant treatments which invariably do occur. And then, if unpredictable events were to take place, the patient might be given additional information early enough so that the processes of inner preparation could reduce the shock of surprise. For example, when a surgical incision turns out to be much more extensive or creates more of a cos-

metic defect than the surgical staff had originally anticipated, it may be possible to give the patient appropriate information about it during the early phase of the postoperative period, before he makes the shocking discovery himself. Even for relatively minor complications, such as Mrs. R.'s discolored bruise, the patient can probably be spared some unnecessary emotional tension if information about the unexpected injury is presented and discussed as soon as the patient is capable of engaging in conversation.

The foregoing discussion has emphasized the probable advantages of giving detailed preparatory information to surgical patients so that they can anticipate correctly and become emotionally prepared for distressing stimuli which they will subsequently perceive. But this emphasis should not be construed as indicating that there is any special advantage to telling surgical patients about the medical aspects of the operation—details about the surgical procedures that will be carried out while the patient is unconscious, the potential risks from the anesthesia, the unusual complications that occasionally arise, and the factors that make for a poor prognosis. In general, there is probably little or no gain from giving any technical information which is not essential for conveying a realistic picture of what the patient will actually perceive. A small amount of background information about the medical aspects may sometimes have a beneficial effect, but only if it serves to correct a patient's misconceptions or if it subsequently contributes to the patient's understanding that nothing untoward is happening to him.

The available evidence suggests that when a physical crisis occurs, prior familiarity with the fear-arousing stimuli tends to lower the chances of emotional shock. But there are some indications in the case study material that detailed medical knowledge does not necessarily help a patient's postoperative adjustment. On the contrary, he may find it much more difficult to feel reassured if he knows a great deal about the dire complications and potential risks which the surgeon is taking into account.

Too much information about the medical aspects of one's own case can create an attitude of sustained hypervigilance that serves no constructive purpose and that may increase one's sensitivity to adverse events. These negative consequences are suggested by the case study material from a number of well-informed and well-educated surgical patients. . . .

NOTE

IRVING L. JANIS
EMOTIONAL INOCULATION—
THEORY AND RESEARCH ON EFFECTS
OF PREPARATORY COMMUNICATIONS*

* * *

In order to specify functional properties of the work of worrying, it is necessary to delineate what occurs in its absence. What happens when, because of lack of opportunity or inadequate motivation, a person remains unworried about an impending danger experience and fails to undergo any inner preparation before it materializes? At the moment when inescapable signs of danger or actual suffering are encountered, efforts at intellectual denial (by minimizing or discounting the likelihood of being personally affected by the danger) will no longer succeed. The person then suddenly finds himself unable to ward off intense fear or fright (which sometimes is experienced as anger or other affects), especially because he has not developed any means for actively protecting himself from the danger. Moreover, the crisis seems to be augmented by the fact that when more danger or suffering is encountered than had been expected beforehand, feelings of helplessness are likely to occur which drastically interfere with the ego's normal reassurance mechanisms. One of the most important sources of reassurance, markedly impaired under these conditions, is the anticipation of being protected from the full impact of the danger by the danger-control authorities or other benevolent parent surrogates.

* * *

From what has just been said about the dynamics of stress behavior, one can predict that a number of interrelated adverse effects will ensue if, for any reason, a person fails to do the work of worrying prior to being exposed to actual danger or loss:

1. The spontaneous tendency to ward off anticipatory fear remains unchecked and the person therefore remains relatively unmotivated to engage in the realistic fantasizing or the mental rehearsing essential for developing two types of effective defense against fright: (a) reality-based cognitions and expectations about opportunities

* 5 *Psychoanalysis and the Social Sciences* 139-143 (1958). Reprinted by permission of the International Universities Press, Inc., New York.

for surviving the impending danger, the subsequent contemplation of which can function as a source of hope and reassurance; and (b) reality-based plans for taking protective actions in case various contingencies arise, the subsequent execution of which can contribute to reducing feelings of passive helplessness.

2. The person's overoptimistic expectations and fantasies remain uncorrected and hence the chances are increased that there will be a marked disparity between the amount of victimization expected beforehand and the amount that is actually experienced, increasing the probability of regressive aggrievement reactions (childlike rage and/or depression).
3. When the person subsequently comes to realize that the danger-control authorities failed to predict or give warnings about the suffering that was in store for him, childhood experiences of resentment against the parents (for unfair or unprotective treatment) are especially apt to be reactivated, thus increasing the likelihood that the danger-control authorities will lose their capacity to give reassurances and will be irrationally blamed for objective dangers and deprivations.

All three reactions to objective danger situations would be expected to occur whenever a person fails to engage in adequate work of worrying beforehand, whether the failure is attributable primarily to the predanger environmental conditions or to exceptionally strong personality needs which predisposed the person to deny clear-cut signs of impending danger. Sometimes absence of the work of worrying is caused by the sudden onset of an unpredictable event (e.g., an emergency operation following an automobile accident). Thus the essential factor may be that the anticipatory period is too short to allow the person time to prepare himself for the emergency. Often, however, people fail to carry out adequate inner preparation even though there is ample time between an initial warning stimulus and the onset of the crisis. In such instances, a major causal factor responsible for the incompleteness of the work of worrying is likely to be *lack of unambiguous warnings and information about the magnitude of the impending danger*. Rosen points out, for example, that surgeons sometimes will "join the patient in his denial of the unpleasant consequences of surgery with an 'everything is going to be all right just leave the worrying to me' attitude." And, of course, at the opposite extreme there are some physicians who severely frighten their patients long in advance of an operation, giving alarming information be-

fore it can properly be evaluated and assimilated, thereby stimulating defensive reactions of extreme denial which preclude the normal work of worrying. Thus, it may often happen that the adequacy of a person's emotional preparation for danger will depend upon the *adequacy and timing of the preparatory communications* to which he has been exposed.

b.

To Choose on Faith or Knowledge?

[i]

W. R. Houston

*The Doctor Himself as a Therapeutic Agent**

* * *

The great lesson . . . of medical history is that the placebo has always been the norm of medical practice, that it was only occasionally and at great intervals that anything really serviceable, such as the cure of scurvy by fresh fruits, was introduced into medical practice. By and large, the doctors were, as reported by that sane and shrewd observer, Montaigne, a danger to their patients. The medical historian is apt to mislead us when he speaks of the learned and skilful doctors of the past. While undoubtedly exceptional instances might be unearthed to show that these physicians accomplished something for the somatic good of their patients, in the large view we are forced to realize that their learning was a learning in how to deal with men. Their skill was a skill in dealing with the emotions of men. They themselves were the therapeutic agents by which cures were effected. Their therapeutic procedures, whether they were inert or whether they were dangerous, were placebos, symbols by which their patients' faith and their own was sustained.

The history of medicine is a history of the dynamic power of the relationship between doctor and patient. Through centuries when doctors were doing more harm than good this dynamic force has sustained the medical profession in the esteem of their clientele, it has inspired their fellow citizens with such faith in its values that they were willing to give economic support to the doctor. However little the doctor had to offer, it was to him that men turned in the distress of illness. When we observe the honor and emolument bestowed on the physician throughout the ages we

* 11 *Annals of Internal Medicine* 1415, 1416, 1420 (1938). Reprinted by permission.

are forced to exclaim, "Oh rare cogency of the relation between doctor and patient!"

* * *

When thoughtfully considered, this situation is not one to be regarded with comfort. Medical men are not without misgivings about the spurious psychotherapy that they are under constant temptation to practice. Yet the path to development of a better psychotherapy is full of obstacles. The doctor's training in the laboratory and the ward has offered few opportunities for the development of any aptitude in dealing with the problems of personality. Doctors consider that their vocation is to deal with things that can be weighed and measured and that the reactions of the cerebral cortex and the autonomic nervous system are too intangible for them to deal with. As a distinguished member of this body, and contributor to this program, recently wrote me:

"I suppose that I am particularly bitter about the people whom we may as well call neurotics, who, as you say, take up so much of an internist's time. They are the people who drove me out of practice. I never could see any sense in paying any attention to them because, as your word picture of them so graphically shows, they have neither sense, nor gratitude, nor any idea of cooperation, nor any qualities that might endear them to man, woman or child.

"I cannot understand why those of us who have trained ourselves to take care of people who have organic disease can't be allowed to take care of organic disease. Why won't these people take our word for it that there is nothing the matter with them and let it go at that? I suppose I have as many somatic sensations as anybody on earth but I explain them to myself in a physiological way. Why can't an intelligent neurotic take the same sort of advice that I give myself? There seems to be no way of handling them except that sort of semi-quackery that some highly respectable members of our fraternity are able to get away with so successfully."

[ii]

Stewart Wolf

*The Pharmacology of Placebos**

* * *

Placebos have been used for centuries by physicians under pressure to "do something," but

wishing to do no harm. Traditionally, the function of the placebo was to pacify without actually benefiting the patient. The benefit, however, has proved to be unexpectedly lavish. Not only has the hopeful reassurance of placebos engendered in patients a feeling of increased well-being, but recent experimental evidence has shown that placebo administration may be followed by substantial and measurable changes in bodily mechanism. Therefore, since placebos do a great deal more than placate or pacify, a new definition may be offered as follows: *Placebo effect = any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties.* Placebo effects derive from the significance to the patient of the whole situation surrounding the therapeutic effort. . . .

* * *

Modell writes that the placebo effect "... is the only single action which all drugs have in common and in some instances it is the only useful action which the medication can exert" . . .

Dubois listed three classes of placebos. The first included simple substances, inert and unpretentious, such as lactose and starch. The second class included pseudomedicaments, extracts of herbs, poisonous metals, superfluous vitamins, and so forth. Such are the ingredients of most proprietary medicines sold over the counter. The third is the placebo effect that goes along with the pharmacodynamic action of a specific therapeutic agent.

* * *

Except in the case of a patient's special need, a physician's special hope, or an experimenter's deliberate manipulation of the situation by suggestion, or otherwise, there appears to be nothing predictable about placebo effects. Placebos may induce in an organ a change in one direction or in another, or no change at all. A vivid example of the way a placebo may produce changes in opposite directions in a single organ is available in the studies of gastric acid secretion in man. Two separate investigators measured gastric secretion in healthy human subjects in response to an oral placebo without verbal suggestion. In one group of 22 subjects a 12 percent increase of gastric acidity was observed and in the other group of 15 subjects an 18 percent decrease following the administration of a placebo. The difference between the two groups was significant at the 0.001 level of confidence.

Several authors have observed toxic reac-

* 11 *Pharmacological Reviews* 689, 690, 692, 694, 696 (1959). © 1959, The Williams and Wilkins Co., Baltimore, Md. Reprinted by permission.

tions in response to the administration of placebos. Sheldon, in a study of reserpine administered to by hypertensive patients, found that the patients who were receiving placebos complained of nasal stuffiness as often as did those who were getting reserpine. Shapiro and Grollman, studying effects of antihypertensive agents given by mouth to ambulatory patients, found that one of their most troublesome and persistent . . . headaches occurred in an individual who was getting placebo at the time. . . .

* * *

It is important to realize that placebo effects are not imaginary. Neither are they necessarily suggestive in the usual sense of the word. For example, certain workers have induced changes in circulating eosinophiles, either during the discussion of meaningful topics or following the administration of placebos. . . .

* * *

There is not universal agreement as to the place of the placebo in therapeutic research. Some investigators have asserted that the placebo control is unnecessary or even misleading, but most agree that it is an indispensable step toward the establishment of the therapeutic efficacy of any new agent. The placebo by no means provides a perfect control procedure, however. Tell-tale side effects of a potent agent may vitiate the attempt to keep the physician or the subject unaware of what is being given. While placebos may induce almost any side effect, they do not produce them as predictably as an active agent. Furthermore, the use of a placebo control may be awkward and cumbersome when establishing a dose range or when looking for serious toxic effects of an agent. In a clinical trial, however, and before the presumed therapeutic action of the agent can be accepted, the placebo must be given and given without the knowledge of either the one who gives it or the one who gets it because, as already pointed out, drug therapy backed by unconscious enthusiasm and solicitude of the physician may result in powerful and measurable bodily changes which are not attributable to the pharmacodynamic effects of the agent in question. A case in point was that of a patient who had had chronic asthma for twenty-seven years. Having suffered almost continuous asthma for the past seventeen, he had become a favorite subject on which to test new drugs. He had become refractory even to epinephrine. Finally, the product of one pharmaceutical company seemed

effective in his case. When he was given the agent, he was free of asthma; when it was stopped, the asthma returned. Accordingly, his physician substituted a placebo without the patient's knowledge. Asthma was not relieved. Shifts from agent to placebo and back again were carried out several times with consistent results in favor of the agent. When the company was approached for an additional supply of the material, their representative acknowledged that, because they had had so much trouble with positive enthusiastic reports, they had, in this instance, sent along the placebo first. It would be hard to find a more vivid illustration of the need for placebo control to be blindly undertaken so that the doctor as well as the patient is in ignorance of what is being administered. Investigators have often been naive in failing to recognize that patients, like dogs and children, are likely to know what is in the atmosphere without our telling them and even when we try desperately to conceal our attitudes.

* * *

NOTES

NOTE 1.

HENRY K. BEECHER
SURGERY AS PLACEBO*

* * *

Various surgical procedures have been recommended and carried out for the relief of angina pectoris. One of these, ligation of the internal mammary arteries, offers material pertinent to the subject of this paper. . . .

At first when this procedure was tried in man, it was believed to be beneficial. Unfortunately, the early studies were uncontrolled; results were not for the reasons thought, and they were fleeting—lasting for a number of weeks. The procedure's relevance to this study is that the benefit was not due to changes in blood flow produced by the ligations: We are now sure of that. Benefit was due to what happened in the minds of the patients and the surgeons involved. It will be shown that both of these can produce significant change, and that the changes are both subjective and objective. . . .

Harken reported on 35 patients with angina who had had internal mammary artery ligation

* 176 *Journal of the American Medical Association* 1102, 1103-1104, 1106 (1961). Reprinted by permission.

with the result that "more than a third have enjoyed complete relief and there has been worthwhile palliation in almost three-fourths of the group." Significantly, how long the relief lasted is not stated. He concludes that "the present experience is indeed exciting," and that "this seems a simple but valuable therapeutic adjunct." Even if one considers only the "more than a third" who found complete relief, here are results achieved by an enthusiastic surgeon far beyond those achieved by the sceptic.

* * *

Adams's paper is important for its early timing since, in the midst of enthusiasm for ligation, it threw doubt on the cause of the improvement. He found that incision of the skin and placement of an untied ligature around the internal mammary arteries of 2 patients produced great subjective improvement which was not increased on subsequent tightening to obstruction of the previously placed ligatures.

Fish, Crymes, and Lovell carried out internal mammary artery ligation in 24 patients with angina pectoris. . . . they approached the procedure with scepticism. Fish and associates say: "It was explained to each patient that the operation was experimental, that there was no generally accepted physiologic basis for apparent good results and that those attending the patient had no idea whether or not the angina would be improved". . . .

In the Fish study: "In 20 of the 24 cases there was an initial period of marked improvement, which usually began in the postoperative period and lasted approximately ten to sixty days. This was reflected by increased exercise tolerance and a reduction of the quantity of nitroglycerin required and in electrocardiographic stability. . . . In the light of subsequent findings, this striking early improvement is difficult to explain." It is no more difficult to explain than all placebo effects, one might add. At the time the Fish paper was written, only 4 of the 24 patients, in their own opinion, had moderate improvement; 2 believed they were slightly improved, while "in the remaining 18, the angina syndrome has resumed its preoperative course."

The quantitative approach has been embodied in several studies, 2 of which are particularly outstanding. Cobb and co-workers set up a well-planned study to test whether any relief of symptoms was produced by the procedure and, if so, whether this was greater than a placebo effect. Seventeen patients seriously limited by angina

agreed to cooperate. They recorded the number of anginal attacks occurring, and the number of nitroglycerin tablets required before, and at specified intervals after, the operation. In addition, a standardized exercise-tolerance test was given before and after operation; so were determinations of respiratory efficiency, blood pressure, and electrocardiograms made during rest and during exercise. The procedure was done under local anesthesia, and only at the time of operation was the surgeon given a card to tell him whether to ligate the arteries or only to make skin incisions. The patients were asked to estimate their improvement, if any, at intervals during the post-operative period. They had been told merely that they were participating in an evaluation of the operation, and were not aware of the double-blind nature of it. The observers did not know, when evaluating the data, whether ligation had been carried out or whether only a skin incision was made. It was quite evident that ligation produced no greater benefit than the sham operation.

It would be a mistake to give weight to a case or 2, but in conjunction with similar material it is interesting to observe that in one patient of this series (not ligated) the skin incisions permitted 10 minutes of exercise without pain and without electrocardiographic abnormality 6 weeks after operation, whereas 4 minutes of exercise before surgery led to pain and striking inversion of T waves. Greatly increased work tolerance and remarkably decreased consumption of nitroglycerin—both easily expressed in objective terms—are the usual findings of nearly all investigators. It is of such "convincing" objective stuff that new operations are made.

* * *

One could argue that, since placebos have considerable therapeutic power, the benefit obtained from them is sufficiently great to justify the risk involved. This point of view hardly holds up when the price may be life itself.

Our aim in medicine is to relieve often, and to cure when we can. Placebo effects are not to be despised; they play a part—sometimes a very important part—in surgical success; but we would be deceived by our own maneuvers if we fail to find out when placebo effects may be the sole agents functioning in a given case. Having understood this, we have gone a long way to control the destructive force of bias.

* * *

NOTE 2.

JULIAN M. RUFFIN, JAMES E. GRIZZLE,
NICHOLAS C. HIGHTOWER, GORDON MCHARDY,
HARRISON SHULL, AND JOSEPH B. KIRSNER
A CO-OPERATIVE DOUBLE-BLIND
EVALUATION OF GASTRIC "FREEZING" IN
THE TREATMENT OF DUODENAL ULCER*

* * *

Gastric "freezing" for the treatment of duodenal ulcer was introduced by Wangensteen and his associates in 1962, and its usefulness was promptly supported by further investigation. Subsequently, this method of treatment was used in many small clinical groups throughout the country. However, the enthusiasm of early publications was soon followed by a wave of skepticism. . . .

In recognition of this need, a double-blind study was initiated in 1963 and conducted simultaneously in five institutions. . . . The same criteria were used by all five institutions in selection of patients, and identical methods employed in the "freezing" procedure, collection of data and evaluation of results. . . .

The specific [objective of the study was]: to evaluate the effects of gastric "freezing" on the natural history of duodenal ulcer. . . .

* * *

The procedure adopted for this study was that proposed by Wangensteen et al. A Swenko hypothermia machine was used in all institutions. The volume of coolant (95 per cent ethyl alcohol) in the gastric balloon ranged from 550 to 700 ml in all the patients. . . . The temperature of the coolant returning to the hypothermia machine from the gastric balloon was maintained at -10°C , and the flow rate of the coolant was maintained between 1200 and 1400 ml per minute. The duration of the procedure (time of circulation of coolant within the balloon) was 50 minutes in all patients.

* * *

An attempt was made to have every aspect of the sham gastric "freeze" identical to the true "freeze" with the one exception of the temperature of the coolant circulating in the balloon. Thus, the exact procedure as described for gastric "freezing"—preparation of patient, volume

of coolant in gastric balloon, duration of procedure and monitoring—was followed.

* * *

The follow-up study was conducted by a physician who was unaware of which procedure had been employed. Provision was made to break the code for the protection of the patient's welfare if the need arose.

* * *

The results of this study demonstrate conclusively that the "freezing" procedure was no better than the sham in the treatment of duodenal ulcer, confirming the work of others. There was no significant difference in relief of pain, secretory suppression, number and severity of recurrences or development of end points in the two groups. It is reasonable to assume that the relief of pain and subjective improvement reported by early investigators was probably due to the psychologic effect of the procedure.

The importance of random assignment of patients to treatment and the double-blind method in clinical trials has been emphasized repeatedly, but these features are still too frequently ignored. Only by strict adherence to such principles and resisting the urge to publish until data have been gathered by these rigorous methods will false leads be kept to a minimum and erroneous conclusions avoided.

NOTE 3.

ABRAM HOFFER
A THEORETICAL EXAMINATION OF
DOUBLE-BLIND DESIGN*

There are at least three major variables in any therapeutic program. The first is that feeling of trust or faith the patient has in his doctor and, therefore, in his therapy. The second factor is the faith or confidence the physician has in himself and in the line of therapy he proposes to use. The third factor is the therapy. The best results are obtained when all three variables are set at their optimum level. . . .

* * *

The double-blind technique makes it difficult to sustain these two variables at their optimum level. It is hardly likely that a doctor will have as much faith in a new drug as he does in drugs with which he is familiar, and when he

* 281 *New England Journal of Medicine* 16-19 (1969). Reprinted by permission.

* 97 *Canadian Medical Association Journal* 123, 124 (1967). Reprinted by permission.

is forced to work in a double-blind way his faith and enthusiasm are reduced to a very low level. It has been our tradition for centuries to abhor the use of placebo or trickery. For centuries doctors have condemned quacks. In the Middle Ages the only difference between quacks and doctors was that while the doctors were more honest, the quacks were more intelligent. Quacks knew their remedies were no good and so sold atmosphere, displays, catharsis and other trappings of non-medical faith. Doctors used similar remedies which were no more therapeutic, but they did have faith in their efficacy. In the end the doctors won because therapies in which we can justly have great faith developed.

* * *

NOTE 4.

DAVID W. MEYERS
THE HUMAN BODY AND THE LAW*

* * *

One ethical difficulty posed by much of medical experimentation is its inevitable reliance on a 'control group': those who take sugar pills, for example, instead of a penicillin derivative and are used as a measure to determine the effects of the experimental substance or treatment. These people must consent to undergo the full rigours of the experimental therapy and cannot be told they will serve only as decoys. This, of course, involves a subtle but patent series of misrepresentations and may be ethically unpalatable to some. However, it is submitted, such a practice is generally recognized as inherent in many experiments involving more than one individual, and people, in offering themselves to act as subjects for (non-therapeutic) experimentation, must be presumed to have understood and accepted this fact.

* * *

NOTE 5.

CHAUNCEY D. LEAKE
ETHICAL THEORIES AND HUMAN
EXPERIMENTATION†

* * *

In designing an experimental study with human subjects, clinical pharmacologists usually devise some sort of a double- or triple-blind technique,

where neither subject, experimenter, nor observer knows whether the test drug or a placebo is being used. It is often claimed that the subject should not even know what the purpose of the experiment may be, in order not to jeopardize the objectivity of the findings. In my opinion, this is not wise. Let the subject know just as much about the design of the study as the experimenter, even to the point of explaining that drugs may be interchanged, with erroneous hints as to how they may act. Such a method could control the possible subjective notions of the experimenter as well as of the subject.

* * *

NOTE 6.

LOUIS LASAGNA
DRUG EVALUATION PROBLEMS IN
ACADEMIC AND OTHER CONTEXTS*

* * *

When one is trying to diminish prejudice for or against a remedy, however, it is probably preferable, at least scientifically, for subjects and observers to be kept in the dark. To begin with, patients told that they may receive a placebo may refuse to participate in the trial. If such refusals are few, they need not inconvenience the experimenter or the experiment. But if they are frequent, not only will the trial be prolonged, but the generalizations possible at the end may be seriously limited, in view of the possibly atypical nature of the sample.

It may be argued that such problems are unfortunate but unavoidable if one is to respect an individual's freedom to say "No." Indeed so. But since society hedges on individual liberties in all sorts of other situations, is it not desirable at least to consider the possibility that individual freedom—provided serious harm is not involved—may have to yield at times to the general welfare?

Placebo trials pose no serious ethical problems for me in most situations: If the true merit and hazard of a new remedy are not established, it is unethical not to perform a proper controlled trial (which may, to be sure, use a standard drug for comparison, rather than a placebo, if such a standard is available). Too often the placebo-treated patients turn out to be the lucky ones in such a trial, "deprived" only of an ineffective and toxic chemical.

I do object, however, to such deceit as the

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† 169 *Annals of the New York Academy of Sciences* 393-394 (1970). Reprinted by permission.

* 169 *Annals of the New York Academy of Sciences* 506 (1970). Reprinted by permission.

use of homeopathic doses of drug as placebo so that patients may be told that they will receive only "varying doses of active drug." It also strikes me as unacceptable to disguise the placebo treatment as "a standard and time-honored remedy that is safe and has been proven to help many people" (true though the statement is!).

On the other hand, I submit that telling patients they will or may receive a placebo changes the rules of the game, with unpredictable Heisenbergian impact. It is a bit like bugging a jury room to observe the jury process at work. It may be reprehensible to do so without asking consent of the jurors, but who would pretend that the behavior of the jurors will be unaffected by the knowledge that they are under surveillance?

* * *

NOTE 7.

THOMAS C. CHALMERS AND LOUIS LASAGNA
EXPERIENCE IN DESIGN, CONDUCT, AND
EVALUATION OF RESEARCH*

DR. CHALMERS: . . . One may explain in great detail the hazards of both procedures, stating that, because one does not know which hazard is greater for the patient, we're going to flip a coin or randomize. Objection can be raised to that technique as bad medical care, because any sensible patient could draw two conclusions from such an elaborate explanation of the technique regarding a decision for surgery; namely, that if the physician can't make up his mind about the operation, the patient will find a doctor who can, or if the difference between surgery and medicine is so small that an elaborate study is required, the patient will choose medical therapy.

In either case, the patient ends up being deprived of the operation. If it should turn out that the operation is better, then we have practiced improper medicine, because we have deprived half of the patients of the opportunity of having the operation. This probability would be an ethical argument in favor of not explaining in great detail the randomization procedure.

On the other side, there is the experience of a number of physicians who explain randomization as a method of deciding on an elective operation to a patient who is not very sick. They claim that full explanation pays off, and the explanation to the patient is proper. Obviously, it is proper, but this depends on what we call full ex-

planation in terms of the details one presents to the patient concerning the operative procedure.

So we must conclude that it depends on what the physician investigator thinks best for his patient. It may be very bad for a sick patient selected for trial of emergency surgery or portacaval surgery to be given all the gory details. In such a case, it may be better medical care or therapy not to explain fully—despite the basic obligations to disclose. However, the family must be kept fully informed.

DR. LASAGNA: The ethical problem here comes in making it clear to potential patients or volunteers what the situation is; namely, that you have two surgical techniques or a surgical technique and a nonsurgical technique of which the relative merits are not known. I assume that you don't do the experiment unless that situation pertains. Now, if that point is made clear, and the willingness of the subject to have one or the other form of therapy is clear, then I submit that it's pointless and cruel to say, "By the way, now we're going to decide by pulling cards out of the file." It seems to be that you can say, "Are you willing to take whichever one is decided for you to undergo?" If the patient then asks how that decision is to be made, you shouldn't lie about it. But why should you go out of your way to detail how the decision is made? I really don't see that. I know some people do, but I think that would be heinous.

DR. CHALMERS: This is the way I feel also.

* * *

[iii]

Lee C. Park, L. Covi, and E. H. Uhlenhuth
*Effects of Informed Consent on Research
Patients and Study Results**

Recent rulings by the National Institutes of Health about research grant applications require a detailed description of the manner in which informed consent of research subjects is obtained. Many researchers have been alarmed by the possibility that informing patients of the research nature of their treatment will severely limit the validity of results. Negative effects of informed consent in patients would include: resentment about being used as research subjects or about being given supposedly inactive treatments (for instance, placebo); anxiety resulting from knowledge that treatments are assigned arbitrarily; poor response to treatments which might be

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* 145 *Journal of Nervous and Mental Disease* 349-354 (1967). © 1967, The Williams and Wilkins Co., Baltimore, Md. Reprinted by permission.

effective in a positively oriented nonresearch atmosphere. Another issue would be the researcher's anxiety and guilt about "using" patients, which might be alleviated by the patient's ignorance of research goals.

With regard to the patient's resentment of inactive treatments, Liberman stated, "If subjects were forewarned of placebo administration, many would not cooperate with the experimenter—such candid statements of placebo use early in the experiment would engender suspicion and perhaps hostility in subjects, making them undesirable if not unwilling candidates for placebo research." However, he did note that when the use of placebo was revealed to patients at the end of his experiment, "Almost all the subjects reacted to the disclosure in a relaxed fashion. Some expressed surprise but most were unruffled and left the room without any sign of resentment or dismay." Bukanz stated, "Indeed, I have been told by some highly qualified investigators that their patients are increasingly reluctant to sign the required consent form, particularly if the use of placebo is involved. It is very difficult to explain to a patient why he should be the one to voluntarily agree to receive no medication if the luck of the draw runs that way. His concern, quite justifiably, is with his own health, not with the advancement of medical knowledge." Similarly, Lasagna stated, "This business of consent has already deterred some investigators from doing research." He reported that a recently proposed study was dropped because less than 20 per cent of the informed patients agree to sign the consent form and he questioned whether valid results could be obtained from such a selective population.

With regard to the possibility that premature disclosures might bring about faulty study findings, Liberman wrote, "To bring greater understanding into the dynamics of placebo reactivity, placebo research must be carried out under conditions as nearly similar to those occurring in *real* drug experiments as possible." Fisher, Cole, Rickels and Uhlenhuth stated: "Patients more often see themselves as being 'treated' rather than 'researched,' and this may provide a highly favorable setting for drug action. In many controlled experiments, the patients become definitely aware that they are participating in a research project (implying 'Let's see if the drugs will help you'), and such a perception could tend to inhibit drug action."

With such an atmosphere of negative expectations, there have been few attempts to evaluate objectively the pros and cons of these issues.

Over the last few years, we have participated in a number of clinical psycho-pharmacological studies in which careful concern was given to patients' attitudes and concerns about research procedures, although at the time it was still considered necessary for valid findings that patients be kept unaware of key facts indicating the research nature of their treatment. In this paper, we present material from some of our studies in which patients have been given information and instructions not usually given in such research and have nevertheless consented to participate. In addition, we discuss the findings of a survey in which patients were asked about their perceptions of the research procedures and goals in a drug study just completed.

In an 8-week double-blind, cross-over study of the effectiveness of imipramine and placebo on neurotic depressed outpatients, carried out in 1959-1960, Uhlenhuth and Park formulated the following statement for the patients: "The kind of trouble you have been telling me about often responds quite well to medicine. We now have two different medicines available that we know help many people with difficulties like yours. However, some people do better with one and other people do better with the other medicine. The best way to find out which of the two medicines is best for you personally is to try them both. So we have set up a treatment program which will give you the opportunity to do just that. You will be able to take each medicine for 4 weeks. At the end of 8 weeks, if necessary, you may continue to take whichever medicine works best for you." This was presented to the patients as treatment rather than as research, although such a presentation of alternative treatments is not made in the usual treatment setting. Rather, patients are usually given one medicine and advised it will help them; then, if the medicine doesn't work, the doctor subsequently may switch to another medicine.

Nevertheless, neither the 42 patients who completed the treatment nor the 8 patients who dropped out indicated any particular interest or concern about this manner of presentation. On follow-up, it was determined that 2 patients were dropped because they were hospitalized, 2 obtained jobs which interfered with appointments, 1 complained that the medicine wasn't helping, 1 complained of side effects, and 1 was ill with a medical condition. There is inadequate information on the other patient. There is some evidence of possible factors influencing drop-outs. For instance, 4 of the 8 drop-outs were patients of one of the seven treating doctors. Thus, informing

patients of an experimental manipulation of medicine—in their own interests—did not appear to result in drop-outs, and, in fact, the study doctors reported that patients appeared to accept the rehearsed speech without reservation. . . .

* * *

To explore . . . the possibility of breaking with the traditional taboo of informing patients of the research nature of treatment, Park and Covi in 1963 carried out a brief (1-week) non-blind treatment of 15 anxious patients with placebo. Each patient was told, "Mr. Doe, at the intake conference we discussed your problems and your condition, and it was decided to consider further the possibility and the need of treatment for you before we make a final recommendation next week. Meanwhile, we have a week between now and your next appointment, and we would like to do something to give you some relief from your symptoms. Many different kinds of tranquilizers and similar pills have been used for conditions such as yours, and many of them have helped. Many people with your kind of condition have also been helped by what are sometimes called 'Sugar Pills' and we feel that a so-called sugar pill may help you, too. Do you know what a sugar pill is? A sugar pill is a pill with no medicine in it at all. I think this pill will help you as it has helped so many others. Are you willing to try this pill?"

Surprisingly, 14 patients completed the treatment and showed symptomatic improvement as a group, on a 65-item symptom checklist, to a greater degree than patients in our double-blind studies of drugs and placebos. In this study, in which patients were asked to participate for only 1 week, no patients showed the expected resentment, although some were skeptical, and some showed friendly amusement, accompanied in at least 1 patient by a report of symptomatic improvement even before the "treatment" began. Furthermore, the social worker who interviewed some of the patients after the study reported that they were very different from patients seen after other drug studies: they appeared much more verbal, comfortable, inquisitive and free with comments.

In spite of the fact that each patient was told the pills were placebos, only three patients were certain of this after the week of treatment. Five additional patients thought the pills probably were placebos. On the other hand, two patients thought the pills definitely contained drugs and four thought they probably contained drugs. Thus, there appeared to be limits in the capabil-

ity of the experimenter to influence established concepts in the patients.

* * *

We learned that clinic outpatients come into our studies with deep feelings of trust and expectations of marked improvement, and they often do not believe they are subjected to research or are given inert medication, even when research paraphernalia are obvious or they are informed of the nature of the treatment. They will obediently perform "unusual" tasks in "unusual" settings without question. In some of our research, patients were given information usually withheld because such knowledge might have a detrimental effect on patients and study results. We found no evidence that this information had negative effects on either patients or findings.³

* * *

A basic purpose of this paper is to suggest that the present anxiety about informed consent may be based partly on preconceived bias and that the process of informing patients is worthy of research in itself. Orne pointed out, "If one were to employ any form of deception, it is crucial to find out whether it is the subject or experimenter who is deceived." We make assumptions that some information may have negative effects and even that some may have positive effects, but there has been little objective experimentation to test these assumptions with distressed patients as opposed to volunteer subjects.

2.

Safeguarding "Life"

a.

How Much Should the Dying Patient Know?

[i]

Donald Oken

*What to Tell Cancer Patients—A
Study of Medical Attitudes**

No problem is more vexing than the decision about what to tell the cancer patient. . . . The manner in which such questions are handled is

³ Our findings, of course, may have been biased by patients' high expectations about Johns Hopkins Hospital as a prominent medical center. Perhaps patients would be less willing to participate as informed research subjects in a small or less-known clinic.

* 175 *Journal of the American Medical Association* 1120-1126 (1961). Reprinted by permission.

crucial for the patient and may determine his emotional status and capacity for function from that time on. It is easy enough to decide to follow a course which will "do least harm," but it is far from simple to determine just what course that is. . . .

* * *

The research on which this report is based represents a further attempt to study physicians' approaches to the problem of what to tell cancer patients. The aim here has been not merely to learn what is done but, more importantly, to understand the attitudes which are underlying determinants of these strategies. . . .

* * *

The initial undertaking in this research was the determination of whether or not physicians tell their patients they have cancer. [T]here is a strong and general tendency to *withhold* this information. Almost 90 percent of the group is within this half of the scale. Indeed, a majority tell only very rarely, if ever. No one reported a policy of informing every patient. . . . No difference between specialties was uncovered. . . . These findings also cut across the hospital staff rank and age. Younger and less experienced men did not have any greater inclination to tell than their seniors.

Use of a questionnaire, of course, forces answers into an artificially rigid mold. But, information derived from the interviews strengthens the finding. Answers indicating that patients are told often turned out to mean telling the patient that he had a "tumor," with strict avoidance of the terms cancer, malignancy, and the like. These more specific words were almost never used unless the patient's explicit and insistent questioning pushed the doctor's back to the wall.

Euphemisms are the general rule. These may extend from the vaguest of words ("lesion," "mass"), to terms giving a general indication that the process is neoplastic ("growth," "tumor," "hyperplastic tissue")—often tempered by a false explicit statement that the process is benign; to a somewhat more suggestive expression (a "suspicious" or "degenerated" tumor). Where major surgical or radiation therapy is involved, especially if the patient is hesitant about proceeding, recourse may be had to such terms as "pre-cancerous," or a tumor "in the early curable stage." Some physicians avoid even the slightest suggestion of neoplasia and quite specifically substitute another diagnosis. Almost every one reported resorting to such falsification on at least a few occa-

sions, most notably when the patient was in a far-advanced stage of illness at the time he was seen.

It is impossible to convey all the flavor of the diverse individual approaches. No two men use exactly the same technique. Each has his preferred plan, his select euphemisms, his favored tactics, and his own views about the optimal time for discussion and the degree of directness to be used. Some have a set pattern, while others vary their approach. But the general trend is consistent.

The modal policy is to tell as little as possible in the most general terms consistent with maintaining cooperation in treatment. Exceptions are made most commonly when the patient is in a position of financial responsibility which carries the necessity for planning. Questioning by the patient almost invariably is disregarded and considered a plea for reassurance unless persistent and intuitively perceived as "a real wish to know." Even then it may be ignored. The vast majority of these doctors feel that almost all patients really do not want to know regardless of what people say. They approach the issue with the view that disclosure should be avoided unless there are positive indications, rather than the reverse. Intelligence and emotional stability are considered prerequisites for greater disclosure only if other "realistic" factors provide a basis for doing so. For the fewer physicians who tell with some frequency, these two factors assume more primary importance.

A few additional consistent themes emerge. Agreement was essentially unanimous that some family member must be informed if the patient is not made aware of the diagnosis. Legal and ethical considerations are by no means the only points of relevance here. Repeated instances were reported of patients who, dissatisfied with the progression of their disease in the face of treatment and desperate for help, were dissuaded from fruitless and unwise shifts to a new physician (or quack) only by the cooperation of an informed relative. Beyond this is the need to have someone to share the awful burden of knowledge. As one man put it, "I just can't carry the load alone." Few responsibilities are as heavy as knowing that someone is going to die; dividing it makes it easier to bear.

Variations in approach also converge to a single major goal: maintenance of hope. No inference was necessary to elicit this finding. Every single physician interviewed spontaneously emphasized this point and indicated his resolute and determined purpose is to sustain and bolster the

patient's hope. Each in his own way communicates the possibility, even the likelihood, of recovery. Differences revolve about the range of belief about just how much information is compatible with the maintenance of hope. While some doctors believe "cancer means certain death and no normal person wants to die," others hold that "knowledge is power": power which can conquer fear. The crux of the divergence centers on two issues: whether cancer connotes certain death, and whether the expectation of death insurmountably deprives the patient of hope. The data indicate that an impressively large number of physicians would answer affirmatively to both.

The approach used by a physician may derive from many sources. Perhaps he acquired it as a result of teaching in medical school or while a house officer; maybe it grows out of his own clinical experience or is a result of personal experiences with afflicted friends and family; it may arise as a result of reading; or perhaps it is a personal conviction which stems from the deeper influences of his personality and individual philosophy. . . .

* * *

Clinical experience would seem to be of overwhelming importance. Only 6 percent (12 of 203) failed to list this as a factor. Other sources are reported with far less frequency, and if reported at all, usually in addition to clinical experience, which is the factor accorded primary importance by more than three-quarters of the group. Medical school teaching apparently plays a minimal role. Internship and residency training is somewhat more often listed. . . . Few people could remember hearing about the subject during their training. When someone did, usually there was no recall of anything specific said, other than the emphasis of the need of the physician to deal with the problem. This silence, like the lack of research, is striking. . . .

Personal factors are reported by only a moderate number of the group. The experience of seeing a close relative (most commonly a parent) die of cancer, was a decisive occurrence for some. This experience, however, did not lead to any difference in policy between these physicians and the group as a whole; they were neither more nor less likely to tell. Less concretely derived personal feelings were reported by a small group. These responses, comprising all but two of those listed as "other," were described in such terms as "my philosophy of life," "my personal

conviction," or "projecting myself into the patient's situation." Interestingly, if such a feeling was reported at all, there was a strong likelihood that it was considered the determining factor.

* * *

[E]xperience can be acquired only over a span of time. A young group, whose graduation from medical school has taken place not many years earlier, might be expected to report that their policy stems largely from other sources. At least they should cite experience less often than their seniors. This is not the case. The group under 45 years of age, or those in the lower staff ranks, are just as likely to list experience as a factor as their older colleagues. Indeed, they are no less likely to cite it as the major determinant. The mean age and the staff level of those who reportedly base their policy on experience does not differ from those who do not. Nor do the policies of the two groups differ.

Experience, moreover, implies a state of knowledge based upon a range of earlier observation, with the opportunity to become familiar with the outcomes of various alternatives. Occasions for some such experience, of course, have been available to all these physicians. Yet only 27 (14 percent) have had the opportunity for first-hand knowledge based on their own trial of any policy different from their current one. More detailed exploration in the interviews cast a great deal of further doubt about the role of experience. It was the exception when a physician could report known examples of the unfavorable consequences of an approach which differed from his own. It was more common to get reports of instances in which different approaches had turned out satisfactorily. Most of the instances in which unhappy results were reported to follow a differing policy turned out to be vague accounts from which no reliable inference could be drawn.

Instead of logic and rational decision based on critical observation, what is found is opinion, belief, and conviction, heavily weighted with emotional justification. As one internist said: "I can't give a good reason except that I've always done it." Explanations are begun characteristically with such phrases as "I feel . . ." or "It is my opinion. . . ." Personal convictions were stated flatly and dogmatically as if they were facts. Thus, "Most people do not want to know," "It is my firm belief that they always know anyway," or "No one can be told without giving up and losing all hope." Highly charged emotional

terms and vivid expressions were the rule, indicating the intensity and nature of feelings present. Knowledge of cancer is "a death sentence," "a Buchenwald," and "torture." Telling is "the cruelest thing in the world," "awful," and "hitting the patient with a baseball bat." It is not necessary even to read the words on the questionnaires. Heavy underlinings and a peppering of exclamation points tell the story. These are hardly cool scientific judgments. It would appear that personal conviction is the decisive factor.

There is direct confirmation of this point. *Subsequent* to the general inquiry: "How did you acquire your policy?" it was specifically asked if personal issues were determinants. Nearly three-fourths (98 of 138) reported that personal elements were involved, in contrast to the much smaller number who listed this originally. These 98 were about equally divided as to whether these factors were the most important.

* * *

Another relevant finding is the doctor's wish to be told if he were the patient. As expected, those who tend to tell their patients wished to be told, themselves, more often than those who do not tell. But the total number of those who said they wished to be told (73 of 122) is far greater than those who tend to tell their patients. The explanation usually given was that, "I am one of those who can take it" or "I have responsibilities." That they did not feel this to be true for all physicians, however, is attested to by their treatment of other doctor-patients. Most of the group said they were neither more nor less likely to tell physicians than other patients. Of the group who did modify their policy, it was just as likely to find that they were *less* prone to tell doctors. It is impossible to draw any precise conclusion from this type of hypothetical question about one's self. But the inconsistency is characteristic of emotionally determined attitudes.

The pros and cons of telling have been discussed so often that there is little point in doing so again. Whatever the reasons for telling, the argument against doing so centers on the anticipation of profoundly disturbing psychological effects. There is no doubt that this disclosure has a profound and potentially dangerous impact. Questions do arise about the capacity of human beings to make a satisfactory adaptation to the expectation of death. Can anyone successfully handle such news without paying a price which mitigates whatever value this knowledge brings? If so, how widespread is the ability to call forth

the necessary psychological defenses? What about time: does this readjustment take place within some reasonable span? Can the emotional cost of such a shattering experience, or of the effort required for mastering it, be weighed and predicted? The truth is that we know very little about these matters.

It has been repeatedly asserted that disclosure is followed by fear and despondency which may progress into overt depressive illness or culminate in suicide. This was the opinion of the physicians in the present study. Quite representative was the surgeon who stated, "I would be afraid to tell and have the patient in a room with a window." When it comes to actually documenting the prevalence of such untoward reactions, it becomes difficult to find reliable evidence. Instances of depression and profound upsets came quickly to mind when the subject was raised, but no one could report more than a case or two, or a handful at most. This may merely follow from the rarity with which patients are told. Such an explanation must be reconciled with the fact that these same doctors could remember many instances in which the patient was told and seemed to do well. It may also reflect the selection of those told. Or perhaps the knowledge produces covert psychological changes which are no less malignant for their subtlety. But actually, the incidence and severity of depression and other psychological reactions in cancer patients, and their relation to being told, are not known.

The same situation holds with regard to suicide. Only 6 doctors could report definite known cases of suicide (2 of these reported two cases and 1 "several"), although about one-third of the group had "heard of" suicides after being told. Further investigation indicated that at least 2 of these patients had never been told. (And it is not altogether inconceivable that they would have felt better, not worse, had this been done.) Actually, the circumstances surrounding all but one or two of these cases are quite vague; it is impossible to feel any certainty about what lay behind the suicide.

* * *

Among the motivations for entering medicine, the wish to conquer suffering and death stands high on the list. Practicing physicians are not the kind of persons who can sit quietly by while nature pursues its course. One of the hardest things for a fledgling medical student to learn is watchful waiting. Few situations are as frustrating as sitting by impotently and "helplessly"

in the face of illness. Fatal illness is felt as a major defeat. . . .

NOTE

HERMAN FEIFEL
THE FUNCTION OF ATTITUDES
TOWARD DEATH*

* * *

An interesting contrast emerges in comparing studies of physicians and patients as to whether the physician should tell or should not tell the patient he is dying. Sixty-nine to 90 per cent of physicians, depending on the specific study, are in favor of not telling the patient. In opposing vein, 77 to 89 per cent of the patients want to know. Our outlook as physicians may be too conditioned by the "healthy" rather than by the seriously ill and the dying.

* * *

[ii]
A Physician
Should Doctors Tell the Truth
to a Cancer Patient?†

* * *

Not so long ago I had to decide whether to tell a patient of mine—a man in his sixties who had just retired from an active, successful career—that he had cancer. I thought a lot about it. In the end I decided not to tell him. I told his children—they were all grown—and they agreed that their father should not be told. Nor should their mother. "Not yet. They've made so many plans for his retirement. If he has a little time, we would like it to be happy time."

The man did have time, he lived quite comfortably for three years. He and his wife traveled and saw a lot of the world. Together they were happy doing all the things he had been too busy to do when he was working. At the end he went pretty rapidly, without prolonged suffering. Two days before his death the children told their

mother the truth. She was very angry with me because I had not told her in the beginning.

"If you had known," I asked, "could you and Bob have enjoyed these last three years?"

She looked at me for a moment. Her eyes were wet, but she went on with the honesty and insight that often come to help people through their hardest hours. "No. No, we couldn't have. Worse, I couldn't have kept the truth from Bob. I've never been able to keep a secret from him."

I think I was right in not telling that patient the truth.

When I was a young doctor I once told a patient flatly that he had inoperable cancer. He was a man in his middle years, respected and successful. He had asked for the truth and he seemed to me to be the sort of man who could take it. But when I told him, he went into shock right there in my office. He never had a happy or relaxed moment until his death some months later. It was a terrible ordeal for him and for his family. And much of it was unnecessary. If I had withheld the truth, or given him only a part of it, some of his remaining months might have been good.

I never forgot that man. I thought of him every time I had to decide whether or not to tell the truth to another patient suffering from incurable cancer. In many cases it began to seem wiser and kinder not to tell. Until one day I found myself looking a patient straight in the eye and saying in reply to a direct question, "No, of course you don't have cancer!" She was a tense, nervous person who had overcome deep apprehension, fear and dread to ask me this question. She was in no state to hear the truth and probably could not accept it without severe emotional damage. She probably had a year or more of reasonably comfortable life ahead. There was a chance of keeping it a happy time for her. Her family had been told the truth about her illness. They wanted it kept from her. And so I lied.

The patient had almost two good years. I think that somewhere in her mind she knew the truth—it is my belief that most people do—but she never asked me the direct question "Do I have cancer?" again. I think most people know without being told. They don't want it put into words. Perhaps in the beginning they do, or think they do, but later on, when they are not feeling so strong, I think they are glad those words are not there.

Now in medicine you always tell the truth—98 per cent of the time. You couldn't practice good medicine if you didn't. And if you find that a patient has cancer, his family must be told even

* *Death and Dying—Attitudes of Patient and Doctor* (Symposium No. 11). New York: Group for the Advancement of Psychiatry 632, 635 (1965). Reprinted by permission.

† *Ladies Home Journal* 65, 108 (May 1961). © 1961, Downe Publishing, Inc. Reprinted by special permission of the Ladies Home Journal.

if the patient himself is not. For a doctor to take on his own shoulders the responsibility of withholding such knowledge is unfair to everyone, including the doctor. . . .

* * *

The patient's own temperament has a lot to do with whether or not you tell him. To some highly intelligent people—like John Foster Dulles or Robert A. Taft—you can tell the simple truth and know that it is not going to destroy them as human beings. Their minds and their emotions are capable of absorbing the knowledge and adjusting to it rationally. A person with less understanding and self-control might not be able to do this. Being told the truth could prove an overpowering shock. He might become so emotionally unstable that he would have to be treated as a mental patient as well as a cancer patient. This makes it tragically harder, not only for him but for his family.

Sometimes you must tell the truth to a man who has a highly responsible job involving the welfare of other people. Or a man who owns his own business and has no relatives or partners to take over. Such men would want—and I think should have—the truth, because they must find someone to carry on for the sake of the many other people who may depend on them.

* * *

Recently a patient of mine, a famous athlete, had to be operated on for an intestinal ailment. We knew right away that we were too late. There was nothing to do but close the incision. His wife and I decided not to tell Jack the truth. He thought that his weakness and loss of weight were simply the aftereffects of surgery and he stayed quite cheerful. He never said a word about cancer.

One day when I stopped in to see him, he grinned and showed me a letter written to him by a friend who had had diverticulitis and made a good recovery from it. "The symptoms were just like yours, Jack," the letter said. Jack lived on that letter. He must have quoted it and showed it to me a dozen times.

Two weeks later Jack died. I had visited him on the morning of that day. "Hello, Jack," I said, "you're looking better today." I meant simply that he was looking better than he had yesterday, but Jack smiled in a pleased way. Later, when I talked to his wife, she said quietly, "Doctor, do you know what Jack told me after you

visited him this morning? He said, "Mary, the doctor says I'm getting well!" "

Mary loved him. He was my friend as well as my patient. We were both happy that Jack could die thinking he was getting well.

NOTES

NOTE 1.

ARTHUR H. BECKER
THE PATIENT WITH A FATAL ILLNESS—
TO TELL OR NOT TO TELL*

* * *

As a hospital chaplain, I have found, however, that the patient hesitates to ask the physician for a variety of reasons: a fear of displaying lack of trust in the doctor, the feeling that the doctor himself is threatened by the possibility of death, or the feeling that the doctor either does not have time, or is not willing to sit down and "work through" the implications of the information with the patient. . . .

* * *

NOTE 2.

THOMAS P. HACKETT AND AVERY D. WEISMAN
WHEN TO TELL DYING PATIENTS THE TRUTH†

* * *

[A] woman with a terminal breast cancer [after weeks of apparent serenity] asked her doctor whether the headache she'd been having might be due to nerves. The doctor said it might—and then asked her why she was nervous. Her reply: "I've lost sixty pounds in a year. The priest comes to see me twice a week when he hardly came at all before. And my mother-in-law's nicer to me than ever, though I'm meaner than ever to her. Wouldn't you be nervous, too?"

There was a pause. Then the doctor said, "You mean you think you're dying?" She said, "I do." He said, "You are."

The smile she gave him actually expressed relief. "Thank God," she said. "Someone's finally told me the truth!"

* * *

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† *Medical Economics* 81, 84-85 (December 4, 1961). Copyright © 1961, by Medical Economics, Inc., A Subsidiary of Litton Publications, Inc., Division of Litton Industries, Inc., Oradell, N.J. Reprinted by permission.

NOTE 3.

J. M. HINTON

THE PHYSICAL AND MENTAL DISTRESS
OF THE DYING*

* * *

As at least three-quarters of the patients here studied became aware that they were probably dying, the question "Should the doctor tell?" loses much of its force. The problem becomes rather more ordinary and more capable of solution. It resolves itself into discovering what the patient knows, and how much more he really wants to know, information that can be gathered with no distress in a quiet, unhurried conversation. Many writers, including Cappon, have felt that it is not justifiable to tell a patient a fact about his approaching death which he does not consciously want to know. This opinion against supplying such gratuitous information was supported in the present study by evidence that awareness was associated with depression and anxiety. This association was found at the initial interview; and the 34 patients who became more aware of dying became at the same time more anxious or depressed. But if a patient sincerely wanted to know his possible fate, and was met by prevarication or empty reassurance, he felt lonely and mistrustful. Then, commonly, while a young nurse was caring for the patient, the vital question was put to her, to the potential embarrassment and distress of both. In my opinion, if the awareness of the patient is so great that he has formulated the question, an honest answer which does not seek to destroy all hope will not add to his distress. Gavey has said that there is more room for frankness in intelligent patients; but in the present study the length of education and the social class, in so far as they indicated intelligence, made no significant difference to mood or to the awareness of dying. It is very probable that a doctor feels better able to tell an intelligent patient, but this does not necessarily mean that the less intelligent may not cope with this knowledge just as well. There are occasions when a patient experiences anguish, ineffectively trying to thrust out the fear that he may die, but yet vaguely aware that he may need to accept the possibility. Leading the patient into talking of this, and not denying the situation, enables an adjustment to take place with less distress. The few patients in the present series who were told that they had a tumour, or some other potentially lethal condi-

tion, were usually sad for one or two days, and then appeared to come to terms with this knowledge. If given some positive information about the plan of treatment they usually kept this in the forefront of their minds, and gained great comfort thereby. The courageous acceptance of the situation by the majority of these patients, and their appreciation of the frank discussion with their doctor, were in accord with the findings of Aitken-Swan and Easson; two-thirds of their patients were glad that they had been told that they had cancer, and only 7 per cent resented such frankness. . . .

[iii]

Paul Rhoads

*Management of the Patient
with Terminal Illness**

* * *

[H]e must tell the patient the facts of his physical condition as truthfully and as fully as the patient wishes to know them—always with a liberal admixture of understanding and hope. Just how and how soon this is to be done will vary with each individual, but it is my firm conviction that, with few exceptions, it must be done. Many patients will make it clear that they do not want to be told the whole truth, whether they say it in so many words or not. And, of course, their wishes must be respected. Most will, in the end, have to be told by someone.

* * *

I was astonished to learn of a survey of the views of a liberal sampling of physicians on this point, in which more than 70 percent stated that they usually did not inform patients that they were facing a terminal illness. Some even attempted to justify giving false information about the diagnosis if they felt patients were unprepared to accept the truth. . . . My own conviction is that never, under any circumstances, should patients be told untruths. This is the surest way to destroy the mutual trust and respect which, in the end, may prove to be the most important therapeutic asset the physician possesses.

William Bean in his essay "On Death" has stated well the attitude I share:

I cannot conceive of the practice of medicine in which there is any breach of absolute trust and confidence between patient and doctor. A good physician cannot lie to his patient. If the truth be bitter he must help the patient face it. On the other hand, I could

* 32 *Quarterly Journal of Medicine* 1, 19 (1963). Reprinted by permission of the Clarendon Press, Oxford.

* 192 *Journal of the American Medical Association* 661-662 (1965). Reprinted by permission.

not bear the practice of medicine if I felt obliged to tell the patient everything I know or think I know. . . .

* * *

NOTE

PAUL TALALAY
A SUMMARY OF COMMENTS*

* * *

In many instances, a serious medical condition may admit of several therapeutic decisions. Suppose that a young woman consults her physician with a sarcoma of the arm. The doctor is confronted with the possibility of giving no therapy, in which case she will certainly die, or of amputating the arm, or of administering various chemotherapeutic agents, or of giving radiation therapy. In practice, the physician selects what appears to him to be the wisest of these alternatives. He sensitively and delicately communicates this decision to the patient. In fact, he is experimenting. The code requires that the nature, the reason, and the risks of the experiment should be fully explained to the patient, who should in turn have complete freedom to decide whether or not to take part in this experiment. But no respected physician who is considerate of his patient would think of telling her all the implications of the disease. The essence of the good doctor is that he must assume responsibility for the management of the patient's illness, and an essential part of this responsibility is not to burden the patient with unnecessary anxieties which would inevitably result from a full exposition of the disease, its implications, and the therapeutic experiment. The good physician must continually interpret the ethical codes and the legal requirements in terms of the best interests of the patient.

* * *

[iv]

Avery D. Weisman
*The Patient with a Fatal Illness—
To Tell or Not To Tell†*

* * *

The central question is not whether or not to tell a patient about his dim outlook, but *who*

* P. Talalay, ed.: *Drugs in Our Society*. Baltimore: The Johns Hopkins Press 269-278 (1964). Reprinted by permission.

† 201 *Journal of the American Medical Association* 646, 647-648 (1967). Reprinted by permission.

shall tell, *how much* to tell, *what* to tell, *how* to tell, *when* to tell, and *how often* to tell.

Who Shall Tell?—Telling a patient is only the beginning, certainly not the end. It is not a painful task to be gotten out of the way, or to be relinquished gladly to someone else, such as to a minister or another family member. For everyone concerned, it is a genuine opportunity to reaffirm the reality of a human relationship. For the physician, it is an obligation and probably a necessary step, if the patient is to have a reasonably tranquil terminal period. Physicians who are most reluctant to talk about death with their patients are sometimes those who are also most reluctant to order sufficient analgesics and tranquilizers in the terminal stage. This suggests that, on both counts, these doctors avoid direct confrontation with death, perhaps to spare anguish for themselves, not for their patients.

How Much to Tell?—Telling a patient about his terminal illness is certainly not like giving him neutral information. A patient should be told only as much as he can use and absorb at the moment. A doctor should give information gradually, often over a series of visits, watching for individual responses and inquiries, allowing for idiosyncratic reactions, and being prepared to modulate the conversation to correct for unexpected complications. Rules and standard policies only approximate the facts; individual variations are the only rules.

What to Tell?—Most patients already have a fairly accurate intimation about the trend of illness by the time the physician and family get around to telling them. When a patient denies concern, he usually does so in order to preserve a relationship with someone on whom he is dependent, and cannot afford to alienate—and this includes the physician taking care of him. It is by no means rare for terminal patients to conceal the extent of their awareness, lest the doctor or family become upset!

Initially, most patients should be advised of the doctor's findings *and the treatment planned*. Frankness does not mean hopelessness, nor does unrealistic denial do more than foster temporary reassurance. At the beginning, the patient need not be told more than the facts of the illness. His doctor's directness should convey a more important, nonverbal message that he will not be abandoned. Gratuitous reassurances, overly precise predictions, and philosophical precepts are to be avoided.

How to Tell?—Plenty of time is needed for a significant human interchange. Information that involves a strong emotion can be given

openly, but in the direction of the patient's strengths. Avoid technical terms, because the doctor's concern about the histological type of tumor, for example, may not be the patient's concern. The predominant concerns of dying patients are usually not with the fact of dying, but with fears of isolation, abandonment, intractable pain, or of being sent off to a nursing home to languish and die. The physician, then, should be prepared for responses that seem to be accepting but are not, for delayed responses, and for anxieties not literally expressed that actually refer to something else. As a rule, the doctor cannot recognize the difference between true acceptance and outright denial without knowing the patient for a long time. Simple sincerity is a better guide to *how to tell* than are clichés or standard formulas which tend to protect the doctor without helping the patient.

When to Tell?—Although families may at first protest about giving the patient any information, lest he give up, become insane, or commit suicide, let them know that these reactions are decidedly uncommon. If the patient does not already know or suspect, families must be assured that soon it will be impossible and even undesirable to keep the "secret." Let them know also that dissimulation risks alienation and abandonment long before the patient is, in fact, ready to die. Families who have been the least accessible to the patient during health are often those who show the most opposition to telling the patient the truth about his illness.

How Often to Tell?—After the initial step of candor and confidence has been taken, subsequent discussions become easier. Because communication is uncluttered with rationalizations and unnecessary apologies, patients can be told about new symptoms and why older symptoms have not responded to treatment. Openness means that patients are told that they will have enough medication to reduce pain and that they will be consulted when procedures which merely prolong survival are being considered. By damaging a patient's sense of being a person, unnecessary procedures may inflict more suffering and exact a greater price than the biological extension of life in terms of days or weeks can justify.

Few patients persist in talking about dying. They accommodate to awareness of death, especially in the advanced stages of illness, and still more when they can face death with their doctor's help. Availability of the doctor leads to acceptance by the patient, even though acceptance may come gradually. Conversely, efforts by the

doctor to encourage denial in the patient may lead to the doctor's denial of the patient as a person. After all, the physician's prime consideration, once death can no longer be postponed, should be to help the patient live as effectively as possible until he dies.

NOTES

NOTE 1.

SAMUEL B. WOODWARD
MEDICAL ETHICS*

* * *

Is it ethical to lie outright to a patient? Has one a right to deceive a patient as to his condition? Must one make public a prognosis if it be unfavorable or bolster up vain hopes of a recovery when the physician well knows that this is impossible? Every tub, medical or otherwise, must stand on its own bottom and these questions can be answered in individual cases according to individual circumstances. Personally I can, I think, truthfully say that in a practice of forty years I never, so far as I can remember, found it necessary to tell an outright lie to a patient about his condition. Tactful and skillful explanations with their ifs and ands, side issues and suggestion of possibilities always sufficiently befogged the issue, satisfied the patient and left my conscience unseared. Few are the patients that really wish to be told that their cases are hopeless. . . .

* * *

NOTE 2.

RICHARD A. KALISH
DEATH AND RESPONSIBILITY—
A SOCIAL-PSYCHOLOGICAL VIEW†

I would suggest that [the patient] not only has the right to know, but he has the right *not* to learn everything all at once. More to the point, he has the right to learn a little bit at a time, to eliminate alternatives as he becomes psychologically able to eliminate them. [The patient] most certainly has the right to get honest answers to direct questions, but he may ask these questions one at a time over a period of weeks. Then he has the right to withdraw and deal with the new bit of evidence. The physician has the obligation to

* 202 *New England Journal of Medicine* 843, 852 (1930). Reprinted by permission.

† 3 *Psychiatric Opinion* 14, 16-17 (June 1966). Reprinted by permission.

answer these questions honestly, but his task will also be less painful because [the patient] is likely to ask only those questions to which he can anticipate the answers.

Thus, I feel, the physician should inform [the patient] that his illness is serious, perhaps very serious, and that he may never fully recover. After that, he can take his cue from [the patient]. If asked to give a date of death, he can be honest in saying he does not know, that medical science is just not that accurate; if pressed, he can speak in terms of "sooner rather than later," or "perhaps before Christmas." If asked about pain and suffering, the physician can answer generally, then more specifically as more specific questions are put to him, always explaining—of course—that individual cases vary. As these questions occur, the physician might open the discussion to what [the patient] would like done for his pain; he might explain something of the effects of various sedatives and let [the patient] consider the pros and cons of being heavily sedated. However, these discussions should not be formal lectures of planned duration, but brief comments and responses to questions. The main point is that [the patient] be made to feel that the channel of communication to his physician remains open.

NOTE 3.

BARNEY G. GLASER AND ANSELM L. STRAUSS
AWARENESS OF DYING*

* * *

Many conditions reduce a doctor's inclination to make a separate decision for each case. Few doctors get to know each terminal patient well enough to judge his desire for disclosure or his capacity to withstand the shock of it. . . . Even when a doctor has had many contacts with a particular patient, class or educational differences, or personality clashes, may prevent effective communication. Some doctors simply feel unable to handle themselves well enough during disclosure to make a complicated illness understandable. If a doctor makes a mistake, he may be liable for malpractice. Some doctors will announce an impending death only when a clear-cut pathologist's report is available. Others do not tell because they fear the patient might become despondent or mentally ill or commit suicide, because they do not want him to "lean" on

them for emotional support, or because they simply wish to preserve peace on the ward by preventing a scene.

At the same time, a number of other conditions encourage disclosure regardless of the individual patient's capacity to withstand it. Some doctors disclose to avoid losing the patient's confidence if he should find out through cues or accidentally. Telling also justifies radical treatment or a clinical research offer; it also reduces the doctor's need to keep up a cheerful but false front. Some tell so that the patient can put his affairs in order and plan for his family's future, or reduce his pace of living; others, because family members request it. Of course, if the chances for recovery or successful treatment are relatively good, a doctor is naturally more likely to disclose an illness that is possibly terminal; disclosing a skin cancer is easier than disclosing bone cancer.

The combined effect of these conditions—some of which may induce conflicting approaches to the same patient—is to make it much easier for doctors to apply to all patients a flat "no, he should not be told." For when people are in doubt about an action, especially when the doubt arises from inability to calculate the possible effects of many factors about which there is little information, it is almost always easier and safer not to act.

* * *

Many of the standard arguments given by doctors both for and against disclosure anticipate a single, permanent impact on the patient. He is expected to "be brave," "go to pieces," "commit suicide," "lose all hope," or to "plan for the future" and such. But the impact is not so simple. Disclosing the truth sets off a generalized response process through which the patient passes. To base the decision about disclosure on a single probable impact is to focus on only one stage in the response process; not only does it neglect the other stages, but also it omits how each stage may be controlled by the staff through appropriate forms of interaction. For example, to predict that the patient will become too despondent is to neglect the possibility that he might overcome this despondency and, with the aid of a chaplain or social worker, prepare adequately for his death and for his family's future. But to expect a patient simply to settle his affairs is to fail to evaluate his capacity for overcoming an initial depression, as well as the capacity of the staff to help him at this stage.

The generalized response process is stim-

* Chicago: Aldine Publishing Co. 119-122 (1965). Reprinted by permission.

ulated by a doctor's *disclosure* to the patient. The patient's initial response is almost invariably *depression*, but after a period of depression he either *accepts* or *denies* the disclosure; and his ensuing behavior may be regarded as an affirmation of his stand on whether he will, in fact, die. Acceptance of the doctor's disclosure may lead to active preparation, to passive preparation, or to fighting the illness. A particular patient's response may stop at any stage, take any direction, or change directions. The outcome depends first on the manner in which he is told, and then on his own inclinations combined with staff management.

A doctor deciding whether to tell the patient, therefore, cannot consider a single impact, but how, in what direction, and with what consequences the patient's response is likely to go; as well as what types of staff are available and how they will handle the patient at each stage. A doctor who says "no" to disclosure because the patient will "lose hope" need not be in conflict with one who says "yes" to give the patient a chance to plan for his family. Each is merely referring to a different stage of the same process. For both, the concern should be with judging whether the patient can achieve the acceptance-active preparation stage.

* * *

b.

Death—At Whose Choosing?

[i]

Glanville Williams

*The Sanctity of Life and the Criminal Law**

* * *

The object of the bill [sponsored by the English Euthanasia Society] was to legalize voluntary euthanasia. The patient desiring euthanasia must be over twenty-one years of age and suffering from an incurable and fatal disease accompanied by severe pain. The bill excluded any question of compulsory euthanasia, even for hopelessly defective infants. . . .

. . . The promoters of the bill hoped that they might be able to mollify the opposition by providing stringent safeguards. Now, they were right in thinking that if they had put in no safeguards—if they had merely said that a doctor could kill his patient whenever he thought it right—they would have been passionately opposed on this ground. So they put in the safeguards. Un-

der the proposals of the bill, the patient must sign a statutory form, in the presence of two witnesses, requesting euthanasia. The form, accompanied by two medical certificates, goes up to an official euthanasia referee appointed by the Minister of Health; he interviews the patient to make sure that he really wants it. Then euthanasia is administered in the presence of an official witness, who must be a justice of the peace, barrister, solicitor, doctor, minister of religion, or registered nurse.

Did the opposition like these elaborate safeguards? On the contrary, they made them a matter of complaint. The safeguards would, it was said, bring too much formality into the sick-room, and destroy the relationship between doctor and patient. So the safeguards were wrong, but no one of the opposition speakers said that he would have voted for the bill without the safeguards.

Much the most important of these opposition speeches were delivered by two of the acknowledged leaders of the medical profession, the late Lord Dawson of Penn and the late Lord Horder. . . .

Lord Dawson for the greater part of his speech seemed to be in sympathy with the views of the bill. He scouted the opposition notion that the only duty of the doctor is to save life. That, he said, was the nineteenth-century view, but medical opinion has changed; we now think that it is also the doctor's duty to relieve pain. Hence anaesthesia in childbirth and dentistry, and all the new drugs to assuage pain and bring sleep and forgetfulness to the troubled mind. Lord Dawson proceeded: "I would say that this is a courageous age, but it has a different sense of values from the ages which have gone before. It looks upon life more from the point of view of quality than of quantity. It places less value on life when its usefulness has come to an end." So "there has gradually crept into medical opinion, as it has crept into lay opinion, the feeling that one should make the act of dying more gentle and more peaceful even if it does involve curtailment of the length of life."

Then Lord Dawson went on: "If once you admit that you are going to curtail life by a single day, you are granting the principle that you must look at life from the point of view of its quality rather than from its quantity under these special circumstances. . . . I would give as my deliberate opinion that there is a quiet and cautious but irresistible move to look at life and suffering from the more humane attitude, and in face of a disease which is undoubtedly incurable, and

* New York: Alfred A. Knopf 333-340 (1957). Reprinted by permission.

when the patient is carrying a great load of suffering, our first thoughts should be the assuagement of pain even if it does involve the shortening of life." This means that the physician will, at the end, drug the patient even though he knows that this will shorten the patient's life. But what if death is still far off? Lord Dawson said: "When the gap between life burdened by incurable disease and death becomes wider, then greater difficulty presents itself, and greater variety in practice holds among individual doctors and patients. None the less there is in the aggregate an unexpressed growth of feeling that the shortening of the gap should not be denied when the real need is there. This is due, not to a diminution of courage, but rather to a truer conception of what life means and what the end of its usefulness deserves."

This remarkable speech seemed not merely to concede the case for euthanasia but to admit that it was actually practised, consciously or subconsciously, by the medical profession. Moreover, the concluding reference to "shortening the gap" seems to be a cautious admission of the principle that euthanasia is permissible, and is practised, not only where this is the only way of avoiding pain, but also where it is the only way of avoiding the prolongation of a life burdened by an incurable disease and robbed of all the quality that makes life worth while. This is a concession of the first importance to the cause of euthanasia.

Although he went thus far with the promoters of the measure, Lord Dawson opposed the bill on the ground that he preferred the present position under which everything was left to the discretion of the doctor. The Archbishop of Canterbury seized upon this idea with approval and relief; at the end of his speech he guardedly admitted that "cases arise in which some means of shortening life may be justified"; but he thought that Parliament should fold its hands because these cases were best left to the medical profession. Apparently the Primate thought that the consent of the patient would not be necessary, for one of his points was that a man racked with pain and full of drugs may be incapable of making a moral judgment. Thus these opponents of the bill, in allowing the doctor to end life without seeking the patient's consent, were in an important way prepared to go further than the proponents of the measure.

Lord Horder's argument was broadly similar to Lord Dawson's, though he did not elaborate it in the same way. He declared that it is outside a doctor's reference to put an end to life; but

"the good doctor is aware of the difference between prolonging life and prolonging the act of dying." The former comes within his terms of reference, the latter does not. On this it may be commented that there must obviously be room for a good deal of difference of opinion on what is meant by "not prolonging the act of dying." It is not, really, a very satisfactory formula, because it appears, misleadingly, to point to simple inactivity. A doctor who is engaged in giving large doses of a narcotic is not merely "not prolonging the act of dying"; he is doing something positive which may well have the effect of shortening the act of dying. There is, also, vagueness as to the temporal limits of the "act of dying"....

* * *

It may be suggested that the most hopeful line of advance would be to bring forward a measure that does no more than give legislative blessing to the practice that the great weight of medical opinion approves. In other words, the reformers might be well advised, in their next proposal, to abandon all their cumbrous safeguards and to do as their opponents wish, giving the medical practitioner a wide discretion and trusting to his good sense.

* * *

... The essence of the bill would ... be simple. It would provide that no medical practitioner should be guilty of an offence in respect of an act done intentionally to accelerate the death of a patient who is seriously ill, unless it is proved that the act was not done in good faith with the consent of the patient and for the purpose of saving him from severe pain in an illness believed to be of an incurable and fatal character. ...

* * *

NOTES

NOTE 1.

GLANVILLE WILLIAMS
EUTHANASIA*

Why is murder a crime? I know that some will give a religious answer, or a mystical answer. They will say that life is a gift of God, and only God can take it away; or they will say that murder is absolutely wrong and must be punished for that reason alone. But most of us now agree that purely religious or metaphysical views are

* 63 *Proceedings of the Royal Society of Medicine* 663-667 (1970). Reprinted by permission.

not a sufficient basis for the criminal law. We have to find mundane justifications, and in this instance they come readily to mind. The reasons underlying the law of murder are particular applications of the reasons underlying the whole of our secular morality: utilitarianism and empathy.

The utilitarian reason for the crime of murder is that if murder were allowed there would be a general sense of fear and insecurity, which would not only be evil in itself but would in its consequences work disaster for civilization. . . .

The second reason for forbidding murder is empathy, or sympathetic identification with the victim. . . .

* * *

Now, neither of these two secular reasons for the law of murder stands in the way of mercy killing. To accelerate the death of a patient at his request for merciful reasons does not increase the sum of human suffering, but diminishes it. Sympathy, so far from requiring us to refrain from killing, may in exceptional circumstances compel us to do so.

[T]he question of mercy killing or euthanasia is not specifically a medical question. It affects doctors, but it is a general moral problem, and it is intimately connected with the right of suicide.

* * *

. . . We now acknowledge, as a society, that the patient may commit suicide without offending against the law. Why, then, should not his parent, spouse or doctor be allowed to help him? And if the doctor is allowed to give the patient tablets to take, why cannot he inject the lethal dose into the patient if that course appears preferable? Morally, there is no difference between assisting suicide and killing another person with his consent.

I have tried to show that this is a general question relating to the proper limits of the criminal law, not specifically a medical question. But legislation aimed to alter the present law as a practical matter naturally concentrates on the doctors, because it is they who have the knowledge and ability to perform mercy killing in a humane manner. . . .

* * *

[W]e are told that no legislation is necessary because doctors can in fact speed their patient's passage, quite morally and legitimately, by the double effect of morphine. The morphine is

given in increasing doses to overcome habituation, and these doses may eventually build up to one that produces respiratory failure. The doctor pretends to himself that he is only relieving pain, but he well knows that the result is to speed the end. He may even deliberately accelerate the doses for this purpose, secure in the knowledge that no one can prove his real motive. That, at least, has been the position. But it was always a precarious solution, dependent upon the accidental fact that morphine, the medically preferred analgesic, carried this side-effect of depressing respiration. There was always the possibility that the doctor's opportunity for benevolent hypocrisy would be ended by the development of an effective analgesic which did not produce respiratory depression; and claims have been made that drugs like dextromoramide and dihydrocodeine already fit this bill. Whether or not it has already happened, the time will surely come when the doctor who administers pure morphine in steadily mounting doses will be seen by the present law for a murderer, because the drug will have ceased to be medically justified. . . .

* * *

What, then, is the legislative proposal? My own proposal would be a simple one: but I must emphasize that it applies only to patients who are suffering severe distress without prospect of relief. In these cases it should not be murder for a doctor, acting at the patient's request and with the concurrence of another doctor, to accelerate the patient's death in good faith and for his benefit. Apart from some small formalities relating to the request I would not put in any other restrictions, leaving those, if any are required, to medical practice. As a layman, I have every confidence that members of your profession will exercise the permission I would give you wisely and humanely. I think it very unlikely that the permission would be over-used: look at the fight you are putting up against being entrusted with an explicit permission at all! The permissive law would much more likely be under-used. If any feared dangers did materialize the law could easily be repealed because no vested interests would be created by it.

* * *

There is only one argument against voluntary euthanasia in these cases worthy of serious consideration, and that is the fear that a change in the law would put a distressing pressure on some old or dying people to accelerate their end

out of consideration for their relatives and those who are looking after them. Although this is a serious argument, my own view is that it does not weigh against the other considerations. It is true that under my measure a patient may ask for euthanasia and through his insistence succeed in getting it because he does not want to continue to be a burden, perhaps for his young daughter who is looking after him. One hears sometimes of persons suffering from severe disability who commit suicide for this noble reason. Lord Soper in the Lords' debate on the recent Euthanasia Bill referred with admiration to the suicide of Captain Oates, whose object was to disembarass Scott of his presence; and a cripple who commits suicide in order to set free his young wife or daughter may be just as deserving of our esteem. I should like to think that I myself would have the courage to do this in such circumstances, though I would certainly not blame anyone for not sacrificing himself. I do not believe that this question of consideration for one's family can be settled by rule, one way or the other. It is an immensely difficult human problem, and is surely best left to be settled by the patient himself, as one of the factors influencing his decision, but subject to the advice and support of his doctors which one knows would be forthcoming.

NOTE 2.

ROYAL SOCIETY OF MEDICINE
DISCUSSION ON EUTHANASIA*

Sir Geoffrey Organe thought Professor Glanville Williams had been confused over one point, that voluntary euthanasia was practised now. He was quite certain that formal debate did not take place between doctor and patient leading to a formal decision to execute the patient. What happened was that if the patient was suffering more than the doctor thought he should suffer, he was helped on his way. Whether this was a good thing or not he did not know.

... He thought that if euthanasia became more formal than it was now, and if affidavits had to be sworn before solicitors or magistrates with the consent of relatives, that there would be much more resistance on the part of doctors than there was at the moment.

* * *

Professor Glanville Williams: As to the distinction between voluntary and involuntary

euthanasia, he knew that medical men did not want to tell their patients that they were dying. They did not want to ask for explicit consent. He was very happy to leave the doctor, if he was willing to take the responsibility, to dispatch the patient without asking him, doing what it was extremely likely that the patient would desire if he knew the truth of the situation, but he knew that this could not be put into legislation. He knew, therefore, that legislation could not do very much, but at least it could do something in the voluntary field and he saw no danger whatsoever that legislation for voluntary euthanasia would ever be extended to allow killing otherwise than to relieve suffering. . . .

[ii]

Vincent J. Collins

*Limits of Medical Responsibility in
Prolonging Life**

In the unconscious or hopelessly ill patient requiring resuscitation, there are three courses of action: (1) active treatment, i.e., prolonged dying vs reanimation; (2) active intervention to end life, i.e., euthanasia; (3) passive management, i.e., shortening the dying process. The first problem that requires serious examination is that of prolonging life, in reality a problem of therapy. Second, in contrast, is euthanasia. This is a problem of a deliberate decision to actively end life; it is not a dilemma. The prolonging of life is the lengthening of life. Euthanasia has as its objective the shortening of life, and this contrasts with passive management, in which the objective is to shorten the dying process.

A physician's approach toward the inevitable ending of life may be either passive or active. Death could occur by actively interceding or by passively discontinuing therapy. In the first instance, one directly causes life to end by an overt act, whereas, by discontinuing therapy, one permits death to occur by omitting an act and permitting nature to take its course.

Euthanasia.—When one actively intercedes, one is, in fact, causing harm to the individual, even though this harm may apparently have a good intent; here man is acting. This course of action is abhorrent and prohibited. Here also there is the dilemma of motives. Behind every good deed is a motive. Motives can be colored. When man is the direct instrument to a

* 63 *Proceedings of the Royal Society of Medicine* 669-670 (1970). Reprinted by permission.

* 206 *Journal of the American Medical Association* 389, 390-391 (1968). Reprinted by permission.

death, the law has historically related this to his intention. The motive may be malice or mercy, but regardless of the intent, whether malice or mercy, the end is murder.

We should now dispose of this question immediately: Shall we perform a deliberate act to positively end a life? That is euthanasia. From the legal standpoint, from the moral codes, and from the guidelines of ethical practice, we find applied the general law that no one is permitted to actively kill, regardless of the intent.

Aspects of Prolonging Life.—The more complicated question is that of *prolonging life*. Can our scientific decisions to prolong life or let a patient die be reconciled with our ethics and morality? Yes! But we must continue to distinguish clearly between letting a patient die and euthanasia.

Every physician is liable for his actions, but every action of a physician requires medical judgment. In saving a life, in preventing death, and then in prolonging the life, the question must repeatedly be asked as to whether the end result is inevitable or irrevocable. Is the end result death, or is the end result of the sustained immediate life mere organic existence?

When one permits death by not continuing therapy, the harm that is done is done by nature acting. This is passive management based on reason and judgment—and shortening the act of dying. It is rational. Therapy is discontinued when the efforts to maintain sound life are manifestly ineffective.

Thus, the problem is a challenge in therapy. It is possible for the physician to support life artificially, at least the traditional vital functions of respiration and circulation. He must know what to do, when to do it, and when to stop. In his therapeutic approach, he will use both simple or ordinary means and extraordinary means to support life.

Ordinary and Extraordinary Means.—A definition of ordinary and extraordinary means is required. Ordinary measures of patient care are recognized as elements of essential care. They represent obligatory, proven, and justified therapies and procedures. They are denoted by the fact that the patient himself can obtain them and put them to his own use. They further represent measures which he can reasonably undergo with only minimal or moderate danger and maximal effectiveness. Such measures are also not an impossible or excessive burden.

Extraordinary measures, on the other hand, are complicated methods. They are impossible

for the patient to use or apply by himself and present a costly and difficult burden. In addition, they represent a high level of danger, and the results expected are not predictable, i.e., the effectiveness is minimal or moderate while the dangers are maximal.

Extraordinary measures sustain life artificially at the level it is found. If, at this point in time, there is no organic deterioration, the measures of resuscitation may then arrest the lethal process. The aim is to gain time in order for natural restorative processes to operate.

Effectiveness of Therapy.—On the basis of medical facts and good judgment, the physician does those things in any situation which will benefit his patient. He must do those things which predictably result in improvement of his patient. The techniques of reanimation are proven, sound, and legitimate. They can and do prolong life, but it must be determined that the nature of the resultant life is not mere biological existence of several organs but totally integrated functional existence at a rational human level. To continue an act or proceed with therapy which produces no improvement, which does not achieve or have the potential to achieve "full human life," and which is demonstrably ineffective in its objectives, is imprudent, illogical, and irrational. This is the essence of medical practice.

When a physician and his team bring together all the knowledge and skill related to sustaining life processes and treating patients with disease, they do so rationally. The effectiveness of therapeutic skill must be constantly assessed. In artificially maintaining life or in arresting a disease process, the physician buys time. By his assistance he provides time for the patient's natural recovery processes to act, to allow natural restoration of functional organization and return of the individual to a spontaneous, personal full life.

If after some time all measures are obviously not effective and are not reversing the dying process, then the measures are failing. Deterioration may be observed. To persist may produce the appearance of life, but this is most often technical or mechanical life. The final decision will then be made in the face of a late phase or a second endpoint, namely, that of biological life. It is the physician's obligation to cease efforts early when they are determined to be ineffective in the total reanimation process and objectives. The patient should then be allowed to die. He has this right; he should not be cheated of a peaceful death when the physician is powerless to

restore consciousness. A vegetating patient, hopeless and unresponsive, and showing no spontaneous activity, should be allowed to die peacefully. Physicians should make the dying process dignified.

* * *

NOTES

NOTE 1.

SAMUEL B. WOODWARD
MEDICAL ETHICS*

* * *

... When your patient is dying from old age, or is in the last stages of cancer, or tubercular infection, unable to swallow food, shall you give nutritive enemata, withhold morphine or by any other means endeavor to postpone the inevitable? There may be reasons for desperate efforts in that direction to enable, for instance, a son, daughter, husband or wife to reach a beloved relative before the end, but in the absence of such or similar motives I hold it to be your duty to smooth as much as possible the pathway to the grave even if life be somewhat shortened. Nor is it necessary to talk it over with friends and relations, nor need you expect them to formally countenance either neglect or expedition. Let that be your affair settled with your own conscience. I have no sympathy with the man who would shorten the death agony of a dog but prolong that of a human being.

* * *

NOTE 2.

KURT R. EISSLER
THE PSYCHIATRIST AND THE DYING PATIENT†

* * *

Actually some of those physicians who uncompromisingly deny patients the beneficence of euthanasia are not superior to their contemporaries in their general ethics, and it is quite possible that this moral stringency is often a concealed manifestation of their sadism. I hasten to add that this is by no means meant as a rule and that in turn one definitely can find among physicians practicing euthanasia fantasies of omnipotence and a deep-seated ambivalence. Euthanasia is not always born out of charity but may mean to the

* 202 *New England Journal of Medicine* 843, 846 (1930). Reprinted by permission.

† New York: International Universities Press 118 (1955). Reprinted by permission of the International Universities Press, Inc., New York.

physician's unconscious the gratification of a murderous impulse.

* * *

NOTE 3.

R. J. V. PULVERTAFT
THE INDIVIDUAL AND THE GROUP
IN MODERN MEDICINE*

* * *

The patient meets his doctor with a very wide mandate. He is anxious, and seeks peace of mind; he is in pain, and seeks relief; with the prospect of death, he asks reprieve. But the mandate goes further, and always there is in his mind the unspoken request: "Some time I must die. As a layman, I cannot tell the choice, if choice there be, of my path; but I trust your greater knowledge to see me through in the kindest way."

It is in the management of malignant disease that, to my mind, surgeons and radiotherapists of today are at times wrongly orientated. There is too much emphasis on the remote chance of "cure," too little on the mitigation of the reasonably certain course of the disease. There is some modern surgery which merely ensures that the patient's remaining days will be spent in convalescence from the operation. And there remains always the distressing fact that a patient or his relatives, faced on the one hand by an honest and correct statement that recovery is impossible and on the other by a statement that it may be ensured in certain especially skilled and expensive hands, will sometimes choose a road that is sadly against his interest. The final degradation of medicine is to become the blackmail of the dying with the fear of death.

* * *

NOTE 4.

THE FIFTH DEATH OF LEV LANDAU†

Six years ago, an auto accident "took the life" of Dr. Lev Davidovitch Landau, one of the world's most brilliant theoretical physicists. But through the determined efforts of medical specialists called to Moscow from as far away as Montreal, the Soviet scientist not only came back from apparent clinical death on four separate occasions, but he learned again to function and to work.

* 2 *The Lancet* 839, 842 (1952). Reprinted by permission.

† *Medical World News* 37 (April 19, 1968). Copyright 1968, McGraw-Hill, Inc. Reprinted by permission.

When his battered body was examined shortly after a truck demolished his car on an icy Moscow highway on January 7, 1962, Czech neurologist Sdenek Kunz grimly announced that "the traumas sustained are incompatible with life." The international team of physicians gathered at Dr. Landau's bedside could find no reason to disagree.

Dr. Landau had multiple injuries, any one of which could have been fatal. The base of his skull was fractured, the fornix cerebri was lacerated, and there were contusions of the frontal and temporal lobes. Doctors counted nine broken ribs and also diagnosed pneumothorax and a dextral hemothorax, rupture of the pubic symphysis; fractures of the os pubis, ischium, ilium, and left femoral neck; severe contusions of the abdominal cavity, and rupture of the urinary bladder. In addition, the patient had paralysis of the left arm, paresis of the right arm and both legs, and steadily increasing respiratory and circulatory distress.

The brilliant scientist was deaf, blind, and speechless, and he showed no reflexes. For two months, he remained unconscious and unresponsive. Despite the seeming hopelessness of the situation, the team of more than 100 physicians who had come to Moscow refused to give up.

Four days after the accident, the Soviet physicist appeared to succumb. His pulse disappeared, blood pressure fell to zero, and the EEG tracing flattened out. Clinically, Dr. Landau was dead. But the persistent physicians at his side refused to turn off the respirator. They opened his left radial artery and infused blood. They gave him intravenous injections of epinephrine, strophanthine, and other analeptics. Gradually life came back. During the next week, death had to be repelled three more times. The prognosis was gloomy at best.

Five weeks later, Dr. Landau's fractures began to ossify, but he was still unconscious, and his extremities remained paralyzed. Then, while an international team of neurologists . . . were consulting on the next step, a close friend and collaborator of the patient . . . burst into the room. "He recognized me. He really did!"

Eleven months after the accident—while Dr. Landau was still tortuously relearning the normal functions of memory, speech, hearing, and muscle control—he was able to sit up in bed and smilingly accept his Nobel Prize from the Swedish ambassador. The prize honored his pioneering work in low-temperature physics.

Recalling the medical "miracle" performed in bringing the physicist back to life, Dr. Boris

Yegorov, director of the Neurosurgery Institute of the Soviet Academy of Sciences, noted that "the patient's brain had been in a state of near-anabiosis for more than 100 days. It was held previously that oxygen deficiency of the brain cells leads to their destruction. The Landau case compels us to reconsider the whole of accumulated medical experience." But another Soviet expert, Dr. V. A. Negovsky, injected a note of controversy into the case when he asserted that Dr. Landau had never been in a state of clinical death.

Dr. Landau returned to the Moscow Institute for Experimental Physics and participated in weekly seminars, but he never fully recovered. He suffered violent gastric and limb pains and had difficulties with his memory that prevented him from continuing his research.

This month, six years after his "fatal" auto accident, the famed Soviet physicist finally succumbed. . . .

[iii]

Renée C. Fox

*A Sociological Perspective on
Organ Transplantation and Hemodialysis**

* * *

Chronic hemodialysis can present the physician with still other troubling, sometimes tragic aspects of his ethical obligation to have a patient's continuing consent for maintenance on the artificial kidney machine. It has been written that ". . . submission, with the reaper smiling grimly behind every movement, knowing that his turn will come, does not lead to a placid temperament and easy acceptance. To the contrary, the person who lives successfully with hemodialysis lives in a state of suppressed inner turmoil, from which there can never be an escape except in death. . . ." The psychological, social, and economic, as well as physical, stresses of being kept alive by intermittent hemodialysis may become too burdensome for a patient. Consciously or unconsciously, he may decide that he does not wish to go on living "on borrowed time," tied by cannulas to an at once "miraculous" and "monstrous" machine. Physicians have noted that under these conditions, certain patients begin to have what appear to be motivated cannula failures: for example, they cease to take care of their cannulas by keeping them clean, or too vigorously exercise the arm or the leg in which they are in-

* 169 *Annals of the New York Academy of Sciences* 416-417 (1970). Reprinted by permission.

sented. Other patients no longer abide by the strict dietary regulations that are requisite for this treatment to be effective, and may go on eating "binges." Occasional patients have explicitly asked the physician to remove them from the chronic dialysis program without offering them a kidney transplantation as an alternative method of definitive treatment. In all these cases, it can be said that the patient has withdrawn his full and free consent to undergo hemodialysis. The agonizing question for the physician is whether or not it is moral and humane to try to persuade such patients that it is worthwhile to continue on the artificial kidney machine, rather than succumb to their endstage renal disease. It overlaps with the more familiar issue of when, if ever, the physician is justified in no longer employing extraordinary means to keep a dying patient alive.

* * *

NOTES

NOTE 1.

W. ST.C. SYMMERS, SR.
NOT ALLOWED TO DIE*

A doctor aged 68 was admitted to an overseas hospital after a barium meal had shown a large carcinoma of the stomach. He had retired from practice five years earlier, after severe myocardial infarction had left his exercise tolerance considerably reduced. The early symptoms of the carcinoma were mistakenly thought to be due to myocardial ischaemia. By the time when the possibility of carcinoma was first considered the disease was already far advanced; laparotomy showed extensive metastatic involvement of the abdominal lymph nodes and liver. Palliative gastrectomy was performed with the object of preventing perforation of the primary tumour into the peritoneal cavity, which appeared to the surgeon to be imminent. Histological examination showed the growth to be an anaplastic primary adenocarcinoma. There was clinical and radiological evidence of secondary deposits in the lower thoracic and lumbar vertebrae.

The patient was told of the findings and fully understood their import. In spite of increasingly large doses of pethidine, and of morphine at night, he suffered constantly with severe abdominal pain and pain resulting from compression of spinal nerves by tumour deposits.

On the tenth day after the gastrectomy the patient collapsed with classic manifestation of

massive pulmonary embolism. Pulmonary embolectomy was successfully performed in the ward by a registrar. When the patient had recovered sufficiently he expressed his appreciation of the good intentions and skill of his young colleague. At the same time he asked that if he had a further cardiovascular collapse no steps should be taken to prolong his life, for the pain of his cancer was now more than he would needlessly continue to endure. He himself wrote a note to this effect in his case records, and the staff of the hospital knew his feelings.

His wish notwithstanding, when the patient collapsed again, two weeks after the embolectomy—this time with acute myocardial infarction and cardiac arrest—he was revived by the hospital's emergency resuscitation team. His heart stopped on four further occasions during that night and each time was restarted artificially. The body then recovered sufficiently to linger for three more weeks, but in a decerebrate state, punctuated by episodes of projectile vomiting accompanied by generalized convulsions. Intravenous nourishment was carefully combined with blood transfusion and measures necessary to maintain electrolyte and fluid balance. In addition, antibacterial and antifungal antibiotics were given as prophylaxis against infection, particularly pneumonia complicating the tracheotomy that had been performed to ensure a clear airway. On the last day of the illness preparations were being made for the work of the failing respiratory centre to be given over to an artificial respirator, but the heart finally stopped before this endeavour could be realized.

This case report is submitted for publication without commentary or conclusions, which are left for those who may read it to provide for themselves.

NOTE 2.

ERICKSON V. DILGARD
44 Misc.2d 27, 252 N.Y.S.2d 705
(Sup. Ct. 1962)

BERNARD S. MEYER, JUSTICE.

This is an application by the Superintendent of the County Hospital for an order authorizing administration of a blood transfusion to Jacob Dilgard, Sr. Testimony adduced by the petitioner shows that Jacob Delgard, Sr., was voluntarily admitted to the hospital and that a diagnosis of upper gastro-intestinal bleeding was made. It was suggested to the patient that he submit to an operation, including blood transfusion to replace lost blood. The patient declined to submit to a

* 1 *British Medical Journal* 442 (1968). Reprinted by permission.

blood transfusion, but did indicate a willingness to submit to the operation without a blood transfusion. His son who is a party respondent in this proceeding also refused to give permission for a transfusion, but was willing to authorize the operation without blood transfusion. Petitioner testified that an operation was necessary to tie off the bleeding site, that in order to offer the best chance of recovery a transfusion of blood was necessary, and that there was a very great chance that the patient would have little opportunity to recover without the blood. He further testified that the patient was completely competent and capable of making decisions on his own behalf, that he had explained to the patient the increased risk of having the operation without the transfusion, and that refusal of a transfusion represented the patient's calculated decision.

The County argues that it is in violation of the Penal Law to take one's own life and that as a practical matter the patient's decision not to accept blood is just about the taking of his own life. The Court cannot agree with that argument because it is always a question of judgment whether the medical decision is correct. Without in any sense impugning Dr. Erickson's opinion, the Court concludes that it is the individual who is the subject of a medical decision who has the final say and that this must necessarily be so in a system of government which gives the greatest possible protection to the individual in the furtherance of his own desires.

The court knows of no precedent relating to adult patients. There are cases in which it has been held that a court will step in as the guardian of an infant or an incompetent and make the decision for the infant or incompetent. In this case, however, there is no question that the patient has been completely competent at all times while being presented with the decision that he had to make and in the making of the decision that he did. That being so, the court declines to make any order directing that blood be administered. The application is denied.

NOTE 3.

JOHN F. KENNEDY HOSPITAL V. HESTON
58 N.J. 576, 279 A.2d 670 (1971)

WEINTRAUB, C. J.

Dolores Heston, age 22 and unmarried, was severely injured in an automobile accident. She was taken to the plaintiff hospital where it was determined that she would expire unless operated upon for a ruptured spleen and that if operated

upon she would expire unless whole blood was administered. Miss Heston and her parents are Jehovah's Witnesses and a tenet of their faith forbids blood transfusions. . . .

Death being imminent, plaintiff on notice to the mother made application at 1:30 a.m. to a judge of the Superior Court for the appointment of a guardian for Miss Heston with directions to consent to transfusions as needed to save her life . . . The court appointed a guardian with authority to consent to blood transfusions "for the preservation of the life of Dolores Heston." Surgery was performed at 4:00 a.m. the same morning. Blood was administered. Miss Heston survived.

* * *

The controversy is moot. Miss Heston is well and no longer in plaintiff's hospital. The prospect of her return at some future day in like circumstances is too remote to warrant a declaratory judgment as between the parties. Nonetheless, the public interest warrants a resolution of the cause, and for that reason we accept the issue.

* * *

It seems correct to say there is no constitutional right to choose to die. Attempted suicide was a crime at common law and was held to be a crime under N.J.S.A. 2A:85-1. It is now denounced as a disorderly persons offense. N.J.S.A. 2A:170-25.6. Ordinarily nothing would be gained by a prosecution, and hence the offense is rarely charged. Nonetheless the Constitution does not deny the state an interest in the subject. It is commonplace for the police and other citizens, often at great risk to themselves, to use force or stratagem to defeat efforts at suicide, and it could hardly be said that thus to save someone from himself violated a right of his under the Constitution subjecting the rescuer to civil or penal consequences.

Nor is constitutional right established by adding that one's religious faith ordains his death. Religious beliefs are absolute, but conduct in pursuance of religious beliefs is not wholly immune from governmental restraint. . . .

Complicating the subject of suicide is the difficulty of knowing whether a decision to die is firmly held. Psychiatrists may find that beneath it all a person bent on self-destruction is hoping to be rescued, and most who are rescued do not repeat the attempt, at least not at once. Then, too, there is the question whether in any event

the person was and continues to be competent (a difficult concept in this area) to choose to die. And of course there is no opportunity for a trial of these questions in advance of intervention by the State or a citizen.

Appellant suggests there is a difference between passively submitting to death and actively seeking it. The distinction may be merely verbal, as it would be if an adult sought death by starvation instead of a drug. If the State may interrupt one mode of self-destruction, it may with equal authority interfere with the other. It is arguably different when an individual, overtaken by illness, decides to let it run a fatal course. But unless the medical option itself is laden with the risk of death or of serious infirmity, the State's interest in sustaining life in such circumstances is hardly distinguishable from its interest in the case of suicide.

* * *

Hospitals exist to aid the sick and the injured. The medical and nursing professions are consecrated to preserving life. That is their professional creed. To them, a failure to use a simple, established procedure in the circumstances of this case would be malpractice, however the law may characterize that failure because of the patient's private convictions. A surgeon should not be asked to operate under the strain of knowing that a transfusion may not be administered even though medically required to save his patient. The hospital and its staff should not be required to decide whether the patient is or continues to be competent to make a judgment upon the subject, or whether the release tendered by the patient or a member of his family will protect them from civil responsibility. The hospital could hardly avoid the problem by compelling the removal of a dying patient, and Miss Heston's family made no effort to take her elsewhere.

When the hospital and staff are thus involuntary hosts and their interests are pitted against the belief of the patient, we think it reasonable to resolve the problem by permitting the hospital and its staff to pursue their functions according to their professional standards. The solution sides with life, the conservation of which is, we think, a matter of State interest. A prior application to a court is appropriate if time permits it, although in the nature of the emergency the only question that can be explored satisfactorily is whether death will probably ensue if medical procedures are not followed. If a court finds, as

the trial court did, that death will likely follow unless a transfusion is administered, the hospital and the physician should be permitted to follow that medical procedure.

* * *

[Affirmed.]

[iv]

Petition of Nemser
51 Misc.2d 616, 273 N.Y.S.2d 624
(Sup. Ct. 1966)

JACOB MARKOWITZ, JUSTICE.

On September 9, 1966, a preliminary hearing was held by this court on petitioners' application to be appointed the temporary legal representatives of their mother, for the specific and limited purpose of executing a consent in her behalf to a transmetatarsal amputation of her right ankle and foot.

As a result of such preliminary hearing, the court appointed a guardian ad litem for the respondent, Sadie Nemser, and subsequently requested an eminent psychiatrist to examine her for the purpose of obtaining competent medical opinion as to her capacity to execute a consent in the form required by the hospital and the attending physicians. In addition, petitioners were directed to join both the hospital and the physician (or physicians) in charge of the care of Mrs. Nemser as parties-respondents, so that all proper parties to this proceeding would be before the court on the continued and subsequent hearings.

[P]etitioners are two of three sons of respondent, Sadie Nemser. A third son, a practicing physician in the City of New York, has refused to consent to the surgical procedure recommended by his mother's attending physicians but, while duly served with the moving papers, he did not appear in court on the return day of the motion, either personally or by counsel, to state his reason for such refusal. At the continued hearing on September 13, 1966, however, he did appear before the court, pro se, and, together with each of his brothers, was afforded an opportunity to set forth fully his position with regard to the instant application.

It appears from the papers before the court that Mrs. Nemser, a widow, eighty years of age, had been a resident of the Jewish Home and Hospital for the Aged in this city from May 1964 to August 22, 1966. She has a history of arteriosclerotic heart disease, has suffered at least three

strokes and an equal number of attacks of pneumonia. On August 22, in a medical emergency, she was moved and admitted to Beth Israel Hospital, where she has since then continuously remained. Her physical condition, in substance, was diagnosed as "diabetic and arteriosclerotic gangrene . . . with infection; . . . extensive gangrene of the right foot and heel with inflammatory reaction about both areas. . . ." While recommending an above-knee amputation, in view of their patient's general condition, the attending physicians of Beth Israel Hospital suggested Mrs. Nemser undergo a transmetatarsal amputation (above the ankle). It appears, however, that if the present local infection extends any higher in the front to the leg, it will militate against the transmetatarsal procedure. Moreover, Dr. George Lowen, under whose care Mrs. Nemser was admitted to the hospital, has expressed the opinion that "If delay ensues, further physical deterioration will surely occur. . . . If the deterioration is allowed to progress, death will follow." In a supplemental affidavit, dated September 12, 1966, Dr. Lowen still maintains that "The recommended operation is distinctly a matter of the difference between life and death for Mrs. Nemser." However, as more fully discussed herein-after, Dr. Lowen's prognosis as to the urgency and immediate necessity of the recommended surgical procedure is not supported by any of the other competent medical evidence and opinion before the court.

In view of the fact that an attending psychiatrist of the staff of Beth Israel Hospital, after an examination of Mrs. Nemser, reported that she "is not capable of understanding the nature of any permit for surgery that she might be asked to sign," neither the hospital nor the surgeon will proceed with the recommended operation unless consent thereto is obtained from their patient's next of kin. Upon the physician-son's refusal to consent, as above noted, these legal proceedings were then instituted by petitioners.

It is noteworthy . . . that Beth Israel Hospital's staff psychiatrist does not categorically state that Mrs. Nemser is mentally incompetent for all purposes. Rather, as noted, he limits his opinion to the belief that she is not competent to consent to the operation which is advised by her attending surgeon.

Both Richard G. Green, Esq., the guardian ad litem, and Dr. Abraham N. Franzblau, the court-designated psychiatrist, after painstaking investigation and thorough examination, have submitted detailed reports to the court. Both con-

clude that Mrs. Nemser is not capable of making for herself an informed judgment of whether the subject operation should be performed. Both, however, recommend that under the circumstances recited in their respective reports, intervention by the court is not warranted.

Dr. Franzblau, after setting forth the facts concerning Mrs. Nemser's advanced age, her medical history and present physical condition, indicates that he has spoken with Drs. Friedman and Schwartz, Mrs. Nemser's two medical consultants, with the patient herself, her two sons (one of the petitioners and respondent Dr. Harold S. Nemser) and with the court-appointed Guardian. Dr. Franzblau's report succinctly states:

1. Some difference of opinion exists as to:
 - a) whether the proposed operation is essential to prolong or save Mrs. Nemser's life;
 - b) the prognosis if it is done or, on the other hand, not done; and
 - c) whether the patient's mental status is such that she can understand the proposed procedure, and the significance of any consent that she might give.
2. Both of Mrs. Nemser's sons whom I interviewed appear to be motivated by love for their mother and a wish to see her life prolonged, free of pain and discomfort. Norman, the lawyer is influenced by the opinions of the medical consultants who he has brought in that a transmetatarsal amputation would arrest the spread of the infection and gangrene, and prolong his mother's life. Harold, the physician, is doubtful of his mother's ability to tolerate anesthesia and surgery, and hopes that, treated conservatively and kept "clean," the gangrenous parts would slough off through auto-amputation. The disagreement between the brothers appears to be further clouded by long-standing familial differences over the support and management of their mother, and over the question of the adequacy of her medical care up to the present episode.
3. There appears to be no disagreement among Drs. Friedman and Schwartz, that:
 - a) The recommended procedure as proposed is not a life-saving measure, nor is it a medical emergency
 - b) Its effectiveness is by no means assured
 - c) The same condition may recur in the stump, after surgery, since such wounds heal notoriously poorly in diabetics
 - d) there is no likelihood of ever applying a prosthesis or achieving ambulation in this patient
 - e) there is very little possibility of proceeding ultimately to do the mid-thigh amputation, which is considered as a second and ultimately beneficial stage, in such cases
4. The patient is clearly unable to understand the situation or to render informed consent. (I agree

completely with the opinion of Dr. Weiss as to her mental status.) However, she is aware of her bodily integrity and wants no amputation of any part of her. She wants both to live and to retain her limb, and is not clearly aware of the conflict implicit in these alternatives. Pressed to make a decision, she would be willing to leave it to the doctors, but she would not do so with clear mind or perception. Her consciousness of pain is mercifully diminished by the partial oblivion which has intervened in her condition.

Accordingly, I do not believe that intervention on the part of the Court is indicated.

In substance, the perceptive and detailed report of Mr. Green is the same and, as above noted, terminates in a similar conclusion.

Thus, it becomes apparent that this proceeding, where responsible members of a family, including a physician-son, unfortunately cannot agree on what is medically necessary or proper for their aged and infirm mother, presents an example of a grave dilemma which confronts those who engage in the healing arts and, on the other hand, some basic and fundamental issues on the nature and scope of judicial power and the wisdom or propriety of judicial intervention.

There can be no doubt at all that the Court, Mrs. Nemser's children, and the doctors are most desirous of prolonging the life of Mrs. Nemser without undue pain and suffering. The sympathetic feelings of the Court, however, are, by themselves, hardly enough to clothe it with the right to authorize the surgical procedure or to entertain favorably the within application, particularly in light of the recommendations of the guardian ad litem, the report, and conclusion of the Court-designated psychiatrist and his noted medical opinions of Drs. Friedman and Schwartz. The Court cannot overlook the fact that petitioners rely solely on the opinion and prognosis of *one* physician, whose "life and death" position is neither supported nor corroborated by any of the other medical evidence in the record. Moreover, regardless of their personal differences, I am certain petitioners will agree that their physician-brother-respondent Dr. Harold S. Nemser has the best interests of their mother at heart. It is, therefore, most significant to note that Dr. Nemser categorically stated in open court he believed "assaultive surgery in a terminal case in the name of emergency is cruelty beyond description." He pointed out that while his mother is "foggy" at times, she is, nevertheless, aware of her body and does not want her foot amputated. Dr. Nemser stressed the fact that the recommended operation is not curative, nor is it a mat-

ter of life or death, as suggested by Dr. Lowen alone. Significantly, Drs. Friedman and Schwartz concur in the opinion that the suggested operation, because of Mrs. Nemser's diabetic condition, will not heal. On the contrary, it appears that such surgical procedure may open new areas of infection.

Dr. Nemser also pointed out to the Court that his mother's condition, without the operation, had vastly improved; so much so, that since September 8, 1966 (for at least the immediate five days prior to the continued hearing) she had not required any antibiotics nor was there present any new infection. He feared that his mother's heart condition, her past history of congestive lung failure (not caused by the gangrene) and the traumatic effect of the contemplated operation, if she survived it, would hasten her demise rather than prolong her life.

* * *

[I]t is apparent that this proceeding was necessitated only because of the current practice of members of the medical profession and their associated hospitals of shifting the burden of their responsibilities to the courts, to determine, in effect, whether doctors should proceed with certain medical procedures definitively found necessary or deemed advisable for the health, welfare, and perhaps even the life of a patient who is either unwilling or unable to consent thereto. Thus, petitioners upon the hearing, indicated their concern that if the pending application were to be denied at this time, their mother's attending physicians and the respondent hospital, in the absence of written consent by the next of kin or prior judicial approval, would still refuse necessary surgical treatment if a sudden reversal of her present improved condition mandated it as a real "life or death" solution.

It seems incongruous in light of the physicians' oath that they even seek legal immunity prior to action necessary to sustain life. As the Court has had previous occasion to note, how legalistic minded our society has become, and what an ultra-legalistic maze we have created to the extent that society and the individual have become enmeshed and paralyzed by its unrealistic entanglements! Certainly, if medical procedures are of an emergency nature or are required suddenly to save the life of a human being, neither a physician nor a hospital should be deterred from the exercise of sound medical judgment with respect to necessary treatment merely by threat of possible legal action. Emergency re-

quirements, if, in fact, they are such, should not be delayed nor the responsibility therefor shirked while fearful physicians and hospitals first seek judicial sanction for a determination which, at the end, must, in any event, be a medical decision rather than a legal one.

The history and triumphs of medicine are replete with the names of "medical giants" whose experimentations, medical procedures, techniques, miracle drugs and other discoveries became a boon to humanity. Men and women such as Semmelweis, Jenner, Curie, Sanger, Salk, Walter Reed, Lister, Pasteur and Wasserman would not be deterred by the mere fear of possible legal consequences of their acts. Many of them risked martyrdom to perpetuate the principles and ideals of the Hippocratic oath. . . .

* * *

Here, we have the consent of two of the three responsible members of the immediate family of the hospitalized patient, yet, without judicial approbation the doctors and hospital refuse to go forward with recommended surgical treatment; this, despite the fact that at least one of the attending physicians (Dr. Lowen) believes that if his patient's condition deteriorates, death will ultimately result. Should this or similar emergency conditions actually arise, are the courts prepared to continue to condone the medical practice of requiring written consent or judicial approval first, or is it time that hospitals and physicians are compelled to shoulder this responsibility of making a medical decision? If there were five, ten or more children or members of a patient's family, will the hospital and physician wait to perform a needed operation which they are morally obligated to perform until and unless *all* consent thereto? Is the court to be made the arbiter in all family disputes as to the wisdom or necessity of medical treatment, or is that, in reality, a medical problem to be resolved by the physician, his patient, where possible, and the family, if necessary?

* * *

It is regrettable that the court here is placed in the position of refusing, or what to many may seem the refusal, to act in order to save a life or to ameliorate suffering. The contrary is the fact. It is because of the court's deep concern for Mrs. Nemser's life and well-being that it is reminding those whose responsibility it actually is, to act appropriately, not arbitrarily, and without fear. The court, likewise, is not unmindful that whatever course is followed by those persons who

are ultimately responsible here, it may prove fatal. Similarly, the court is aware that on occasions where other agencies of government or society fail to act, it must intervene for the common good. . . .

* * *

. . . I am constrained to hold that the application to be appointed her temporary legal representatives for the specific and limited purpose of executing a consent to a transmalleolar amputation is denied and the petition is dismissed.

NOTES

NOTE 1.

E. E. MENESEE

THE RIGHT TO LIVE AND THE RIGHT TO DIE*

* * *

The decision as to when it is best to push ahead with all resources or best to withhold or even draw back slightly is one that should not and cannot be made by the physician alone. The immediate and responsible family members must make the decision, but with the guidance, advice and help of the physician. . . .

Let me give you an illustration. I have a brilliant professional man as a patient. He has bronchogenic carcinoma with metastases to the skeletal system. It was severe pain that first took him to his personal physician. Full doses of radiation therapy have given only enough relief to make life bearable provided he lies perfectly still. The slightest motion precipitates paroxysms of excruciating pain. Neuro-surgical procedures have failed to give relief. Chemotherapy has made him symptomatically worse. For eight long weeks we have struggled along. I believe that, with intravenous feedings, oxygen therapy, constant nursing care, antibiotics, attention to correction of electrolytes, et cetera, we may be able to extend his span for two or three months. Should we? I have never thought of doing or giving anything that would shorten his life, but as a physician I wonder how determined I should be in extending a hopeless situation. If the patient had his full faculties, would he choose two months of pain? Would he prefer his financial resources to be spent on two more months of hospital and medical care, or would he think it better to use them to complete the college education of his children? Twice, when he has begun to develop pneumonia, we have checked his rapid

* 95 *Medical Times* 1171, 1178-1179 (1967). Reprinted by permission.

downhill course with antibiotics. If the same situation arises the third time, should I again start intensive drug therapy, and use oxygen and fluids and transfusions, or should I let him slip rapidly away? . . . If I were the patient, I think I should prefer comfort and solace to science. Nevertheless, key members of the family feel we should continue to put forth our maximum effort. We shall do so unless they change their minds. I feel it my duty to let them have the full facts, to let them see the situation as it is, but it is not my duty to try to persuade them. They have confidence in me and I am sure they will feel free to come to me and say, "This is enough," if they reach that decision.

In another instance, we were faced some years ago with a very personal problem when a loved member of our family developed a hopeless and painful disease. After she recovered enough from her second operation—pinning a pathological fracture—we decided to bring her home. We did not give fluid by hypodermoclysis nor did we insist she eat when it was agony to do so. We did not gavage her, nor did we give oxygen or blood or antibiotics. We did give love and support and care, and enough drugs so that she could get some rest and be relatively free from pain. She died in peace and in dignity, with only her family in attendance. I have never regretted that decision.

There is another aspect of prolonged hospital care and terminal illness which must be considered. This, in brief, is the question of whether, with the shortage of hospital rooms and personnel which exists now and perhaps for the foreseeable future, we as physicians have a right to tie up space that might otherwise be utilized for actually saving lives. The Federal Government has recognized this problem in its Medicare laws by requiring careful review of patients' records to make certain not only that they are receiving the best medical care but that hospitalization is necessary. As a member of the Utilization Review Committee in my hospital, I am aware of certain patients who have been maintained actually for years. This is certainly a tribute to medical science, hospital facilities, and devoted nursing care. On the other hand, the utilization of hospital space and personnel in this manner has meant that at least 200 other patients have been denied admission. There are not enough beds to admit everyone. Is it correct and is it proper that we should prolong life by using the hospital facilities and at the same time refuse other patients a chance which might mean not only the difference between life and death but

perhaps, as well, a complete recovery and return to a useful place in society?

NOTE 2.

FRANK J. AYD, JR.
VOLUNTARY EUTHANASIA—THE RIGHT
TO BE KILLED*

* * *

All ill people are obligated to use ordinary means to preserve life, but they are not bound to seek extraordinary treatment except in unusual circumstances. As one moralist puts it: "At times one may be bound in charity to one's dependents or to one's fellow citizens to employ extraordinary means to preserve one's life. In order that such an obligation be present, two conditions must be fulfilled: (1) One is necessary to one's family or fellowmen. (2) The success of the extraordinary means is very probable."

An ill person is not obligated to do what is physically or morally impossible. Hence, he can validly refuse treatment which would entail great suffering, which would overtax the will power and courage of the normal person, or which would financially impoverish his survivors, especially if the anticipated benefits would be of limited value and brief duration. Likewise, a physician, with the patient's consent, may licitly desist from administering treatments that are demonstrably ineffective and be satisfied with alleviating the patient's suffering. No one is required to do what is practically useless. A doctor is not under compulsion to make every effort to prolong every patient's life. Hence, what physicians call negative euthanasia in certain circumstances is not only morally permissible but can be obligatory. In fact, this is not euthanasia and should not be called even negative euthanasia.

* * *

There should be no need for positive euthanasia and there would be no demand for it if doctors acknowledge that it is neither scientific nor humane to use artificial life-sustainers when death is imminent and inevitable and realistic hope of recovery has evaporated. Also there should be no need or demand for positive euthanasia if physicians unhesitatingly administer whatever amount of pain-relieving drugs a dying patient needs. The medical profession already has the power to make any demand for legalized euthanasia seem pointless, or even mischievous.

* *Medical Counterpoint* 12, 20-22 (June 1970). Reprinted by permission.

All doctors have to do is apply their skills prudently, as they are morally and legally empowered to do. . . .

No one has the right to be killed and physicians should oppose strenuously any proposal to legalize euthanasia. There are many reasons for this. It would be very dangerous indeed to empower doctors to kill, on demand, the patients they cannot cure. For the conscientious doctor it would be a most difficult and strainful task to decide at what stage of an illness a patient would qualify for euthanasia. It also would be extremely difficult for such a doctor to be sure that the patient knew what he was doing when he requested euthanasia. (For the unscrupulous doctor, and there are such, there would have to be very rigorous safeguards against loopholes for murder.) And even with the conscientious doctor there would be patients at risk, for none of us are 100 per cent psychologically and morally sound and perversions could creep into the practice of legalized euthanasia. It is better for the community to tie the hands of a good doctor by refusing to legalize voluntary euthanasia, in order to restrain an unscrupulous one from violating the rights of the individual.

* * *

If voluntary euthanasia were legal, there would be a standing risk of a person consenting to his extinction on an erroneous calculation of his prospects. If it were to become an acknowledged function of the medical profession to end life prematurely, could patients place themselves with complete trust in the care of physicians? A patient's trust in his doctor is important both for his peace of mind and for his recovery.

* * *

NOTE 3.

JOSEPH FLETCHER
VOLUNTARY EUTHANASIA—
THE NEW SHAPE OF DEATH*

* * *

[T]here are four distinguishable and different forms of death as chosen rather than coming willy-nilly or perforce. This typology is based on the formal categories of ethics and moral theology.

First, there is euthanasia as a *direct voluntary*; that is, the patient chooses to end it all,

whether it is done with or without medical help. . . .

Second, there is euthanasia as an *indirect voluntary*; that is, the patient gives others the discretion to end it all as the situation requires—especially if the patient is too comatose to decide. . . .

Third, there is euthanasia as an *indirect involuntary*; that is, the incompetent patient's wishes are not known and others have to choose for him. This is, of course, the most common case. It happens in thousands of hospitals every day. . . .

* * *

Fourth, there is euthanasia as a *direct involuntary*; that is, the simple "mercy killing" of another, with or without his present or past request—as when an idiot is given a fatal dose or a man trapped inextricably in a blazing fire is shot to end his suffering.

* * *

For a while in the past it seemed worthwhile to use the term "euthanasia" for only the direct form, and to call the indirect form ("letting the patient go") by the cumbersome neologism "anti-dysthanasia." But subsequent thought and experience has shown this to be a mistake. The problem of a good death is at stake in every and all forms. Nothing is won by playing the word game, and those who are locked in and committed to opposing euthanasia are not really being helped by linguistic escape hatches. . . . They might well quote Pascal's observation: "Since men have not succeeded in eliminating death, they have decided not to think of it."

In our investigation of the problem of elective death we should give very serious consideration to the distinction between merely biological life and truly human life. If it is a valid and important distinction, as this writer thinks, then it may provide some cross-illumination of our problems at both ends of the life spectrum. "When is life gone?" if seriously asked, becomes the question "When is *human* life gone?" whether biological life continues or not. . . .

* * *

In absolutistic and divine-natural law ethics some things, like euthanasia, are never open to responsible decision and choice (i.e., they are removed from the forum of conscience and morality); but in situation ethics all things (including birth and death) are subject to responsible decision. What is not open to choice is unmoral or

* *Medical Counterpoint* 13, 17-23 (June 1970). Reprinted by permission.

non-moral, outside the range of ethical problems. . . .

Years ago at a meeting of the American Cancer Society the essence of medical objections to euthanasia in any of its forms was expressed by Dr. David Karnofsky, whose work at the Sloan-Kettering Institute was a great step forward in research. He said that physicians are duty bound to do anything and everything they can to keep life as long as is technically possible. Like so many earnest and able people in medicine, Karnofsky was saying in effect that *biological* life, not human life, is the first-order value, the highest good or *summum bonum* to which, if necessary, all other values should be subordinated. This is what philosophers call ethical vitalism, and it is opposed by all those who prize *human* life—such as dignity and self-possession and rationality—more than the sheer or mere facts of respiration, digestion or (alas) incontinent excretion! Humanism or personalism, rather than vitalism, is by far a better faith-foundation for medicine. As I have put it in another essay, "Doctors who will not respire monsters at birth—the start of life—will not much longer have any part in turning people into monsters at the end of life."

I used to think that the physicians' Hippocratic Oath contradicted itself because it promised both to preserve life and to relieve suffering, while in some situations one or the other must be chosen. Further examination of the best texts of the Oath, however, have made it clear that it contains no such logical error. The Oath says nothing at all about preserving life. It says that "so far as power and discernment shall be mine, I will carry out regimen for the benefit of the sick and will keep them from harm and wrong." Whether we find any reason ever for euthanasia depends upon how we understand "benefit of the sick" and "harm" and "wrong." Dehumanized biological life is sometimes real harm and the opposite of benefit, and to refuse to welcome or even introduce death would be quite wrong.

The day will come when people will be able to carry a card, notarized and legally executed, which explains that they do not want to be kept alive beyond the *humanum* point, and authorizing the ending of their lives in *extremis* by any of the distinguishable methods which seems appropriate. . . .

In the same vein Dr. Charles Hofling of the Medical School at Washington University (St. Louis) says, "Hospitals of the future will have 'death boards' . . . to discontinue the artificial

measures by which life is being maintained" to act upon a patient's request or a next-of-kin's or a physician's. Such proposals at least have the merit of rising above a lot of the present-day dishonesty and sub-rosa euthanasia, even though many physicians prefer to keep the under-the-rose policy because it gives them sole control. . . .

NOTE 4.

ARVAL A. MORRIS
VOLUNTARY EUTHANASIA*

* * *

. . . Voluntary euthanasia can be justified by reference to three basic values of western civilization: (1) prevention of cruelty; (2) allowance of liberty; and (3) the enhancement of human dignity, an ultimate goal which is achieved by adhering to the first two values.

All civilized men will agree that cruelty is an evil to be avoided. But few people acknowledge the cruelty of our present laws which require a man be kept alive against his will, while denying his pleas for merciful release after all the dignity, beauty, promise and meaning of life have vanished, and he can only linger for weeks or months in the last stages of agony, weakness and decay. In addition, the fact that many people, as they die, are fully conscious of their tragic state of deterioration greatly magnifies the cruelty inherent in forcing them to endure this loss of dignity against their will. . . .

Beyond such direct cruelties, our current law also indirectly results in other cruelties as well, and these must all be weighed in the balance. For example, it seems exceedingly cruel to compel the spouse and children of a dying man to witness the ever-worsening stages of his disease, and to watch the slow, agonizing death of their loved one, degenerating before their eyes, being transformed from a vital and robust parent and spouse into a pathetic and humiliated creature, devoid of human dignity. The psychological trauma that comes from witnessing such a spectacle may deeply affect, or permanently impair, the mental and physical health of both children and spouse. Finally, we cannot ignore the residual, indirect cruelty which survives the death of the afflicted person, and burdens the surviving family with the costs incurred in the treatment of the prolonged illness. Enormous medical debts can impair or destroy a child's educational opportunities, for example, and recogni-

* 45 *Washington Law Review* 239, 251-255 (1970). Reprinted by permission.

tion of such gloomy prospects will undoubtedly prey heavily on the mind of the terminally ill parent or relative, adding to the pain and suffering which he already endures.

* * *

The second social value which supports the case for voluntary euthanasia, and promotes the cause of human dignity, is that of liberty. In this context, our law has got the shoe on the wrong foot from the very beginning. Why does our law provide that when a person participates in voluntary euthanasia it constitutes the crime of murder? To have fidelity to liberty, the question should be reversed. We should start from the assumption that all voluntary acts are permissible, and, in the absence of some legitimate reason to deny it, we would presume that a doctor and a patient are free to act as they wish. The question should not be: "Why should people have a legal right to voluntary euthanasia?" but rather, the appropriate question should be: "Why should our criminal law restrain the liberty of the doctor

and the patient, denying them from doing what they want?" In a free society it is the restraint on liberty that must be justified, not the possession of liberty. The criminal law should not be called upon to repress an individual's conduct unless such repression is demonstrably necessary on social grounds. Further, in the case of voluntary euthanasia, this demonstrably compelling interest must be secular, not religious. Yet it is entirely unclear what secular social interest is so compelling that it justifies preventing the incurably ill sufferer from exercising his liberty of choice to accelerate death by a few hours, days, or even months; or what interest justifies the application of criminal deterrents to a voluntary euthanasia case.

... Why should the law deny a man the ultimate decision about what to do with his life? In the final analysis, control over one's own death is a matter of human dignity, and it should not be denied without some very compelling reasons.

* * *

B. In Society's Interests?

1.

Overruling Consent to Prevent "Harm"

a.

Alexander M. Kidd Limits of the Right of a Person to Consent to Experimentation on Himself*

* * *

[Consider] the question of experimentation on persons—with their consent—not for any disease and not for any direct benefit to the patient, but solely for the advancement of science. How far can one consent to serious injury to himself? The analogies are not close. Abortion, except for therapeutic reasons, is a crime, and the consent of the woman is no defense for the doctor. A person cannot legally consent to his own death; it is murder by the person who kills him. Societies in England and the United States are trying to legalize euthanasia for those suffering from incurable disease, and juries have sometimes acquitted a parent who has put a suf-

fering child out of his misery. If it had been his dog instead of his child, he would have been punished for not killing it. In the case of the birth of monstrosities the doctor may perform the killing and no one be any the wiser, but legally it is murder. A person may not consent to a serious injury amounting to a maim. The classical case was the man who cut off his hand to make himself a more successful beggar. Injuries inflicted to avoid military service are not unknown, and are criminal.

Sterilization presents a more difficult problem. The late Lord Riddell seemed to condemn it without exception but, in the same volume, approved it for the feeble-minded. Statutes concerning the feeble-minded have been sustained. In this country what little authority there is seems to permit sterilization where death, insanity, or serious disability would result from pregnancy. Economic considerations based on the number of children are a doubtful basis, and it probably would not be sanctioned simply to avoid the possibility of having children.

These situations all involve serious injury inflicted by consent for the direct advantage of the one permitting it. The motive of the advancement of science presents a different case.

* 117 *Science* 211, 212 (1953). Reprinted by permission.

. . . No prosecution seems to have followed where antivaccinationists have been encouraged to receive smallpox germs, or religious fanatics to submit to snake bites. Although there are no cases, it could not be considered a crime of the experimenter where the highest public praise is accorded to those incurable who offer themselves for experimental purposes in order that persons may not have to suffer in the future as they have. The airmen who have died in pressure experiments to make air travel possible for others, the Walter Reeds who have risked disease germs to determine causation where animal experimentation has failed, and other martyrs to science who have missed success except in a negative way so that that particular experiment need not be repeated, are heroes.

* * *

NOTES

NOTE 1.

MATTHEW V. OLLERTON
90 ENG. REP. 438, COMBERBACK 218 (1693)

. . . If I licence a man to beat me, such licence is void.

CURIA. The defendant may refer to the plaintiff himself, if he will; but licence to beat me is void, because 'tis against the peace. . . .

NOTE 2.

BRAVERY V. BRAVERY
[1954] 3 ALL E. R. 59

* * *

DENNING, L. J.:

* * *

. . . An ordinary surgical operation, which is done for the sake of a man's health, with his consent, is, of course, perfectly lawful because there is just cause for it. If, however, there is no just cause or excuse for an operation, it is unlawful even though the man consents to it. . . .

. . . Take a case where a sterilisation operation is done so as to enable a man to have the pleasure of sexual intercourse without shouldering the responsibilities attaching to it. The operation then is plainly injurious to the public interest. It is degrading to the man himself. It is injurious to his wife and to any woman whom he may marry, to say nothing of the way it opens to licentiousness; and, unlike contraceptives, it allows no room for a change of mind on either side. It is illegal, even though the man consents to it, for it comes within the principle stated by

STEPHEN, J. (who was a great authority on criminal law), in *R. v. Coney* (2) (8 Q.B.D. 549):

The principle as to consent seems to me to be this: When one person is indicated for inflicting personal injury upon another, the consent of the person who sustains the injury is no defence to the person who inflicts the injury, if the injury is of such a nature, or is inflicted under such circumstances, that its infliction is injurious to the public as well as to the person injured.

* * *

NOTE 3.

H. L. ROXBURGH
EXPERIMENTS ON HUMAN SUBJECTS*

* * *

In England there is no statute which specifically controls the conditions under which experiments can be done. . . .

A civil action might arise as a result of an accusation of assault, or trespass to the person, in the absence of injury. This is unlikely to be successful provided that a valid consent has been obtained, on the principle of *volenti non fit injuria*. Should it be alleged, however, that a subject had suffered injury or death as a result of an experiment, the matter seems not so simple. Judgment would depend in large part on, in *Ladimer's* phrase, "How the investigator proceeded and how he checked himself." Courts might well construe any evidence in favour of the plaintiff if doubt existed, and it is useful to analyse this phrase in some detail. . . .

That a subject is a volunteer is not alone sufficient and, although he might weaken any case by volunteering, this would have to be decided in the courts, and he would still have the remedy in law against any negligence that had been committed. Suppose, however, there has been no negligence and an experimental procedure by its nature must have an unknown outcome, what is then the position if death or injury results? Obviously a consent valid in law is a prime essential. The subject must comprehend the nature and extent of the risks involved, and no element of force, fraud, duress or coercion may be used. . . .

Regarding criminal aspects, the following principles of English law appear to have relevance.

- (a) No one has the right to consent to the infliction upon himself of death or of

* 3 *Medicine, Science and the Law* 132, 134-136 (1963). Reprinted by permission.

any injury likely to cause death, except for necessary surgical purposes.

- (b) It is uncertain to what extent any person has the right to consent to his being put in danger of death or bodily harm by an act of another.

As distinct from civil actions, the question of consent is of little relevance, for if the experiment be itself criminal, agreement of the subject is immaterial. Justification of the experiment would not be recognised as a valid defence in law for any criminal action, though it might be accepted in mitigation of the gravity of an offence. The justification might change from time to time, for example in time of war the moral justification for any procedure might be increased by the urgent national need to gather data quickly.

Considerations of public policy may have significance in connection with experimental work for the general benefit of the state and its subjects, and exceptions to the general legal rules may have application. Well established exceptions do not, however, include any situation directly parallel to that under consideration. For example, the case of those who "cause injury in recreations for a trial of skill or manhood or for improvement in the use of their weapons" is quoted as an exception because "bodily harm was not the motive on either side" (*R. v. Donovan* [1934] 2 K.B. 498). Whether a court would, in fact, accept this as analogous cannot be stated with certainty. . . .

* * *

b.

Spead v. Tomlinson
73 N.H. 46, 59 A. 376 (1904)

* * *

Case to recover for damages alleged to have been suffered by the plaintiff at the hands of the defendant, who is a Christian Science healer. . . . In April, 1898, the plaintiff, who was then about 55 years old, suffered from an attack of appendicitis, employed a medical practitioner for several months, and learned in a general way the course pursued by physicians in the treatment of that disease. During the summer of 1899 she became interested in the doctrines of Christian Science, and attended meetings where the defendant told of wonderful cures he had performed. November 13, 1899, the plaintiff noticed symptoms similar to those which had ushered in the previous attack of appendicitis, visited the defendant at his home, informed him of the nature of her trouble and her dread of a

surgical operation, and employed him to treat her. The defendant told her that a surgical operation was not necessary, that she was not to take any medicine, and that he could and would cure her if she continued his treatment. He directed her to read "Science and Health," to continue her usual diet of solids, and to take her accustomed exercise. He also read to her extracts from "Science and Health," and administered treatment by sitting in front of her in an attitude of prayer. The plaintiff employed the defendant for several days, and during this time her illness increased. She finally placed herself in the hands of physicians, submitted to a surgical operation, and was cured. There was evidence tending to show that the defendant's treatment was injurious to the plaintiff, and that, if it had been persisted in, a cure would have been impossible. . . .

ON REHEARING

* * *

YOUNG, J.

By "public policy" is intended the policy of the state as evidenced by its laws. . . . If the plaintiff is to recover on the ground of public policy, she must establish (1) that it was illegal for the defendant to give her such treatment; (2) that the duty of not giving it was imposed on him for her benefit; and (3) that no illegal act of hers contributed to cause her injuries. It is the general rule that the plaintiff in an action sounding in negligence must show that the defendant failed to perform a duty owed him, and that his own failure to perform a duty owed the defendant did not contribute to cause his injury; or, in other words, he must show the defendant's fault and his own freedom from fault. Assuming (without deciding) that such treatment is forbidden by the provisions of section 8, c. 278, Pub. St. 1891, which makes the killing of a human being by culpable negligence manslaughter, or by the provision of the common law which makes it unlawful for any one to do what is liable to endanger the life or health of others, and that the duty of not doing what is forbidden by either provision was imposed on the defendant for the plaintiff's benefit, the question still remains whether the plaintiff's own wrong contributed to cause her injuries. It is elementary that, if it was illegal for the defendant to treat the plaintiff as he did, it was equally illegal for her either to knowingly employ him to give her such treatment, or to consent to be so treated. So far as

the evidence goes, her knowledge in respect to the disease from which she was suffering and the treatment prescribed for it by regular physicians in good standing, and in respect to the way the defendant proposed to treat her, was at least equal to his.

It does not follow, as a matter of law, from the fact that the plaintiff cannot recover in this action on the count in negligence, that the defendant would not have been guilty of manslaughter if the plaintiff had died from the effects of his treatment. If he had been indicted under the provisions of section 8, c. 278, Pub. St. 1891, the state would base its right of action on his failure to perform a duty the law imposed on him for its benefit. The state has a direct interest in the lives and health of all its citizens. Every one who has to do with the lives and health of others not only owes the individuals with whom he comes in contact a legal duty, but also owes the state the duty of using ordinary care to do nothing which will endanger their lives or health. In an action by the state it would be no answer to show that, if the deceased had used ordinary care to avoid being injured, he would not have died; for the defendant is not indicted for his failure to perform a duty the law imposed on him for the deceased's benefit, but for his failure to perform one imposed on him for the benefit of the state. . . .

* * *

. . . The plaintiff fails because of the insufficiency of her evidence to prove the facts necessary to maintain her case.

Exceptions overruled.

C.

Edmond Cahn Drug Experiments and the Public Conscience*

* * *

[S]ometimes a consent will be unacceptable because of extrinsic circumstances that convert it into an exploitation of sickness or need, for example, the consents to irreversible sterilization that certain states in India have been purchasing from untouchables for small sums of money. At other times, a consent is unacceptable because of intrinsic circumstances, that is, circumstances having to do with the prospective consequences of the experiment and their relation to human dignity. One can conceive conditions un-

der which a consent might be acceptable even where the experiment might involve a serious risk of death. Where however the experiment involves a serious risk of permanent physical or psychic mutilation, the consent should not be accepted. For example, a consent would be unacceptable if the experiment involved a serious risk of converting a subject who was mentally normal into a psychotic. On the other hand, as every physician knows, there are psychiatric conditions grievous or critical enough to warrant even the risk of psychic mutilation, but in such conditions the justification for taking the risk must be found in the possible benefit to the ailing subject, not alone in his consent or in possible increment of scientific knowledge.

* * *

[A]s I see it, it is not primarily a question of what a subject can consent to, for under sufficiently extreme circumstances he may insist that he can consent to almost anything, and who has the right to contradict him without having had personal experience of just such circumstances? The moral impossibility is on the other side, *our* side. It is we who *cannot accept* certain consents that are ostensibly free and voluntary; it is we who are unable to accept a profit from human sacrifice. The ceiling price that we impose on scientific progress is the product of our own moral self-image, our enduring convictions and our social conscience.

* * *

2.

Demanding Consent to Prevent "Harm"

a.

Louis L. Jaffe Law as a System of Control*

* * *

[N]either in law nor in practice is the process of consent a single, clearly defined entity. Consent is a function of the relation between experimenter and subject and is modulated by the degree of risk, the alternative treatments (in a therapeutic situation), and the value of the experiment. There is wide range of opinion as to

* Paul Talalay, ed.: *Drugs in Our Society*. Baltimore: The Johns Hopkins Press 255. 264-265 (1964). Reprinted by permission.

* 98 *Daedalus* 406, 420-422 (1969). Reprinted by permission of Daedalus, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

the significance of consent. Dr. Louis Lasagna has said:

I want to take issue with Dr. [Jay] Katz's notion that consent is the pre-eminent question. Consent is primarily important in the abstract and appeals to those who are interested in civil libertarian problems. The major protection of the patient, however, comes from the review of protocols by peer and non-peer groups, from the competence of the investigator, and all the ancillary facilities at his disposal, and from monitoring the performance of experiments.

Such an opinion may reflect two quite different and opposed attitudes: the angry and contemptuous attitude of the investigator who finds his project complicated by requirements of consent so elaborate that his experiment is impeded; and, on the other hand, the attitude, if you accept Dr. Lasagna's epithet, of "the civil libertarian" who is afraid that the will of the subject may be easily overborne or even disregarded, and who may take refuge from his concern in the hope that other safeguards will protect the subject.

The common law sets a high value on consent to physical invasions that threaten the health or psychic integrity of the individual. The law rightly recognizes that the body is his fortress. Nevertheless, the inviolability of the body is not absolute. . . .

. . . Consider the case of *O'Brien v. The Cunard Steamship Lines* . . . 28 N.E. 266 (1891), which had to do with an immigrant who was being brought into the port of Boston. All the immigrants were lined up rather ignominiously to be vaccinated. When she passed by the vaccinating physician, Mrs. O'Brien said that she had already been vaccinated. Nevertheless, the doctor told her to hold up her arm and she was punctured. She later claimed that she did not consent. The Court held that her actual state of mind was irrelevant; that the consent should be looked at from the point of view of the defendant. Had the plaintiff in this situation been submitting to serious risk, the Court would not have focused on the defendant alone, though as pointed out by Professor Calabresi there is a risk (though slight?) of encephalitis. There were, of course, great pressures on her to accede to vaccination that in another situation would be held to negate completely the idea of consent. (Her only alternative was to turn around and go home or perhaps into quarantine.) But given the kind of relationship, the

interests of the state, the interests of getting the vaccinations done effectively and quickly, the law was prepared to take a cavalier attitude toward the claims of Mrs. O'Brien's personality. This case exemplifies the notion that in any situation, as should be true whether or not the medical personnel are public officers, the law will look at the structure of the situation to see what is demanded in terms of the interest of society, on the one hand, and the interests of the individual, on the other.

* * *

NOTES

NOTE 1.

JACOBSON V. MASSACHUSETTS
197 U.S. 11 (1904)

MR. JUSTICE HARLAN delivered the opinion of the court:

* * *

. . . The defendant insists that his liberty is invaded when the state subjects him to fine or imprisonment for neglecting or refusing to submit to vaccination; that a compulsory vaccination law is unreasonable, arbitrary, and oppressive, and, therefore, hostile to the inherent right of every freeman to care for his own body and health in such way as to him seems best; and that the execution of such a law against one who objects to vaccination, no matter for what reason, is nothing short of an assault upon his person. But the liberty secured by the Constitution of the United States to every person within its jurisdiction does not import an absolute right in each person to be, at all times and in all circumstances, wholly freed from restraint. There are manifold restraints to which every person is necessarily subject for the common good. On any other basis organized society could not exist with safety to its members. Society based on the rule that each one is a law unto himself would soon be confronted with disorder and anarchy. Real liberty for all could not exist under the operation of a principle which recognizes the right of each individual person to use his own, whether in respect of his person or his property, regardless of the injury that may be done to others. This court has more than once recognized it as a fundamental principle that "persons and property are subjected to all kinds of restraints and burdens in order to secure the general comfort, health, and prosperity of the state; of the perfect right of the legislature to do which

no question ever was, or upon acknowledged general principles ever can be, made, so far as natural persons are concerned." *Hannibal & St.J. R. Co. v. Husen*, 95 U.S. 465, 471, . . . In *Crowley v. Christensen*, 137 U.S. 86, 89 . . . we said: "The possession and enjoyment of all rights are subject to such reasonable conditions as may be deemed by the governing authority of the country essential to the safety, health, peace, good order, and morals of the community. Even liberty itself, the greatest of all rights, is not unrestricted license to act according to one's own will. It is only freedom from restraint under conditions essential to the equal enjoyment of the same right by others. It is, then, liberty regulated by law". . . .

* * *

NOTE 2.

COMMITTEE FOR SAFEGUARDING HUMAN DIGNITY COMPULSORY POST-MORTEM OPERATIONS IN ISRAEL*

* * *

The [autopsy] law in effect [in Israel] at present is the Anatomy-Pathology Law of 1953. Paragraph six of this law states:

A doctor may dissect a body in order to determine the cause of death, or to use parts of the body for healing purposes, if three authorized doctors sign a certificate attesting to the fact that the post-mortem operation will serve one of these purposes. (Sefer Hachukim 184, 4.8.1953).

Neither the deceased nor his family are mentioned in or recognized by this law. They have been denied the right to make the decision on a matter in which they are vitally involved, and, in their stead, three doctors, who *need not even consult* the family, have been given the power to authorize a dissection.

* * *

NOTE 3.

R. A. McCANCE THE PRACTICE OF EXPERIMENTAL MEDICINE†

* * *

. . . I would feel happier, however, for the future, if patients could be made more aware

* Jerusalem: The Committee for Safeguarding Human Dignity (1968).

† 44 *Proceedings of the Royal Society of Medicine* 188, 194 (1950). Reprinted by permission.

that at some hospitals—the best hospitals—experimental work is carried out not only for the benefit of the immediate sufferers, but also for the benefit of mankind, and that they themselves owe incalculable advantages to work of this kind which has already been done on others; furthermore, that if they or their children are privileged to be admitted to these hospitals, they may be expected to co-operate. In the form given to patients on admission to one hospital I know, there is a small paragraph and the addition of a few words to it illustrates the sort of thing I have in mind. The additions proposed are in italics. "The hospital staff seeks your assistance in carrying out the hospital's duty to the community in the *investigation of disease and in the training of doctors and nurses*; if a member of the staff wishes to *make a special study of your condition* or to explain it to a medical student, doctor or nurse, it is hoped that we may have your co-operation."

* * *

NOTE 4.

WALTER MODELL THE ETHICAL OBLIGATIONS TO THE NONSUBJECT*

The problem of the obligations of the experimenter to his human subject is generally recognized as a highly charged one. . . . It seems, to me, however, that the forgotten man is the innocent bystander, the patient whose medication will depend on the outcome of experiments on other men, the nonsubject whose apparent nonparticipation is only temporary since he will ultimately participate by virtue of the medication he is given. Eventually, collectively, the nonsubject is an interested party, albeit a late comer. It is he who, sooner or later, will suffer or benefit from experiments or from the failure to perform the right ones. . . .

* * *

b. Oscar M. Ruebhausen and Orville G. Brim, Jr. Privacy and Behavioral Research†

* * *

While the knowledgeable, freely given consent of a participant should be a basic ground

* 1 *Clinical Pharmacology and Therapeutics* 137 (1960). Reprinted by permission.

† 65 *Columbia Law Review* 1184, 1201-1202 (1965). Reprinted by permission.

rule for all behavioral research, there is, of course, a need for exceptions. There must be, indeed, a fundamental exception to cover the many instances where society will accept the invasion of privacy as permissible and reasonable. Thus, when the general welfare requires it and due process is observed, our society permits the taking of private property without consent. There is no reason to doubt that, under similar circumstances, society will permit at least a limited invasion, or taking, of private personality. Circumstances under which the community tolerates the probing into private areas without the consent, and, if necessary, without the knowledge of the examinee do, in fact, exist. A number of examples can be easily found in law enforcement, in selection for military service, in social welfare work, in the protection of the public health, in the national census, and in the selection of employees for the Central Intelligence Agency or as airline pilots.

A public trial may also invade the privacy of the individuals involved in the litigation. Yet since our society is persuaded that a public hearing is essential to a fair trial and to social order, it finds entirely reasonable that the individual claim to privacy must yield in this instance. even here, however, the equilibrium between the competing values is sensitively preserved and there are occasions when the court is cleared, or the testimony sealed.

Even where the public interest may warrant the taking of private property or of private personality, no absolute license is justified. The taking should be reasonable, it should be conducted with due process, and it should be limited to no more than what is necessary for the fulfillment of the public purpose which, in fact, warranted the invasion.

* * *

PART FOUR

The Authority of Professional and Public Institutions

This Part explores the role of professional and public institutions in formulating, administering, and reviewing the human experimentation process. The preceding analysis of the authority of the investigator and the subject disclosed the limits of their capacity to make "acceptable" and "informed" decisions and indicated that society has an interest in encouraging or discouraging certain investigations. We now inquire whether, despite these considerations, the human experimentation process should nevertheless be left to the initiative of investigators and to the arrangements they make with their subjects because the participation of other decisionmakers would impose greater burdens than benefits on the process. If, on the other hand, the private ordering between investigators and subjects is found wanting, we must scrutinize how and to what extent it should be supplemented by other mechanisms of guidance and control exercised by the professions (*e.g.*, hospital committees, professional associations, and editorial boards), the state (*e.g.*, administrative agencies, courts, and legislatures), and other public or private groups (*e.g.*, the press, public interest organizations, and private litigants).

We have previously spoken of "subjects" as a group without taking into account differences among them. This reflects in part the lack of consensus about the ambit of experimentation and in part the lack of agreement on who is a fit subject for research. We now introduce a distinction between volunteers* (subjects who are not patients at the

* We have been unable to coin a better term for this group of subjects. The more precise term "nonpatient-subject" seems too cumbersome, and the simpler label "subject" is better suited as a generic term for all subjects be they patients or nonpatients. However, the use of the label "volunteer" must not foreclose a searching inquiry into the voluntariness of all subjects' participation.

initiation of a research project) and patient-subjects (subjects who are also patients at the initiation of the research project). This distinction should alert the student that the label "volunteer" has been employed all too indiscriminately to include, among others, "healthy" individuals and patients who undergo experimental manipulation; "healthy" individuals and patients who serve as controls for investigations; and incompetent individuals who are "volunteered" by others as subjects for investigation.

The distinctions between volunteers and patients suggest that differences in status among subjects require analysis. The examination of consent in Part Three has already uncovered major limitations on the capacity of some subjects, particularly when they are also patients, to give meaningful, informed consent. In light of such considerations, the framework of the chapters in this Part is built around a division of subjects into several groups. Chapter Eleven is primarily concerned with the general subject population who are considered capable of giving consent and who participate in research either as volunteers or as patients. In the three chapters which follow, the focus shifts to investigations with uncomprehending, captive, and dying persons, respectively. The division of subjects into these groups is based on the assumption—which must be carefully examined—that there are distinctions among these groups which require the development of special rules and mechanisms to reflect and respond to the varying capacity of the individuals in each group to participate understandingly in the experimentation process. Moreover, examining each of these groups separately highlights difficulties common to the human experimentation process as a whole; for example, the analysis of the special problems raised by investigations with prisoners illuminates the impact of external pressures which, though often not as clearly perceived, affect non-captive subjects as well.

The case studies which precede the analytic sections of these chapters are designed to provide data for the analysis of the interactions between the professions and state and the different groups of volunteers and patient-subjects. In addition, many of the case studies presented in the earlier chapters may bear re-examination. They have already suggested the need for professional and state participation in decisionmaking; they may now contribute further data for the ultimate task of this volume—analyzing the role of all participants in the human experimentation process.

Throughout we ask:

1. What persons and institutions should have the authority to formulate, administer, and review the human experimentation process?
2. Should the authority of these persons and institutions differ at each decisionmaking stage?
3. To what extent should this authority be modified once subjects are labeled "volunteer," "normal," "diseased," "competent," "uncomprehending," "captive," or "dying"?

CHAPTER ELEVEN

Experimentation with Volunteers and Patient-Subjects

As a prologue to the subsequent analysis, this chapter opens with an expression of views by a governmental commission, a theologian, a physician, a judge, a lawyer, and a philosopher on the competing interests of science, society, and the individual. Their common quest is for a balancing of society's interests which at one and the same time will protect the individual's well-being and right to self-determination and encourage the acquisition of knowledge through scientific investigation.

The case studies in this chapter on the discovery of a reliable oral contraceptive pill and the search for an effective surgical treatment of mitral stenosis focus on the role assumed by professional and public institutions in experimentation with subjects who are sufficiently "competent" to participate in the decisionmaking process. Both investigations involved risktaking with only an approximate idea of the relative benefit and harm to individuals and to society.

Distinctions have traditionally been drawn between research conducted by investigators on "normal volunteers" in purely experimental settings and by therapist-investigators on "patients" in treatment settings. It has generally been assumed that more stringent controls should be placed on investigators whose actions are designed to gain knowledge rather than to promote the subject's "best interests." Yet in most situations it is difficult to draw lines between "normal volunteers," "patient-subjects," and "patients." Moreover, the "therapeutic" setting may be the one which deserves the closer scrutiny. While a volunteering subject can be alert to protect his own self-interest, a patient-subject's need for treatment may cause him to overrate the benefits and underestimate the risks of a research technique.

Thus, an important question to be explored in this chapter is the extent to which additional safeguards should be imposed on experimentation-with-therapy lest investigators, even unwittingly, expose "consenting" patient-subjects to "unreasonable" risks.

In examining the two case studies, consider the following questions:

1. For what purposes and to what extent should professional and public institutions intervene in the private interactions between investigators and subjects?

2. How and to what extent should the authority of each participant in the human experimentation process be affected by:

a. the likelihood of immediate benefits to patient-subjects?

b. the possibility of future benefits to patient-subjects?

c. the degree of certainty with which known and speculative risks can be predicted?

d. the availability of alternative procedures?

3. How should the authority of each participant in the human experimentation process be affected when:

a. an investigation is conducted for the benefit of future patients or of society?

b. an investigation, though conducted for the benefit of subjects, is also designed to test the efficacy of a new procedure for society at large?

A.

Balancing the Interests of Science, Society, and the Individual

1.

Office of Science and Technology Privacy and Behavioral Research*

* * *

[T]here exists an important conflict between two values, both of which are strongly held in American society.

The individual has an inalienable right to dignity, self-respect, and freedom to determine his own thoughts and actions within the broad limits set by the requirements of society. The essential element in privacy and self-determination is the privilege of making one's own decision as to the extent to which one will reveal thoughts, feelings, and actions. When a person consents freely and fully to share himself with others—with a scientist, an employer, or credit investigator—there is no invasion of privacy, regardless of the quality or nature of the information revealed.

Behavioral science is representative of an-

other value vigorously championed by most American citizens, the right to know anything that may be known or discovered about any part of the universe. Man is part of this universe, and the extent of the Federal Government's financial support of human behavioral research (on the order of \$300 million in 1966) testifies to the importance placed on the study of human behavior by the American people. In the past, there have been conflicts between theological beliefs and the theoretical analyses of the physical sciences. These conflicts have largely subsided, but the behavioral sciences seem to have inherited the conflict that arises when strongly held beliefs or moral attitudes—whether theologically, economically, or politically based—are subjected to the free-ranging process of scientific inquiry. If society is to exercise its right to know, it must free its behavioral scientists as much as possible from unnecessary restraints. Yet behavioral scientists, in turn, must accept the constructive restraints that society imposes in order to establish that level of dignity, freedom, and personal fulfillment that men treasure virtually above all else in life.

* Washington, D.C.: U.S. Government Printing Office 3-5, 9-10, 14-17 (1967).

The root of the conflict between the individual's right to privacy and society's right of discovery is the research process. Behavioral science seeks to assess and to measure many qualities of man's mind, feelings, and actions. In the absence of informed consent on the part of the subject, these measurements represent invasion of privacy. The scientist must therefore obtain the consent of his subject.

To obtain truly informed consent is often difficult. In the first place, the nature of the inquiry sometimes cannot be explained adequately because it involves complex variables that the nonscientist does not understand. Examples are the personality variables measured by questionnaires, and the qualities of cognitive processes measured by creativity tests. Secondly, the validity of an experiment is sometimes destroyed if the subject knows all the details of its conduct. [I]f behavioral research is to be effective, some modification of the traditional concept of informed consent is needed.

Such a change in no sense voids the general proposition that the performance of human behavioral research is the product of a partnership between the scientist and his subjects. Consent to participate in a study must be the norm before any subject embarks on the enterprise. Since consent must sometimes be given despite an admittedly inadequate understanding of the scientific purposes of the research procedures, the right to discontinue participation at any point must be stipulated in clear terms. In the meantime, when full information is not available to him and when no alternative procedures to minimize the privacy problem are available, the relationship between the subject and the scientist (as well as with the institution sponsoring the scientist) must be based upon trust. . . .

Occasionally, even this degree of consent cannot be obtained. Naturalistic observations of group behavior must sometimes be made unbeknownst to the subjects. In such cases, as well as in all others, the scientist has the obligation to insure full confidentiality of the research records. Only by doing so, and by making certain that published reports contain no identifying reference to a given subject, can the invasion of privacy be minimized.

Basically then, the protection of privacy in research is assured first by securing the informed consent of the subject. When the subject cannot be completely informed, the consent must be based on trust in the scientist and in the institution sponsoring him. In any case the scientist and

his sponsoring institution must insure privacy by the maintenance of confidentiality.

In the end, the fact must be accepted that human behavioral research will at times produce discomfort to some subjects, and will entail a partial invasion of their privacy. Neither the principle of privacy nor the need to discover new knowledge can supervene universally. As with other conflicting values in our society, there must be constant adjustment and compromise, with the decision as to which value is to govern in a given instance to be determined by a weighing of the costs and the gains—the cost in privacy, the gain in knowledge. The decision cannot be made solely by the investigator, who normally has a vested interest in his own research program, but must be a positive concern of his scientific peers and the institution which sponsors his work. Our society has grown strong on the principle of minimizing costs and maximizing gains and, when warmly held values are in conflict, there must be a thoughtful evaluation of the specific case. In particular, we do not believe that detailed governmental controls of research methods or instruments can substitute for the more effective procedures which are available and which carry less risk of damage to the scientific enterprise.

* * *

Science has made its contributions to human welfare by virtue of its freedom to inquire. The investigator pursuing knowledge, whether his subject is man or some other aspect of the natural world, must not feel constrained to limit his study to those things which have current social approval. Freedom of inquiry is a part of the general concept of intellectual freedom and has been built into the value structure of every university.

Behavioral science is obligated to explore all aspects of human behavior to the degree that such inquiry contributes to improved understanding of the nature of man and his society. The study of human behavior is challenging and difficult. When the scientist seeks to develop a meaningful and consistent set of concepts about some aspect of man's relations to others, he uses and must be free to use every means at his disposal to gain knowledge. In his search for truth he is less likely to think of social consequences of his work than he is of scientific consequences. In fact, most scientists in any discipline take the position that the search for truth should seek to replace myths, prejudices, and misconceptions,

and hence they view with great suspicion any limitation on their endeavors.

* * *

The values held by an individual or by a society are, and must be, in competition since no single value can be absolute. Even the right to life is supervised by a society seeking to protect itself from criminal behavior. Thus the conflict between the claim of the individual to his privacy and the needs of society to become better aware of human characteristics is no rare or isolated phenomenon.

In each instance of conflict, the decision must rest on the totality of all the relevant issues and the result will vary from one occasion to another, and from one setting to another depending on the context within which the issue arises and the process by which a conclusion is reached. No general rule can be formulated to apply in each situation; rather, persons desiring to uphold our society's diverse values must make judgments. The strength of our society lies in pluralism and diversity. The shifting tensions among our values and in the relative primacy accorded them provide strong assurance for the continuance of the diversity on which much of our freedom and our growth are built.

* * *

Even the rights to bodily integrity and privacy of property, which are recognized within our system of law and accepted generally as inalienable, are not really absolute. Every highway that is built involves personal and social cost, especially for those who are displaced or diminished by the construction. Indeed, there is hardly a social act that does not involve some social or human cost. There is no escape from the fact that limits exist for every basic value. Failure to limit any single one inevitably circumscribes another. In summary, it is a logical impossibility to have freedom without limits or values without qualification.

* * *

The decision concerning proposed behavioral research therefore must be a balancing process without arbitrariness, rigidity, or absolutes. If both privacy and the pursuit of knowledge are to be accorded their due, no choice between them can be made without considering the circumstances of a particular case.

In this balancing process many factors must be considered and weighed.

One factor is the proposed research. Is it

desirable? Has it been done before? If so, is it worth repeating? Is it well designed and strongly staffed? Has the privacy issue been taken into account? Is it possible to redesign the experiment so as to avoid offense to privacy and obtain the same knowledge?

In weighing the benefits expected from an experiment, the value of the knowledge it is hoped to obtain and the probability of obtaining it must be taken into account. This value judgment must be made both in terms of social utility and in terms of the likely contribution to our general understanding of human behavior. Although a stronger weight is given to knowledge which is expected to yield social benefits, our society attaches worth to pure knowledge, recognizing that pure knowledge often develops unexpected utility.

In practice, we deal with specific proposals, designed to answer specific questions through the use of specific research techniques. When a proposal involves a conflict between protection of privacy and pursuit of knowledge, a technical issue must be resolved at the outset. This issue is whether the investigator's experimental design minimizes the conflict or whether it can be reduced by redesigning the study. Since conflicts between privacy and the pursuit of knowledge can, in many cases, be reduced by the proper design of studies, it is essential that reviewers of research proposals examine this question first. Only after the research has been designed to assure that the knowledge will be obtained at minimum cost in terms of privacy, need the basic issues posed by conflicting values be examined.

If an invasion of privacy cannot be avoided, the extent and character of the invasion must be scrutinized. Is it actual or theoretical, real or technical? Is there potential harm to the subject? If so, is the harm substantial or insignificant, lasting or fleeting? Is the invasion minimal? For example, surveillance (by one-way mirror, camera, or monitoring devices) challenges directly and fundamentally the claim to privacy when the focus is on an individual. The challenge is drastically reduced if the focus is not on an individual but on social interactions: for example, at a bus stop or a street light.

* * *

While the community at large has an important stake in the outcome of this balancing process, it cannot play an effective role in most of the review. Few laymen can be effective critics of a research design and few scientists are

willing to submit to a review by laymen. Review of a research proposal only by scientists in the same field as the investigator, however, fails to assure adequate representation of the values of the whole community. How to solve this dilemma without making the review process arbitrary, capricious, or irrelevant is a difficult problem which will require continuing experimentation and study.

This discussion of the balancing and decisional process has emphasized that the claim to privacy is not an automatic barrier to research. Nor is every intrusion on privacy automatically unreasonable. A wise and discriminating society has found, and will continue to find, that many invasions of privacy are tolerable and necessary for the health of the community.

* * *

2.

His Holiness, Pope Pius XII The Moral Limits of Medical Research and Treatment*

* * *

Is there any moral limit to the "medical interests of the community" in content or extension? Are there "full powers" over the living man in every serious medical case? Does it raise barriers that are still valid in the interests of science or the individual? Or, stated differently: Can public authority, on which rests responsibility for the common good, give the doctor the power to experiment on the individual in the interests of science and the community in order to discover and try out new methods and procedures when these experiments transgress the right of the individual to dispose of himself? In the interests of the community, can public authority really limit or even suppress the right of the individual over his body and life, his bodily and psychic integrity?

To forestall an objection, We assume that it is a question of serious research, of honest efforts to promote the theory and practice of medicine, not of a maneuver serving as a scientific pretext to mask other ends and achieve them with impunity.

In regard to these questions many people have been of the opinion and are still of the opinion today, that the answer must be in the affirmative. To give weight to their contention they cite the fact that the individual is subordinated to the community, that the good of the individual must give way to the common good and be sacrificed to it. They add that the sacrifice of an individual for purposes of research and scientific investigation profits the individual in the long run.

The great postwar trials brought to light a terrifying number of documents testifying to the sacrifice of the individual in the "medical interests of the community." In the minutes of these trials one finds testimony and reports showing how, with the consent and, at times, even under the formal order of public authority, certain research centers systematically demanded to be furnished with persons from concentration camps for their medical experiments. One finds how they were delivered to such centers, so many men, so many women, so many for one experiment, so many for another. There are reports on the conduct and the results of such experiments, of the subjective and objective symptoms observed during the different phases of the experiments. One cannot read these reports without feeling a profound compassion for the victims, many of whom went to their deaths, and without being frightened by such an aberration of the human mind and heart. But We can also add that those responsible for these atrocious deeds did no more than to reply in the affirmative to the question We have asked and to accept the practical consequences of their affirmation.

At this point is the interest of the individual subordinated to the community's medical interests, or is there here a transgression, perhaps in good faith, against the most elementary demands of the natural law, a transgression that permits no medical research?

One would have to shut one's eyes to reality to believe that at the present time one could find no one in the medical world to hold and defend the ideas that gave rise to the facts We have cited. It is enough to follow for a short time the reports on medical efforts and experiments to convince oneself of the contrary. Involuntarily one asks oneself what has authorized, and what could ever authorize, any doctor's daring to try such an experiment. The experiment is described in all its stages and effects with calm objectivity. What is verified and what is not is noted. But there is not a word on its moral legality. Never-

* 44 *Acta Apostolica Sedis* 779, 784-789 (1952); Rome: 3 *Proceedings of the First International Congress of Neuropathology* 713, 719-725 (1952). (Translated from the French by the N.C.W.C. News Service). Reprinted by permission.

theless, this question exists, and one cannot suppress it by passing it over in silence.

In the above mentioned cases, insofar as the moral justification of the experiments rests on the mandate of public authority, and therefore on the subordination of the individual to the community, of the individual's welfare to the common welfare, it is based on an erroneous explanation of this principle. It must be noted that, in his personal being, man is not finally ordered to usefulness to society. On the contrary, the community exists for man.

The community is the great means intended by nature and God to regulate the exchange of mutual needs and to aid each man to develop his personality fully according to his individual and social abilities. Considered as a whole, the community is not a physical unity subsisting in itself and its individual members are not integral parts of it. Considered as a whole, the physical organism of living beings, of plants, animals or man, has a unity subsisting in itself. Each of the members, for example, the hand, the foot, the heart, the eye, is an integral part destined by all its being to be inserted in the whole organism. Outside the organism it has not, by its very nature, any sense, any finality. It is wholly absorbed by the totality of the organism to which it is attached.

In the moral community and in every organism of a purely moral character, it is an entirely different story. Here the whole has no unity subsisting in itself, but a simple unity of finality and action. In the community individuals are merely collaborators and instruments for the realization of the common end.

What results as far as the physical organism is concerned? The master and user of this organism, which possesses a subsisting unity, can dispose directly and immediately of integral parts, members and organs within the scope of their natural finality. He can also intervene, as often as and to the extent that the good of the whole demands, to paralyze, destroy, mutilate and separate the members. But, on the contrary, when the whole has only a unity of finality and action, its head—in the present case, the public authority—doubtlessly holds direct authority and the right to make demands upon the activities of the parts, but in no case can it dispose of its physical being. Indeed, every direct attempt upon its essence constitutes an abuse of the power of authority.

Now medical experiments—the subject we are discussing here—immediately and directly

affect the physical being, either of the whole or of the several organs, of the human organism. But, by virtue of the principle we have cited, public authority has no power in this sphere. It cannot, therefore, pass it on to research workers and doctors. It is from the State, however, that the doctor must receive authorization when he acts upon the organism of the individual in the "interests of the community." For then he does not act as a private individual, but as a mandatory of the public power. The latter cannot, however, pass on a right that it does not possess, save in the case already mentioned when it acts as a deputy, as the legal representative of a minor for as long as he cannot make his own decisions, of a person of feeble mind or of a lunatic.

* * *

In the domain of your science it is an obvious law that the application of new methods to living men must be preceded by research on cadavers or the model of study and experimentation on animals. Sometimes, however, this procedure is found to be impossible, insufficient or not feasible from a practical point of view. In this case, medical research will try to work on its immediate object, the living man, in the interests of science, in the interests of the patient and in the interests of the community. Such a procedure is not to be rejected without further consideration. But you must stop at the limits laid down by the moral principles we have explained.

Without doubt, before giving moral authorization to the use of new methods, one cannot ask that any danger or any risk be excluded. That would exceed human possibilities, paralyze all serious scientific research and very frequently be to the detriment of the patient. In these cases the weighing of the danger must be left to the judgment of the tried and competent doctor. Nevertheless, as our explanation has shown, there is a degree of danger that morality cannot allow. In doubtful cases, when means already known have failed, it may happen that a new method still insufficiently tried offers, together with very dangerous elements, appreciable chances of success. If the patient gives his consent, the use of the procedure in question is licit. But this way of acting cannot be upheld as a line of conduct in normal cases.

People will perhaps object that the ideas set forth here present a serious obstacle to scientific research and work. Nevertheless, the limits we have outlined are not by definition an obstacle to progress. The field of medicine cannot be

different in this respect from other fields of man's research, investigations and work. The great moral demands force the impetuous flow of human thought and will to flow, like water from the mountains, into certain channels. They contain the flow to increase its efficiency and usefulness. They dam it so that it does not overflow and cause ravages that can never be compensated for by the special good it seeks. In appearance, moral demands are a brake. In fact, they contribute to the best and most beautiful of what man has produced for science, the individual and the community.

* * *

3.

**Andrew C. Ivy
Cross-Examination before the
Nuernberg Military Tribunal—
June 13, 1947***

* * *

DR. SERVATIUS: Witness, take the following case. You are in a city in which the plague is raging. You, as a doctor, have a drug that you could use to combat the plague. However, you must test it on somebody. The commander, or let us say the mayor of the city, comes to you and says, "Here is a criminal condemned to death. Save us by carrying out the experiment on this man." Would you refuse to do so, or would you do it?

Witness Dr. IVY: I would refuse to do so, because I do not believe that duress of that sort warrants the breaking of ethical and moral principles. That is why the Hague Convention and Geneva Convention were formulated, to make war, a barbaric enterprise, a little more humane.

Q: Do you believe that the population of a city would have any understanding for your action?

A: They have understanding for the importance of the maintenance of the principles of medical ethics which apply over a long period of years, rather than a short period of years. Physicians and medical scientists should do nothing with the idea of temporarily doing good which,

when carried out repeatedly over a period of time, would debase and jeopardize a method for doing good. If a medical scientist breaks the code of medical ethics and says, "Kill the person," in order to do what he thinks may be good, in the course of time that will grow and will cause a loss of faith of the public in the medical profession, and hence destroy the capacity of the medical profession to do its good for society. The reason that we must be very careful in the use of human beings as subjects in medical experiments is in order not to debase and jeopardize this method for doing great good by causing the public to react against it.

Q: Witness, do you not believe that your ideal attitude here is more or less that of a single person standing against the body of public opinion?

A: No I do not. That is why I read out the principles of medical ethics yesterday, and that is why the American Medical Association has agreed essentially to those principles. That is why the principles, the ethical principles for the use of human beings in medical experiments, have been quite uniform throughout the world in the past.

Q: Then you do not believe that the urgency, the necessity of this city would make a revision of this attitude necessary?

A: No, not if they were in danger of killing people in the course of testing out the new drug or remedy. There is no justification in killing five people in order to save the lives of five hundred.

Q: Then you are of the opinion that the life of the one prisoner must be preserved even if the whole city perishes?

A: In order to maintain intact the method of doing good, yes.

* * *

Q: You then, despite the order, would not carry out the order, and would prefer to be executed as a martyr?

A: That is correct, and I know there are thousands of people in the United States who would have to do likewise.

Q: And do you not also believe that in thousands of cities the population would kill the doctor who found himself in the position?

A: I do not believe so because they would not know. How would they know whether the doctor had a drug that would or would not relieve? The doctor would not know himself, because he would have to experiment first.

* 2 *Trials of War Criminals before the Nuernberg Military Tribunals (The Medical Case)*. Washington, D.C.: U.S. Government Printing Office 42-44 (1948).

Q: Witness, I put a hypothetical case to you. If we are to turn to reality other questions would arise. I simply want to hear now your general attitude to this problem. You are then of the opinion that a doctor should not carry out the order. Are you also of the opinion that the politician should not give such an order?

A: Yes. I believe he should not give such an order.

Q: Is this not a purely political decision which must be left to the discretion of the political leader?

A: Not necessarily. He should seek the best advice that he can obtain.

Q: If he is informed that this one experiment on this one prisoner would save the whole city, he may give the order despite the fact that the doctor does not wish to carry it out, is that what you think?

A: He could then give the order, but if the doctor still believed that it was contrary to his moral responsibilities, then the doctor should not carry out the order.

Q: That is another question, whether or not he carries it out, but in such cases you consider it is permissible to give that order, is that what I understood you to say?

A: After he has obtained the best advice on the subject which he can obtain.

Q: Then he can give the order. Yes or no?

A: Yes.

* * *

4.

Warren E. Burger Reflections on Law and Experimental Medicine*

* * *

Science unrestrained would be somewhat like an absolute monarch—a great servant, but a terrible master. Law is inherently restraint; it is a restraint on science as it is a restraint on kings, congresses, and presidents, and none of them really likes it very much. Those who become impatient with the slow pace of the law's response to the needs of science must remember that the history of Western philosophy shows

that we cherish many values above scientific advances; science must function within this framework.

Theologians, philosophers, and lawgivers must be receptive and alert to these new and changing problems. Experimental medicine presents a wide range of problems for which no unitary attitude or approach can provide a universal guide. Organ transplants and use of mechanical devices to preserve life present one kind of problem. But planned or controlled genetics presents quite another, for there one deals largely with future beings. The lay mind cannot avoid a feeling or intuitive reaction that some of those who speak in terms of "managing" the development of a better strain of human beings may at best be confusing genetics with animal husbandry and at worst talking about plans for a "master race." Obviously there are certain genetic drawbacks to letting people reproduce themselves indiscriminately, but absent some specific disqualification where medicine can predict certain tragic consequences of a union between certain genetic types, ordinary mortals will continue to mate on an emotional rather than a scientific plane. Others will see some disturbing portents in any "planned propagation" however socially desirable and notwithstanding the benefit of breeding a disease-resistant race. It was one thing for Henry Wallace to make better and richer corn or for wealthy folk to breed better horses and dogs, but quite another to tinker with the human race. Perhaps some of the prize fight and professional football managers would like to pick mates for their stables of athletes and I am willing to assume they could propagate some superb gladiators. Perhaps no one could restrain willing participation in a program to breed better athletes, but one must shudder at the prospect of governmental intervention in this area of private choice.

* * *

One of the great episodes in legal history is that in which Lord Coke, as Lord Chancellor of England, first announced what was then a radical, indeed treasonable doctrine of English jurisprudence: Even the King was not above the law. Catherine Drinker Bowen relates that Lord Coke threw himself prostrate in front of the throne symbolically acknowledging that he was below the Crown just as he insisted the King was below the law.

Science and medicine, like kings, presidents,

* 15 *UCLA Law Review* 436, 441-442 (1968). Reprinted by permission.

and parliaments must remain below, but let us hope not immobilized by, law.

NOTE

PAUL FREUND
ETHICAL PROBLEMS IN HUMAN
EXPERIMENTATION*

* * *

[I]f the law is conservative, it is also creative and responsive. As the law has raised up a right of privacy, a creative, innovating doctrine, so it may come to recognize a right of experimentation on human beings. Social interests and expectations, if they are in fact justified, can expect eventually to be reflected in the law. For example, the duty of corporate directors to their stockholders, a duty that was long thought to be the single-minded obligation to provide the maximum profits to the shareholders, has not prevented recognition of a privilege to contribute corporate earnings to educational and charitable causes, a doctrine for which the medical schools and the hospitals have reason to be grateful. The social responsibility of the corporation has thus qualified the single-minded duty of the directors to their shareholders in the light of social concerns and social pressures.

* * *

The law has indeed yielded in its absolutes where some worthy risk has pressed for acceptance. . . . The crux of the matter is to find the inner checks or other safeguards that will mitigate and justify the risks.

* * *

5.

Hans Jonas
Philosophical Reflections on
Experimenting with Human Subjects†

* * *

[W]e must face the somber truth that the *ultima ratio* of communal life is and has always

* 273 *New England Journal of Medicine* 687 (1965). Reprinted by permission.

† 98 *Daedalus* 219, 223-224 (1969). Reprinted by permission of Daedalus, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

been the compulsory, vicarious sacrifice of individual lives. The primordial sacrificial situation is that of outright human sacrifices in early communities. These were not acts of blood-lust or gleeful savagery; they were the solemn execution of a supreme, sacral necessity. One of the fellowship of men had to die so that all could live, the earth be fertile, the cycle of nature renewed. The victim often was not a captured enemy, but a select member of the group: "The king must die." If there was cruelty here, it was not that of men, but that of the gods, or rather of the stern order of things, which was believed to exact that price for the bounty of life. To assure it for the community, and to assure it ever again, the awesome *quid pro quo* had to be paid ever again.

Far be it from me, and far should it be from us, to belittle from the height of our enlightened knowledge the majesty of the underlying conception. The particular *causal* views that prompted our ancestors have long since been relegated to the realm of superstition. But in moments of national danger we still send the flower of our young manhood to offer their lives for the continued life of the community, and, if it is a just war, we see them go forth as consecrated and strangely ennobled by a sacrificial role. Nor do we make their going forth depend on their own will and consent, much as we may desire and foster these: We conscript them according to law. We conscript the best and feel morally disturbed if the draft, either by design or in effect, works so that mainly the disadvantaged, socially less useful, more expendable, make up those whose lives are to buy ours. No rational persuasion of the pragmatic necessity here at work can do away with the feeling, mixed of gratitude and guilt, that the sphere of the sacred is touched with the vicarious offering of life for life. Quite apart from these dramatic occasions, there is, it appears, a persistent and constitutive aspect of human immolation to the very being and prospering of human society—an immolation in terms of life and happiness, imposed or voluntary, of few for many. . . . We can never rest comfortably in the belief that the soil from which our satisfactions sprout is not watered with the blood of martyrs. But a troubled conscience compels us, the undeserving beneficiaries, to ask: Who is to be martyred? in the service of what cause? and by whose choice?

* * *

B.

Medical Innovation and the State—A Case Study of Oral Contraception

1.

**Experimentation, Therapy, and Success—
The First Phase (1951–1960)**

a.

**Gregory Pincus
The Control of Fertility***

* * *

In 1937, Makepeace, Weinstein, and Friedman noted the effectiveness of progesterone as an ovulation inhibitor in the rabbit, but the logical extension of this observation into a more intensive study of the nature of the progesterone action as well as the action of certain derivatives and putative metabolites were not reported by us until 1953.

Why this "logical extension" occurred after a latent period of approximately 16 years is a question concerning which we have raised some speculation. Certainly, judging by publications, there was a period during which our own activities in this field fell to a minimum, both absolutely and relatively. An examination of the bibliography of any book concerned with reproductive phenomena discloses similarly a minimum number of publications during the period 1942–1945, and a significant rise in output from 1950 on. In our own case, the special demands of "war" research accounted for a shift of interest to studies of adrenocortical function, particularly in relation to physical and mental stress, and this interest has continued to a greater or lesser degree. Indeed, World War II probably accounts for the lapse observed generally. In our case, the increase of activity as indicated by publications from 1950 on has been due to two overtly ascertainable factors: (a) a visit from Mrs. Margaret Sanger in 1951 and (b) the emergence of the appreciation of the importance of the "population explosion."

At the time of her visit, Mrs. Sanger's interest in the world-wide dissemination of information on birth control was at high tide. Her experience as President of the International Planned Parenthood Federation had made her aware of the deficiencies of conventional con-

traceptive methods, particularly in underdeveloped areas of the world. Her hope, expressed to us, was that a relatively simple and fool-proof method might be developed through laboratory research. Drs. Chang and Pirie and I had already had some experience with hyaluronidase inhibitors in the rabbit but we had found that such potent inhibitors could act only on direct contact with sperm and that there was no possibility of an effect by parenteral administration. Although some preliminary experiments by the late Dr. Abraham Stone had indicated that at least one of these inhibitors might be quite active as the component of an intravaginal preparation in the human, the limitations to its use still appeared to be rather formidable. Accordingly, Dr. Chang and I drew up a modest project proposal that received support under a grant from the Planned Parenthood Federation of America. Work under this grant resulted in the paper on the rabbits mentioned above and in the finding that the compounds that we found to be potent as ovulation inhibitors in the rabbit were also quite active as antifertility agents in the rat.

The impetus to research, particularly on the physiology of reproduction, given by the recognition of the population explosion has been described a number of times. Although the physiologist has generally been called upon to undertake research which might lead to easily effective and acceptable means of birth control, his role is indeed a much wider one. The modern-day investigator cannot be satisfied with the invention of a "cunning device." The present accumulated knowledge concerning reproductive processes indicates that the production of gametes, their transport and mating, their fusion, and the fate of the fertilized egg involves an intricate and delicately balanced set of sequential events. Interfering with this sequence at any of a large number of stages may have physiologic consequences that are not apparent on the surface. The research worker is therefore compellingly motivated to arrive at as complete an understanding as possible of the processes involved in the great act of reproduction. Furthermore, the understanding which the physiologist seeks must be imparted to others. Often both the nature and the degree of information that must be imparted for thorough understanding may be highly technical and even abstruse to professionals such as

* New York: Academic Press 5–8 (1965).
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physicians in family planning clinics and public health workers.

Under the ivory tower conception of scientific research, much of the foregoing is irrelevant. More simply stated, the job of the scientist is to undertake experimentation and to publish the results of such experimentation. What happens thereafter is allegedly not his business. This concept has been dealt demoralizing blows, particularly during and since World War II. The rapid transition from the research laboratory to the world-wide application of significant discovery has demanded the attention of the scientist to [the] . . . consequences of his activity. . . .

Although in the opinion of many the population problem facing the community of men is as important as the problem of the development of atomic energy, the biological scientist has thus far not been vigorously communicative. . . . The physiological research worker thus far has for the most part confined his publication to scientific journals, and the publications by members of the medical profession have been chiefly concerned with medical practice in relation to birth control. The call-for-action programs have largely passed over the research laboratory.

I suspect that the working physiologist is not too unhappy about being neglected by the "pointing-with-alarms." It is not merely the residue of ivory-tower psychology that animates him. It is primarily his feeling that so much remains to be learned about the basic processes of reproduction, let alone practical control measures. . . .

* * *

NOTES

NOTE 1.

GREGORY PINCUS

SOME EFFECTS OF PROGESTERONE AND
RELATED COMPOUNDS UPON REPRODUCTION
AND EARLY DEVELOPMENT IN MAMMALS*

In several publications we have indicated the rather remarkable role that progesterone, the characteristic corpus luteum hormone, plays in mammalian reproduction. Consider that progesterone: (a) is a significant conditioning substance for normal mating reflexes in a number of animals; (b) has its special effect upon both tubal and uterine contraction while the eggs and sperm

are travelling through the oviducts; (c) may in certain dosages act as an inhibitor of fertilization in vivo, perhaps because of its effect on oviductal contractility; (d) is essential for ovum implantation, the maintenance of the fetus, and of normal uterine tone during pregnancy; (e) inhibits ovulation during normal pregnancy, and can do so on administration to preovulatory animals; and (f) plays a role in parturition. Therefore, any experimental alteration of its normal action or abnormal intensification of certain of its effects may be expected to interfere with reproduction in the female. Experimental studies may take two courses: they may seek to antagonize or inhibit effects of progesterones, *e.g.*, by estrogens or specific progesterone antimetabolites, or they may be designed to induce progesterone effects at critical stages, *e.g.*, ovulation inhibition, during the follicular phase of the cycle by progesterone or other progestins.

Our efforts have largely been directed to the latter objectives. There have been a number of reasons for this. First of all the progestational phenomena are physiologically normal and unlikely to be accompanied by untoward and unwanted side-effects. Thus progesterone is a non-toxic steroid tolerated in large dose and in fact secreted endogenously in large amount during pregnancy. The human use of progesterone has long been established as a safe and efficacious procedure in a variety of conditions and diseases, and its effectiveness by oral, parenteral or intravaginal routes has been demonstrated. Finally, since our interest has been in the control of the early stages of the reproductive process, *i.e.*, ovulation, fertilization, ovum development and implantation, the use of a compound having established effects during these stages seemed advantageous.

* * *

Basing our initial investigations upon the known effects of progesterone as an inhibitor of ovulation in rabbits, rats and other mammals, *i.e.*, guinea pigs, mice, sheep and cow, we have observed that this inhibitory effect is proportional to dosage in the rabbit (by subcutaneous injection). In these two species also progesterone administered orally is a significant inhibitor of ovulation. This led us to examine the effects of oral progesterone upon the human menstrual cycle. Using a standard dosage (300 mgm. per day) and regime of administration (from days 5 to 20 of the menstrual cycle), we have observed a significant suppression of the usual signs

* Report of the Proceedings of the Fifth International Conference on Planned Parenthood. London: International Planned Parenthood Federation 175-182 (1955). Reprinted by permission.

of ovulation, *i.e.*, the characteristic basal temperature rise, the typical secretory endometrium and the "ovulation" flush of vaginal cornification. Since these indirect signs of ovulation are normally the result of the secretion of progesterone by the corpus luteum, the suppressive effect of oral progesterone would appear to involve an inhibition of endogenous corpus luteum hormone production with, in certain instances at any rate, little or no progestational effect of the administered hormone. There is some suggestion in our data of a somewhat greater inhibitory action of progesterone in successive cycles of administration. This is supported by our findings on direct inspection of ovaries in ten cases at laparotomy; these were examined from days 20 to 26 of the first cycle in which they received oral progesterone; five of the ten patients had no corpora lutea and an indication of abnormal corpora was had in three others. We may therefore conclude that progesterone taken by mouth during the follicular phase of the cycle tends to suppress ovulation in the human female. One undesirable feature of our data is the exhibition of escape bleeding during progesterone medication in approximately 18 per cent of the cycles.

There is a suggestion in our data that in women exogenous oral progesterone may act as an antifertility agent for reasons other than its ovulation-inhibiting action. The frequent occurrence of atypical endometria and . . . indication of suppressive action on endogenous progestin suggest possible effects on ovum and sperm transport and implantation. The fact that in 71 cycles of progesterone treatment there were no pregnancies, whereas in 44 cycles following its discontinuance four pregnancies occurred would tend to support this notion, particularly since our follow-up studies indicated prompt restoration of ovulation and normal cycle lengths in post-medication cycles.

We have described our studies with a series of steroid compounds administered to rabbits and rats. Some 15 compounds have acted as ovulation inhibitors in the rabbit, and three of these proved to be clearly more potent than progesterone on a dosage basis. One of these three, 17- α -methyl progesterone, was highly effective by the parenteral route but lacked effectiveness when administered orally. Two, 19-nor ethinyl testosterone (XIII) and 17-ethinyl oestroneolone (XIV), were much more effective than progesterone by either route. This same relationship was observed in the rat. XIII and XIV have been administered orally in low dosage to a limited

number of patients. Each gave notable indication of ovulation inhibition not only by our indirect indices, but most strikingly by an almost complete prevention of pregnanediol excretion. With neither thus far has there been any escape bleeding.

. . . We cannot on the basis of our observations thus far designate the ideal antifertility agent, nor the ideal mode of administration. But a foundation has been laid for the useful exploitation of the problem on an objective basis. The delicately balanced sequential processes involved in normal mammalian reproduction are clearly attackable. Our objective is to disrupt them in such a way that no physiological cost to the organism is involved. That objective will undoubtedly be attained by careful scientific investigation.

* * *

NOTE 2.

SIR SOLLY ZUCKERMAN
SUMMING UP RESEARCH INTO BIOLOGICAL
METHODS OF CONTROLLING FERTILITY*

* * *

Promising though they may have appeared at first sight, I think it is also fair to conclude that the observations reported by Dr. Pincus do not bring us as close as we should like to the goal of our researches. We can all agree with him that progesterone is capable of inhibiting ovulation in rabbits, and the results which he has reported for rats are also best interpreted on this hypothesis. We are in difficulties, however, about the conclusion that progesterone, when taken by mouth, can also inhibit ovulation in women. This view was not shared by Dr. Masaoami Ishikawa, who, however, thought it possible that the treatment could prevent fertilization through changes induced by the hormone in the cervical epithelium; nor by Dr. Abraham Stone, who, too, has experimented with this form of treatment. When considering the results of all this work we need, however, to remind ourselves that we have little in the way of direct observation to go on. Dr. Pincus inferred the suppression of ovulation from a variety of indirect signs, as diagnosed for him by Dr. Rock: for example, changes in the basal body temperature; the character of the endometrium as revealed by biopsy; and the nature of the vaginal smear. But if we

* *Report of the Proceedings of the Fifth International Conference on Planned Parenthood*. London: International Planned Parenthood Federation 212 (1955). Reprinted by permission.

accept the views of other authorities, these indices are by no means 100 per cent certain; nor are they made more so by the few observations we have of ovaries at laparotomy, or by observations on pregnanediol excretion. Not until we have very many more fertility records of the kind to which Dr. Pincus has also referred will it, in fact, be possible to draw conclusions about the effectiveness of the oral administration of progesterone; or, indeed, about the more promising but smaller number of results which Dr. Pincus has reported about the use of 19-nor-17-ethinyl-testosterone and 17-ethinyl oestroneolone.

* * *

b.

**Hale H. Cook, Clarence J. Gamble, and
Adaline P. Satterthwaite
Oral Contraception by Norethynodrel—
A 3-Year Field Study***

In the many areas of the world where the standard of living is at subsistence level, each specific improvement in death control serves to depress that standard. As the living standard goes down, malnutrition grows, ill health increases, and the death rate rises. Furthermore, such low income levels leave little money available for public health activities. In these areas widespread provision of effective and acceptable methods of pregnancy spacing is essential to further health improvement. It is encouraging that statesmen in many countries are now becoming aware of this problem.

Methods of contraception have been available for years. Most of them involve some interference with the normal pattern of sexual intercourse, its prelude or postlude; others are of questionable reversibility (vasectomy and salpingectomy) or are considered dangerous (intrauterine and intracervical devices). Experience has shown that contraception can be widely effective when made available to all and promoted with enthusiasm. Yet, because of the disadvantages of present methods, the wish is commonly expressed for an oral contraceptive, preferably long lasting, and certainly easy to take.

The observation that certain western American Indians ate the leaves of *Lithospermum ruderale* to prevent conception suggested that oral contraception might be practical. Pharmacologists found that this and related plants contain substances that inactivate pituitary gonadotro-

pins in vitro and in vivo with failure of the gonads to develop in immature animals and reversible cessation of the estrous cycle in those already mature. Preliminary trials in humans were disappointing.

The observation by Nag that rats fed field peas (*Pisum sativum*) were less fertile stimulated Sanyal to isolate metaxylohydroquinone as the active substance. He reported that this apparently nontoxic and inexpensive substance reduced the pregnancy rate of women by 50 to 75 per cent. Such incomplete effectiveness inhibits widespread patient acceptance; the method has not gained general approval.

Antihyaluronidases are reported to be effective contraceptives when used as vaginal suppositories. Most investigations testing them by mouth have not shown any significant effect. Also recently under trial are cirantin, an oil extract of orange skins, and rottlerin, an extract of a Philippine milkweed. Mode of action and clinical effectiveness are under preliminary investigation.

Progesterone in pregnancy blocks ovulation and so prevents a superimposed pregnancy. Simulating this hormonal balance characteristic of pregnancy should thus be a form of contraception approximating normal physiology. Progesterone itself has been tried, but for oral use 300 mg. daily is required. This is expensive for general use. Several progestin-like synthetic steroids have been developed within the last 10 years. Tests by Pincus and associates show these effectively suppressed ovulation when given by mouth to animals and to women. Three of these compounds have reached commercial production: 17 α -ethinyl-19-nortestosterone, 17 α -ethyl-19-nortestosterone, and 17 α -ethinyl-5(10)-oestroneolone, known as norethynodrel.

The ideal contraceptive must be effective in preventing conception, safe for the persons using it, psychologically and economically acceptable, and reliably reversible. Although no present method is ideal on all counts, the preliminary work with norethynodrel suggested that it might closely approach this ideal. Therefore, in 1957 we decided to test this product in the field.

Method

A region in which population pressure is a public health problem was sought—one which has a high birth rate, low death rate, and low per capita income. Puerto Rico has a birth rate which averaged 41 per 1,000 population from 1946 to 1950 and declined to 35 by 1956. The death rate dropped steadily from 1935 to 1955 and is now between 7 and 8 per 1,000 population. The an-

* 82 *American Journal of Obstetrics and Gynecology* 437-442, 444, 445 (1961). Reprinted by permission.

nual income per person rose rapidly in the last 10 years; it reached \$410 in 1955. That for continental United States in the same year was \$1,866. The population doubled during the last 50 years despite a net loss by migration of half a million people. The island contains 675 people for each of its 3,435 square miles, although half the land is steep and noncultivable. Population density is comparable to the flat and fertile Ganges River Valley and the Malabar Coast of India.

Headquarters for field work was Humacao, the twelfth largest municipality in Puerto Rico, population 35,000 in 1950, and demographically typical of the island. The study was under the auspices of the Ryder Memorial Hospital. Its gynecologist and obstetrician (A.P.S.) had medical supervision of the study, made the physical examinations, and arranged for social service workers to distribute the contraceptive materials and instructions, keep records, and visit patients as necessary. The data were analyzed at the Harvard School of Public Health after field visits to organize the plan of investigation and to collect the needed details.

* * *

The present report concerns two groups of women. Work with the R series started in April, 1957. Each family in three crowded urban areas was paid a home visit by a social worker. In the first two of these areas 1,107 persons were found living in one-story houses on 7 acres of land. This is five times the density for the city as a whole. Subsequently, one rural and one suburban area were surveyed; here poor families live on government land allotted to them for housing. All women living with their husbands, having at least 2 children, not then pregnant, and aged 40 years or less, were invited to use the contraceptive pills which the social worker offered to bring them, without charge, every month.

The second group, called the P series, was recruited, starting in May, 1957, from women who came to the Ryder Memorial Hospital Out-patient Clinic for contraceptive aid, met the R series requirements, and chose to try this method. Alternative methods offered were the diaphragm, vaginal jelly or foam, and condoms. Most of the early P cases were recruited from women coming for postpartum examinations; to these women contraception is regularly offered. As word spread that the pills were available, without charge other than the initial \$2 clinic registration fee, increasing numbers came specifically to secure norethynodrel.

All women in both groups were given an initial pelvic and general physical examination. Each was provided a bottle of 20 tablets and instructed as follows:

Take one pill each day with your evening meal. Begin on the fourth day after the day on which menses start. Stop when your bottle of 20 pills is empty. Wait until your next menses and secure another bottle of pills. Start the pills again on the fifth menstrual day. If, by any chance, you do not have a period within 10 days of stopping, get a new bottle and start taking the pills that evening. If you wait longer than 10 days you may become pregnant.

If you begin to bleed while still taking the pills, take 2 pills every day until the bleeding stops, then one pill daily until the bottle is empty. If anything prevents you from getting the next bottle of pills until later than the fifth day of menstruation, start again by taking 2 pills each day for as many days as you started late, after the fifth day, then one pill every day.

Those with postpartum amenorrhea were directed to begin the pills immediately.

After their initial visit, women in the R series were given supplies each month in their homes while those of the P series were instructed to return to the hospital for further supplies when menstruation had begun. A record was made at each visit of the date of starting the tablets, the date, character, and duration of the menses, frequency of intercourse, and any symptoms or difficulties noted during the preceding interval. Women who had used the method regularly for several months without difficulty were given 2 months' supply. Those who did not return were followed up by a personal visit from one of the social workers or by letter if they lived too far away. Care was taken to find out why they had stopped using norethynodrel but no effort was made to influence them to resume the program.

Information available in 1957 suggested that 9.85 mg. of norethynodrel combined with 0.15 mg. of the synthetic estrin, ethynylestradiol-3-methyl ether, was the optimal daily dosage. Subsequent experience suggested that a smaller dose was equally effective and less apt to give certain unpleasant symptoms; therefore early in 1959 we began giving half the previous daily dose, tablets containing 5.0 mg. of norethynodrel with 0.075 mg. of ethynylestradiol-3-methyl ether.*

... Our report is based on all recorded experience of the first 150 R cases and the first 400 P cases through February, 1960. All women us-

* The 10 mg. and 5 mg. tablets, known as Enovid, have been supplied by G. D. Searle and Company.

ing the method, plus all who had discontinued it and could be located within 20 miles of the hospital, were interviewed beginning in November, 1959; a comprehensive questionnaire was filled out, and, on those who could come to the hospital, a pelvic and general physical examination was made. . . .

Results

During the 518 woman-years of experience with norethynodrel accumulated by the 550 women in this study 11 pregnancies occurred. Of these, 4 had started before norethynodrel was begun. Three occurred when the women waited more than the prescribed 10 days for the return of menses (one woman waiting 15, one 20, and one 30 days). The other 4 followed failure of the women to take the tablets daily; trustworthy details as to number and sequence of omissions could not be secured.

Tietze has defined three measures of the effectiveness of contraceptive methods: *physiologic* effectiveness is that measured when a given method is used according to instructions on every occasion of need; *clinical* effectiveness when in the hands of users under actual use conditions; and *demographic* effectiveness by the reduction of the birth rate of an entire population who have been instructed in the given method and to whom materials are available whether the individuals are using them or not.

No woman who followed instructions has become pregnant during 518 woman-years of use. Norethynodrel is thus physiologically completely effective. If the 11 pregnancies are attributed to faults in the method, the pregnancy rate for all users is 2.1 conceptions per 100 years of exposure. In Puerto Rico the fertility rate is approximately constant from age 20 years to age 30, after which it decreases. Our population, married an average of 8.7 years, was aged 27.5 years at the beginning of this trial. The rate of 2.1 thus contrasts directly with their pre-instruction rate of 110 pregnancies per 100 years of exposure.* Preceding attempts at contraception had not affected fertility; the 176 women reporting previous experience with one or more contraceptive methods had a rate of 106 pregnancies per 100 years of exposure, while the 328 reporting no such experience had a rate of 110.

* "Years of exposure" are the total years married less 10 months for each full-term delivery and 4 months for each abortion. Time of living separately, though appreciable for a few families, was not enough for the whole to warrant consideration in the calculation.

Considering the population of those who at any time tried norethynodrel one can compare the "community" preinstruction pregnancy rate . . . for all women who could be followed up, combining active and discontinued cases, of 17 per 100 years of exposure. The rate after stopping for all women who stopped was 91 pregnancies per 100 years of exposure. These results demonstrate that *physiologic* effectiveness is complete, *clinical* effectiveness is great, and *demographic* effectiveness, though reduced by the continued fertility of those who have discontinued the method, is marked.

No method of pregnancy spacing, even though highly effective, is justifiable if it endangers life or health. Only 2 women have died while using this method, one from burns and one from chronic hypertension with congestive heart failure. Another woman developed pulmonary tuberculosis, controlled by therapy. None of these effects could in any way be attributed to norethynodrel. Hemoglobin levels of 137 women were determined after an average of 14 months of use; these women showed an average of 10.4 ± 0.11 (standard error) Gm. per cent as compared with 10.6 ± 0.13 Gm. per cent for 79 women of comparable age (28.6 years) and parity (3.7 pregnancies) attending the Ryder Memorial Hospital Outpatient Clinic but not using norethynodrel. Blood pressure was neither raised nor lowered significantly as shown by observations on 179 users (average 13 months' use) compared with 85 controls. Biochemical studies made on 300 users by Pincus and associates showed no evidence of hidden toxicity after as many as 33 months of use. Psychological effects . . . have not been detected.

Popular rumor had it that this procedure caused cancer. A definitive answer is impossible within 3 years and with as small a sample as now available. Careful watch has been kept for suggestive indications, especially during the final physical examinations. During 698 woman-years of observation (518 woman-years of use and 180 woman-years of post-use experience), no signs of cancer, other than cervical, have been noted.

Cervical biopsies were taken on 40 women and were examined histologically by Rock and Garcia at the Free Hospital for Women, Brookline, Massachusetts. Carcinoma in situ was reported once, in a woman 33 years old, after 6 months' use of norethynodrel. Eight months after this biopsy she discontinued the method. At that time and also 6 months later biopsies were negative. Lee found by biopsy of 3,149 healthy Puerto

Rican women that 25, or 0.79 per cent, had carcinoma in situ. After 3 years' observation without treatment none had invasive carcinoma. Other studies showed 28 per cent invasive after 5 years and 33 per cent invasive after 9 years, without treatment.

Epidermoid carcinoma, Grade II, was found in another woman. On starting the method she had normal pelvic findings. A vaginal smear 18 months later was reported suggestive of cancer. A cervical biopsy was made after 21 months' experience, carcinoma found, norethynodrel stopped, and radiation treatment begun. To be allowed to enter the series, this patient first gave her age as 36; actually she was 46 years old. The rate for cervical cancer in the 45 year age group in Puerto Rico is now 1.18 per 1,000 women per year, though only 0.25 at the average age for our group. Two cases during 698 woman-years of experience is well within the limits of what may be expected from chance alone.

Epigastric distress, nausea, and vomiting; headaches and dizziness; changes in accustomed menstrual pattern, including premenstrual tension and nervousness; pelvic pain; chloasma; and changes in weight and appetite were the more common side effects noted.

Some complaint was recorded in 18 per cent of the cycles; of the 550 users, 388 or 71 per cent voiced such complaints at least once. Symptoms were most common during the first 3 months of use, but could occur at any time, even after 30 months of trouble-free use. Withdrawals from the study because of side effects were at the rate of 6 per cent of cases in the first month of experience, 4 per cent in the second, 3 per cent in the third, and 1 per cent each month thereafter. Women of the R series and those in the P series receiving 5 mg. dosage from the outset have shown only two thirds the average withdrawal rate. Users described most symptoms as likely to be more severe when starting a medication cycle or in the interval between the twentieth tablet and the following menses, that is, during a change of the hormonal level of the body. For 121 persons, 22 per cent of all users, side effects were so unpleasant that the method was discarded. The other 267 complainers, finding the reactions could be tolerated until they disappeared, continued the method, at least until some other reason for stopping occurred.

Many of the changes observed are commonly associated with early pregnancy, for example, nausea, vomiting, dizziness, headache, increased vaginal discharge, and chloasma. Pa-

tients frequently volunteered that they felt pregnant. Softening and bluing of the cervix occasionally led other doctors examining these women to make a diagnosis of early pregnancy whereupon contraceptive treatment was stopped and the women did become pregnant.

* * *

The ratio of observed to expected pregnancies is a measure of the effectiveness of the program. In their preceding married lives during which their average age was 24 years, the users of norethynodrel had had 59 pregnancies per 100 woman-years. The first significant drop in fertility in Puerto Rico occurs after age 30 years, a greater age than the average for women of this series at the end of the study. The preceding rate thus may be used as a base for comparison. During 518 woman-years of experience 316 pregnancies would be expected, and 90 per cent or 284 would have resulted in live births. Only 11 children were born. Use of norethynodrel by the 550 women has apparently prevented the birth of 273 unwanted children.

* * *

Norethynodrel has proved in this field trial an effective, safe, reversible, and fairly acceptable method for the spacing of births. Its suitability in public health programs, applicable to a community within the usual resources of funds, physicians, and the habits of people remains to be tested.

NOTES

NOTE 1.

EDRIS RICE-WRAY
FIELD STUDY WITH ENOVID AS A
CONTRACEPTIVE AGENT*

* * *

The angle I have taken will interest anyone who is interested in Enovid as a contraceptive and also those who are interested in doing a field study because this is a report of an actual field study. There are many things you have to learn by trial and error, such as how to handle the patients, how you present the project and what you say to them so they take it. . . .

. . . Puerto Rico is one of the most densely populated countries in the world. We are all in-

* *Proceedings of a Symposium on 19-Nor Progestational Steroids*. Chicago: G. D. Scarle & Co. 78-82, 92-93 (1957). Reprinted by permission.

terested in finding some reliable contraceptive which is cheap, acceptable to the people, easy to take and something the people themselves would be interested in taking. We are happy to say they have liked the oral tablet method very much.

Selection of Subjects

The women chosen for this (field) study were from the low income population living in a housing development project in a slum clearance area. They were chosen because of accessibility and because the stability of such a housing development population is greater than that of others.

Our objective was to have a case load of 100 subjects but, since some of them kept dropping out for various reasons which will be discussed later, we had to keep adding new subjects to keep from falling below 100.

Before starting the program, we interviewed the superintendent of the housing development to get his cooperation and to make sure that he would not oppose our work. We found him to be a very intelligent man with much enthusiasm for the work of reducing the birth rate in Puerto Rico. We were gratified to have him promise his wholehearted cooperation. He made available to us the records of the families living in the housing development and requested that his staff give us the cooperation necessary. The social worker on this program formerly worked with the housing authority and was already acquainted with a fair number of the people living in the area. She studied the records in the files of the housing development and selected names of families in which the mother was less than 40 and had one or more children. These were then visited in order to pick out 100 who were suitable for the program. Many of them were automatically unsuitable because they had been sterilized or were pregnant. Others had moved away.

Preliminary Interview

The worker introduced herself as the executive secretary of the Family Planning Association of Puerto Rico. She explained that it was a private agency such as the "National Foundation for Infantile Paralysis" or the "Cancer League" and had no connection with the government of Puerto Rico. It was made clear that the objective of this association was to help mothers and fathers to plan their families so that they do not have more children than they can properly take care of, and also so that they can have their children when they want them.

Of the group that was visited, only one did not accept because of religion. In one instance the husband was opposed to using any method. The rest were very receptive to the idea of avoiding pregnancies by a method so simple as that of taking tablets.

The control group was chosen the same way. The worker explained to these women that she was making a survey of families to learn something of the size of the families in the housing development. There were 125 in this control group, so as to allow for those who would move away or those who would not match with the study group. (They were being matched as to age of mother, number of children, number of pregnancies and years married.) All the people in this area are similar in their economic status and educational level. These women were questioned as to the number of children, the ages of their children, whether they used any contraceptive or not and, if so, since when.

We began giving the medication early in April. These women were advised to start taking the tablets five days after the start of the menses, whether they were bleeding or not. They were told to take one tablet daily for twenty days and then stop. They were told that during the period when they have finished the twenty tablets and are waiting for the menses, they may have intercourse without fear of pregnancy. They were made to understand that two or three days after stopping the medication they would have the menses. It was explained to them that it is necessary to use the method properly if they want to succeed or do not want to have escape bleeding during the month. They were told that if they were to stop the tablet one day the next day they would probably have bleeding. If this occurred they were instructed to double the dose for two days and, if it did not stop then, to take three for one day. In our experience, this always stopped bleeding.

A few weeks later, a reporter of Puerto Rico's "yellow sheet" called on the Secretary of Health and questioned him concerning a program of giving contraceptive tablets to people in Rio Piedras. He claimed that public health nurses were working in the program. The Secretary of Health called the writer, who was the director of the public health services in Rio Piedras, to find out about it. He was told that such a program was in progress and that the writer was directing it, but was doing so on her own time, apart from her public health duties. He replied that it was difficult to see how the two could be separated,

whereupon he was told that since this is a democracy, the writer felt that any government employee had the right to spend his spare time as he pleased. He asked numerous questions concerning the project and, finally, when he was assured that none of these patients was being examined in the Health Department, nor were public health personnel working on the project on government time, he answered the reporter accordingly and apparently dropped the matter.

The next day an article appeared in the newspaper stating that Dr. Rice-Wray had "confessed" to directing the project and quoting Dr. Pons as saying that he did not consider it proper for government employees to engage in neo-Malthusian activities, and that he did not approve of the Department being used as "bait" for such a project.

Whether Dr. Pons actually said these things or not is uncertain because this newspaper is most unreliable. However, the very fact that the article did appear caused momentary harm to the program and prompted some of the patients to withdraw.

Problems Encountered

The first two months of the study the worker gave the patient just one bottle of twenty tablets. It was felt that this would make it easier for the patient to know when to stop the medication. Later it was decided to leave her two bottles of twenty tablets each, for two months. This was done because it was often found difficult to interview the patients at the proper time. A list was made of dates to visit the patients. The idea was to visit each one within a few days after she stopped the medication. This did not work out very well. . . .

* * *

However, it was found that when two bottles of tablets were left with the patients, 1 or 2 per cent kept on taking them without stopping the five days for the menses. In the beginning, several patients came to the office in a state of great excitement when the tablets were used up and the worker had not come to give them more. In spite of the careful instructions given, they thought that they were going to get pregnant if they did not take the tablets every day. This showed us the necessity of having to repeat and repeat the instructions given to these women. We cannot assume that having given the instructions once, or even twice, that they will be understood completely. To eliminate this prob-

lem, we supplied the patients with some printed instructions so that they could refer to them after the worker was gone. Most of these women can read and write, but for those who cannot there is always a school child in the family or a neighbor who can read them to them.

Sometimes people say to the patients: "How do you know what this is? It might be dangerous." This does not bother most of those who can reply: "I have been taking it eight or nine months and I am happy and I don't get pregnant." In the beginning, because of the newspaper article, some patients became afraid when hearing such remarks and stopped taking the tablets.

Analysis of Results of Study, Up to December 31, 1956

The total number of subjects who have taken the tablets is 221.

Adding the number of months of those patients who have been taking Enovid more than two months, we have a total of forty-seven patient years. During this time we have not had one single pregnancy that could be attributed to method failure. There was one woman who thought she only had to take the tablets when her husband was home. He traveled and she said: "I didn't take them when he was away. I took them only when he was here, of course." That is one of the women with whom we had a problem. She got pregnant.

There were seventeen pregnancies due to patient failure because they stopped the medication. Eight stopped it because of reaction, six because of carelessness (they forgot to take it), two because of fear of the medication already referred to, and one because she thought she had to take it only when her husband was home (his work caused him to be away often a week at a time). It was found that although the patients were often careless and forgot to take their tablets, they did not always get pregnant. . . .

* * *

Discussion

DR. [WARREN O.] NELSON: If I may, I should like to make a few remarks relevant to the use of this compound as a contraceptive measure. If it should be used in this capacity I believe there are certain considerations of importance.

* * *

I think there are at least two reasons for shortening the period of administration. Firstly, the matter of economy in countries where peo-

ple really need an antifertility measure such as this compound might be. Secondly, the question of eliminating the need to administer so much drug for so long a time.

The latter consideration deserves attention since many people regard with concern the use of steroids or related substances over long periods of time. In the present instance, it is reasonable to suppose that a woman marrying at the age of 18 would begin to use the compound then. At that age she would have twenty-five to thirty years of reproductive expectancy. If we allow her four, five or six years off the drug while she has her planned family of two, three or four children, she still would be taking it for as long as twenty-five years. What would be the effect of this or any related compound over such a period of time? Obviously that question cannot be answered until such a study is actually made.

* * *

NOTE 2.

GREGORY PINCUS, JOHN ROCK, AND
CELSE R. GARCIA
FIELD TRIALS WITH NORETHYNDREL AS AN ORAL
CONTRACEPTIVE*

* * *

In the earliest report of the San Juan study Rice-Wray recorded the occurrence of unpleasant reactions . . . in approximately 17 per cent of the subjects. These side effects included occasional occurrence of nausea, dizziness, vomiting, headache, and gastralgia. We have noted previously that these reactions preponderate in the first few cycles of medication and that they are usually readily relieved by the administration of an antacid or of a placebo tablet consisting of lactose. . . . Again, it is suggestive that the frequency of occurrence is highest in the groups at the highest economic levels and lowest in the groups at the lowest economic levels. We have suspected a psychogenic element in these reactions since, on the initiation of each project, each subject was told she was to undertake a new type of contraception and that she should note the occurrence of special symptoms.

In Puerto Rico we have tested the possibility of a psychogenic element by studying two groups of women. In the first group were 15 women liv-

ing in a slum clearance area in a town quite distant from San Juan. They were offered the medication as a tried contraceptive, and no suggestion of the occurrence of side effects was made. The second group consisted of 28 women using other contraceptives who were told to continue with their accustomed method but to take the tablets for a few months to see if they were suited to continue with the new method later. To 15 of these women coded placebos were given, and to 13 coded true medication. The social workers distributing the tablets did not know which was which. . . . The percentage of reactions was lowest in the "no admonition" group, next highest in the group on placebos, and highest in the group receiving the true medication. The difference between the latter two groups is not significant statistically, and that between the "no admonition" group and the true medication group is marginally significant. The higher frequency of breakthrough bleeding in the true medication group is probably attributable to the medication . . . and is reflected in the lower mean cycle length. The amenorrhea incidence appears to be a matter of chance; but it is interesting to note that breakthrough and amenorrhea characterize the placebo group, the former doubtless representing the frequency of natural occurrence of short cycles. In brief, a psychogenic element in reaction rate is clearly indicated by these data, and it certainly accounts for the majority of the reactions.

* * *

[A] number of these subjects were given physical examinations from time to time. These examinations ordinarily involved a simple physical check-up, a thorough pelvic examination, and the taking of an endometrial biopsy. In the San Juan project there were 138 such examinations made during medication and 17 following cessation of medication [out of 438 subjects]; in the Humacao-R project there have been 13 examinations during medication [out of 117 subjects]; and in the Haiti project 19 in medication cycles and four post-medication [out of 149 subjects]. In the Humacao-P project practically every subject was given a pelvic examination before medication was initiated, and a little less than half the subjects were similarly examined at least once during medication. No obvious pathology was detected in the patients in the San Juan series except for a few conditions (e.g., a vaginal herniation, a few cervical infections, uterine fibroma) either antedating the medica-

* *Report of the Proceedings of the Sixth International Conference on Planned Parenthood*. London: International Planned Parenthood Federation 216, 220-224 (1959). Reprinted by permission.

tion or ascribable to acute events irrelevant to the medication. Similar unremarkable observations were made of the Haiti and Humacao-R subjects.

[T]he pre-medication and post-medication notes on the pelvic examinations . . . indicate: (a) that in the course of medication a large proportion of the small, involuted uteri tend to return to normal size but not to hypertrophy, (b) that cervical lesions tend to increase in frequency with increasing cycles of medication, and (c) that no significant change is observable in the adnexa. The apparent increase in cervical erosions may be ascribed to closer observation in the medication cycles, as only grossly observable lesions were recorded in the pre-medication examinations. Since in several instances erosions observed in one examination in fact declined in the next, this may indeed be a question of close observation. Also, the pre-medication and post-medication examinations were not always made by the same individual.

In the San Juan project, 16 individuals have been examined in early medication cycles and then considerably later. . . . It is obvious that there is no consistent trend in the state of the organs and tissue examined. The latter appears to respond typically to the medication in cycle after cycle. Generally, the state of the reproductive organs appears to be unaltered after many months of medication, with the previously noted tendency for a mild uterine growth response being exhibited in a small proportion of the subjects. The lack of systematic change in the cervical surface (except perhaps for a slight trend to improvement of erosions) suggests that the changes observed are a function of individual hygiene and practice.

NOTE 3.

INTERNATIONAL PLANNED PARENTHOOD FEDERATION DISCUSSION OF ORAL METHODS OF FERTILITY CONTROL*

* * *

[DR. EDWARD T. TYLER]: The issue that I would like to present at the moment is the question of whether, when dealing with these com-

pounds, we are getting the major antigonadotrophic effects from the estrogen or from the progestin. This, again, is more than just an academic question. Progestin is the really expensive part of the compound, so far as I know, whereas estrogen is relatively cheap. If, for example, these compounds can contain a sufficient amount of estrogen and a minimal amount of progestin, they may be able to reach large masses of people a great deal sooner, assuming that they are safe.

To carry this one step further. Why haven't estrogens been employed for this purpose and why are doctors reluctant about this? I think the answer may be somewhat simple. For many years there has been a feeling among physicians that the use of estrogens in some patients, at least those who have had a tendency towards malignancy in the family, should be limited. Whether this is reasonable or not I am not in a position to say, but I am in a position to say that many physicians are concerned about this possibility.

In my opinion it is doubtful whether we need be concerned about cancer-producing effects at this dosage level. We have not tried to run routine Papanicolaou stains on our patients and it isn't because we haven't been interested in doing this. But there is a problem in connection with it, and that is the simple one that if you run routine Papanicolaou smears among large numbers of patients you are bound to get suspicious ones regardless of whether they are taking medication or not. Once you get something suspicious-looking, you are bound to follow it further and you get into a problem where you are in the situation of performing gynecologic therapy, or at least involving yourself in diagnosis and treatment of patients when you shouldn't be. This has been our attitude until recently. However, we feel that our study has progressed far enough now for it to be necessary to get more involved in the matter of doing Papanicolaou smears routinely.

* * *

[DR. PINCUS]: The other questions which I will deal with very briefly are concerned with how we manage to get the women to take these pills with the regularity that they allege they take them. One of the things that I forgot to mention is that we distribute a calendar to the women. We ask them to mark the calendar daily, and most important are the visits of the social worker. The social worker is extremely important in this whole business. I cannot say more

* *Report of the Proceedings of the Sixth International Conference on Planned Parenthood*. London: International Planned Parenthood Federation 231-232, 234, 235 (1959). Reprinted by permission.

than that right now, but with an alert, careful, highly motivated social worker, the results are excellent. The lowest rate of withdrawal, you remember, was in one of the Humacao projects. Here the social worker was extremely faithful. She had the women under her control in almost every sense psychologically and she certainly did her job well. . . . Why Dr. Tyler is less successful than we in having this faithful continuance is probably a sociological problem rather than a biological one. It may be that women in continental United States are somewhat more temperamental.

* * *

[DR. WARREN O. NELSON]: Dr. Rock, may I direct this question to you? What happens if women swallow several tablets at once, as villagers might well do?

DR. JOHN ROCK: I haven't the slightest idea. One patient took three tablets and telephoned to find out if it would do her any harm. I assured her, without much background, that it wouldn't and it didn't. I cannot imagine it doing any harm. Hormones don't cause generalised disturbances. They are used up.

* * *

NOTE 4.

P. ECKSTEIN, J. A. H. WATERHOUSE,
GLENYS M. BOND, W. G. MILLS, DOROTHY M.
SANDILANDS, AND D. MARGARET SHOTTON

THE BIRMINGHAM ORAL CONTRACEPTIVE TRIAL*

In March, 1960, the Birmingham Family Planning Association embarked on its first oral contraceptive trial. Its objects were twofold. First, in view of the existing widespread dissatisfaction with conventional techniques of birth control, it seemed desirable to assess the efficacy and acceptability of the method among British women. Second, while the ability of relatively large doses of oral contraceptives to control fertility had been adequately established, there was next to no information about the effect of lower doses with regard to both the suppression of ovulation and the incidence and severity of side-effects. With these aims in mind—and that of reducing the substantial cost of the larger dosage—the Executive Council of the Birmingham F.P.A. decided to conduct a trial on a reasonably large

scale and under carefully controlled conditions laid down and supervised by a specially enlisted Medical Advisory Committee.

Messrs. G. D. Searle and Co. Ltd. agreed to support the trial both financially and by supplying adequate quantities of the test material (norethynodrel) to the Medical Advisory Committee.

* * *

All volunteers . . . were asked to agree to remain in the trial for a minimum of six months, and during that time to use no other form of contraceptive. It was explained to them that the efficacy of the method could not be guaranteed, and all accepted the possibility of another pregnancy in the event of failure of the tablets. In addition, each woman was required to return a consent form signed by both her husband and herself; her medical practitioner was also informed.

* * *

The compound selected was norethynodrel . . . 2.5 mg. with 0.05 mg. of the highly potent oestrogen, ethinyloestradiol-3-methyl ether (EO-3-ME). Subsequent chemical analysis carried out in the manufacturer's laboratories in the United States revealed, however, that the oestrogen content of the batch of tablets actually used in the trial was less, and amounted to 0.036 mg.; the concentration of norethynodrel proved to be approximately correct (2.3 mg.). The tablets supplied during the 2 OC trials contained 5 mg. of norethynodrel and 0.075 mg. of EO-3-ME.

* * *

The tablets were generally acceptable, but, although taken in strict conformity with instructions, failed to control fertility.

Of 48 subjects enrolled, 14 (29%) conceived, resulting in 11 pregnancies and three miscarriages. Ten single babies and one pair of twins have been born; all were healthy and there were no signs of virilization of females or other noticeable abnormalities among them.

The remaining 34 volunteers who had not conceived before the trial was closed were changed over to tablets containing 5 mg. of norethynodrel and 0.075 mg. of oestrogen. No pregnancies have occurred in the women who continued to take this dosage as instructed.

During the trial side-effects such as headache, nausea, tender breasts, and abdominal pain were relatively frequent but were usually slight and tended to diminish with time; the same was

* 2 *British Medical Journal* 1172-1173, 1178 (Supplement, 1961). Reprinted by permission.

true of changes in weight. No participants withdrew because of these effects.

The tablets, however, caused derangement of the cycle, as a rule towards prolongation, short cycles (or breakthrough bleeding) being unexpectedly rare.

The results obtained are compared with those of similar trials reported in the literature.

It is suggested that with doses of norethynodrel as low as 2.5 mg. the concentration of oestrogen becomes critical and, if below it, may reduce or abolish the contraceptive activity of the compound, probably by delaying ovulation rather than completely inhibiting it.

* * *

2.

Therapy, Complications, and Experimentation— The Second Phase (1960–Present)

a. Ad Hoc Committee for the Evaluation of a Possible Etiologic Relation with Thromboembolic Conditions Final Report on Enovid*

For centuries man has been interested in mechanisms and factors affecting the normal menstrual cycle, as well as those believed to be effective in either increasing or decreasing fertility. The artifacts of many civilizations attest to this. Therefore it should arouse no surprise that when a preparation which suppresses ovulation became available in tablet form it should be rapidly accepted and widely used. Such a tablet consisting of norethynodrel with ethinylestradiol 3-methyl ether (Enovid) has now been used by well over 1.5 million women for either contraception or for the treatment of disturbances of gynecologic endocrinology. It is believed that this substance acts by inhibiting the synthesis of gonadotropin by the anterior pituitary gland and in this manner suppresses ovulation in a high percentage of users.

It was soon recognized that Enovid produced a variety of side effects, including nausea and vomiting (sufficient to require discontinuation of the treatment in about 25 per cent of the cases) and there have been reports of edema,

weight gain, changes in thyroid or adrenal function, thyroiditis or toxicosis, hair loss or growth, dermatitis, cholestatic jaundice, chloasma, toxemia or pregnancy-like syndromes and others. Except for nausea and vomiting the proof that these have been a direct result of the use of Enovid is in most instances open to question and is not within the scope of this report.

Beginning in 1961 reports began to appear from numerous sources of thromboembolic conditions, including thrombophlebitis and pulmonary embolism, occurring in women who had taken or were taking Enovid. Some of these patients died. While the index of suspicion was raised it was also recognized by the scientific community that a very large number of young and middleaged females were involved, that such conditions do occur with and without obvious explanation, and that the coincidental factors involved in such situations are not necessarily etiological. One solution would have been to scrutinize carefully each case history in detail, select those which appeared to be idiopathic in all other aspects, but who had the common denominator of exposure to Enovid, and compare these with a proper sampling from the population as a whole to determine whether there was evidence of an increase in the incidence of thromboembolism and deaths in the exposed series. Unfortunately, the incidence of thromboembolism in the United States in this or any other population group is not known despite efforts in a few areas to obtain such figures. This type of condition is not reportable so that most of the patients which are not hospitalized are never recorded at all or the records remain in the physician's files. Once the attention of the medical profession and the general population was drawn to a possible relationship with Enovid, reporting of all types and severity of thromboembolic conditions in patients who had taken this drug was inevitably accentuated and comparable statistics became even more difficult. The death rate from thromboembolism in females of a comparable age group during the same period was not known, although this was obtained in the course of the present investigation.

In January of 1963 the Commissioner of the Food and Drug Administration, of the Department of Health, Education and Welfare established an ad hoc committee to review and analyze this situation and to determine if the use of Enovid resulted in an increase in the incidence of death from thromboembolic conditions. This constitutes a report of the efforts of the commit-

* I. S. Wright, M.D., Chairman, Washington, D.C.: Food and Drug Administration 1-15 (September 12, 1963).

tee to resolve the questions involved. The committee was composed of representatives with broad interests but especially experienced in the fields of gynecology and obstetrics, vascular diseases, thromboembolism, hematology (especially coagulation), and statistics, and epidemiology.

The committee has not been unmindful of the complexity of the overall considerations involved in this area. These include not only the medical implications but also those involving the biological, psychological, social, philosophical and religious aspects. The relationship of all of these to the population explosion must be of interest to all intelligent citizens. Nevertheless these factors were not permitted at any time to cloud the immediate issues which constituted the commission of the committee.

Background material was obtained from the Food and Drug Administration and G. D. Searle and Company. The representatives of both organizations were completely co-operative throughout this study. More than 350 case reports of both thromboembolism and death from the files of both sources were reviewed by the members of the committee together with much additional data. After this it was concluded that, because of the impossibility of obtaining solid comparable statistics regarding thromboembolic complications as they occur in the usual population groups, it was essential to concentrate on deaths where the documentation is more complete and valid.

* * *

The committee reviewed and evaluated the clinical records, the autopsy reports, the death certificates and other pertinent material of each patient alleged to have died from thromboembolic disease who had taken or was taking Enovid. From the records a list was developed consisting of those patients who were considered to have died of idiopathic thromboembolism. . . . There were 10 cases which were unanimously agreed upon as idiopathic. These cases plus two additional cases about which there was lack of unanimous agreement were accepted for the statistical analysis. . . .

* * *

From the beginning of the committee's deliberation, it was very apparent that an assessment of the true quantitative values for morbidity from thrombophlebitis would be fraught with great uncertainties. As suggested above such factors as the broad spectrum of the severity of the disease

and hence the seeking of medical care for diagnosis with obvious variation in reporting, diagnostic acumen, geographic differences in occurrence, and the number of unhospitalized and medically untreated cases could contribute in a differential way between groups of Enovid users and non-Enovid users and hence create artifactual differences which did not in reality exist.

* * *

. . . The incidence of deaths among all Enovid users was 12.1 per million users. It will be noted that the unadjusted rate for the general population is 7.9 deaths per million. On adjustment of the general population for the age distribution of the Enovid user population this rate becomes 8.4. In either case the difference between the Enovid and population rates is not statistically significant ($p = .14$) utilizing Poisson probability for small expected rates. . . .

Inasmuch as the population number for Enovid users estimated from available data is not an exact figure, but based on drug distribution figures, some attempts were made to determine the effects of a 50 per cent decrease and a 10 per cent decrease in the estimated population of white users to see what effect this might have on the mortality rates among Enovid users and the significance of any difference from those in the general population.

Any increase in this estimate of users would obviously reduce the user death rates and these rates would approach those in the general population. This would be particularly true if we deducted too many as Negro users, a possibility which remains. A 50 per cent decrease in the estimate of users would double the Enovid rates. This would make the overall rate as well as the rates in the 20-24 and 40-44 year age groups very significantly greater. A 50 per cent decrease in the population estimate represents an extreme possibility rather than a probable estimate and is deemed highly unlikely. A 10 per cent decrease in our user-population estimate (which might represent a reasonable error) would, however, not yield Enovid-user death rates significantly different from the general population rates (total and individual 5-year age groups) at the level of $p = 0.05$.

In summary, on the basis of the available data and if the above outlined assumptions are reasonably correct, no significant increase in the risk of thromboembolic death from the use of Enovid in this population group has been demonstrated.

There is a need for comprehensive and critical studies regarding the possible effects of Enovid on the coagulation balance and related production of thromboembolic conditions. Pending the development of such conclusive data and on the basis of present experience this latter relationship should be regarded as neither established nor excluded.

Although a detailed study is not within the scope of this report it is recognized that in judging the overall risk from and the values of the use of Enovid, data concerning the risks of pregnancy and induced abortion in each age group would be extremely important.

Any firm reliance on the risks as calculated is tempered by the assumptions made. This committee recommends that a carefully planned and controlled prospective study be initiated with the objective of obtaining more conclusive data regarding the incidence of thromboembolism and death from such conditions in both untreated females and those under treatment of this type among the pertinent age groups.

NOTES

NOTE 1.

LETTER FROM THE FOOD AND DRUG
ADMINISTRATION TO SENATOR GAYLORD
NELSON—JUNE 3, 1970*

... The information requested for the record during Commissioner Charles C. Edwards' testimony on March 4, 1970, before the Senate Select Committee on Small Business, Subcommittee on Monopoly is herewith submitted:

* * *

Senator McIntyre requested that we comment on the quality of the data submitted in support of the first oral contraceptive approved for sale in this country on June 23, 1960.

Much of the data submitted in support of this oral contraceptive seem to be rather super-

ficial in content in the light of our present state of knowledge regarding oral contraceptives. Some of the data are little more than testimonial or opinionative in character. Many areas of investigation that would now be required were either not carried out or were not evaluated to an acceptable extent. The studies conducted were certainly not of as high a quality as we now demand, based in part on our hindsight.

The material submitted appears to have been deficient with regards to data relative to 1) carbohydrate and lipid metabolism, 2) ophthalmological evaluation, 3) follow-up on newborns (resulting either subsequent to method discontinuance or as a result of method or patient failure) for anomalies or genetic defects, 4) cervical cytological studies, conducted before, during, and after medication, 5) renal function studies, 6) cardiovascular evaluation, 7) thorough physical examinations including breast examinations, prior to, during, and after termination of drug use, 8) adequate liver function studies, 9) long term efficacy studies, 10) animal studies, 11) coagulation and other clinical pathology studies.

Senator McIntyre asked how soon after the approval of the original new drug application for an oral contraceptive did the first report of thromboembolism side effects come to the Agency's attention.

A report in our files indicates that a number of reports of thromboembolic episodes associated with the use of oral contraceptives appeared in the literature in 1961. One report was in *The Lancet* on November 18, 1961. While we do not believe that it is possible to determine from our files when the first report of this effect first came to the attention of the FDA, we were certainly aware of them when they appeared in the literature.

* * *

NOTE 2.

EDWIN J. DeCOSTA, M.D.
BIRTH-CONTROL PILLS—
HAVE THEY SIDE EFFECTS?—
AN AUTHORITATIVE ANSWER TO A QUESTION
MANY WOMEN ARE ASKING*

"But doctor, are they really safe?" No wonder that after the thalidomide tragedy many patients worry about the possible harm from taking the new birth-control pills. And there have been a few medical reports—plus many rumors—of

* Except as otherwise indicated, all materials in the NOTES in this section are reprinted from *Hearings on the Present Status of Competition in the Pharmaceutical Industry before the Subcommittee on Monopoly of the Senate Select Committee on Small Business*, 91st Congress, 2d Session. Washington: U.S. Government Printing Office (1970). Members of the Subcommittee were Senators Nelson (Chairman), Sparkman, Long, McIntyre, Bible, Hatfield, Dole, Cook, and Javits. Benjamin Gordon served as staff economist, and James P. Duffy, III, was minority counsel.

* *This Week Magazine* 13 (July 12, 1964). Reprinted by permission of the author.

dangerous side effects. Without considering the controversial social or religious aspects of birth control, let us take a look at the medical facts about this important discovery.

First, no other method of birth control is as simple. The small hormone pills are taken at bedtime for 20 days each month. Apparently they work by suggesting to the body's master gland, the pituitary, that the woman is already pregnant, so the pituitary doesn't instruct the ovaries to produce an egg that month. When the patient stops taking pills after 20 days the lining of the uterus is sloughed and bleeding follows. Then the pills are started again for the next cycle. This simple method approaches 100 per cent effectiveness.

But . . . and there is always a but . . . there may also be undesirable effects when the pills are used. Generally, these effects are not serious—only nuisances similar to those experienced by some women during early pregnancy. They may become, for reasons we can't explain, bloated or nauseated, have fullness and soreness of the breasts, suffer from headaches or even changes in their personality. Some women also gain weight rapidly, some have disturbance of their menstrual flow. Rarely, the menses do not return for some time after the pills are discontinued—which, of course, makes the patient fear she is pregnant.

Fortunately, in most instances these complaints disappear within a couple of months, as in pregnancy. But not always. At times, the weight gain, bleeding and personality changes may be sufficiently disconcerting to warrant discontinuance of the pills.

But these are just nuisance factors. What about the reports of more serious problems? I have heard oral contraceptives accused of masculinizing female babies if taken inadvertently during early pregnancy, of interfering with future fertility, of causing uterine fibroids or even cancer. Most of these charges are palpable nonsense—there is no evidence to support any of them. Indeed, many patients report getting both physical and psychological benefits from the pills.

There is, however, one other widely reported problem connected with oral contraceptives. From time to time women taking them have developed blood clots (thrombosis) in the veins of their pelvis or legs. This can be serious—even fatal—but studies do not indicate that pills cause the clots. Thrombosis also occurs in men, and in women who are not taking contraceptive pills.

I am reminded of a recent medical meeting

where a doctor reported several instances of leg clots occurring in patients taking the pills. Another doctor promptly rose. His patient too had been given a prescription for the pills, and had developed leg clots. But she had forgotten to have the prescription filled!

Do I myself prescribe the pills? I do, whenever I think they are indicated. But to avoid even the most remote risk, I would not prescribe them to women who have had blood clots, varicose veins, heart or kidney disease, or malignancy.

To sum up, my own answer to anxious patients is yes, there is good reason to believe that oral contraceptives are safe for normal women under their physicians' supervision.

NOTE 3.

MORTON MINTZ

ARE BIRTH CONTROL PILLS SAFE?—
SOME DOCTORS DOUBT THAT THE DRUG
HAS BEEN TESTED WELL ENOUGH FOR
POSSIBLE SIDE EFFECTS*

A small but growing number of physicians, including some in key research posts, have been expressing concern about the scientific quality of the testing done to establish that oral contraceptives do not seriously endanger the women who use them.

One of these physicians is Dr. James A. Shannon, director of the National Institutes of Health. When the matter came up at a hearing of a House Appropriations subcommittee last Feb. 17, Rep. John E. Fogarty (D-R.I.) remarked, "So people are really taking a chance" (in using them).

"I believe so," Dr. Shannon replied. "There are a great many studies on experimental animals that indicate that they can be taken without hazard, but there has not been adequate human exploration to be certain."

* * *

[T]he millions [of women] who have turned to birth control pills . . . have had an almost unquestioning trust that the pills pose no serious dangers.

Necessarily, their trust reflects the confidence of a majority—probably the great majority—of the medical profession, because the oral contraceptives are prescription drugs.

* *The Washington Post* E 1, col. 1, E 5, col. 1 (December 19, 1965). © 1965, The Washington Post. Reprinted by permission.

The physicians' confidence, in turn, has been furthered by assurances such as these:

"If the instructions of the physician are followed in taking . . . the pills, I can imagine no danger whatsoever. . . . I can think of no condition in which these pills would not be safe to take."—Dr. Joseph W. Goldzieher, a consultant to Eli Lilly & Co., in an interview recorded last November 6 by "This Hour Has Seven Days," a Canadian Broadcasting Corp. program.

"The effects of birth control pills have been studied possibly more thoroughly and for a longer continuous time on the same persons than any other drug."—G. D. Searle & Co., manufacturer of Enovid, the first oral contraceptive.

Among critics, there is a growing belief that the confidence of most of the medical profession in the pills is, at least in part, a result of inadequate information, wishful thinking and questionable scientific and statistical analysis.

In the Searle statement, for example, critics say the word "possibly" automatically raises questions about the quality of the testing.

They also make a more serious objection. Because the pill studies have not been controlled, the data are less meaningful than that from scientific investigations made of other drugs in fewer people over shorter periods.

* * *

The advocates contend that the incidence of harmful effects is extremely low. But the fact remains that they have not established that the rate is low, or that it is even as low as they say it is, or that it is not actually many times higher than they say it is.

In addition, there is a widespread, resentful, "don't rock the boat" attitude in the medical profession.

Recently, one manufacturer said that if warnings about the pills are widely circulated, "literally millions of American women could be thrown into panic regarding the safety for all oral contraceptives."

Dr. Gregory Pincus, co-developer of the pill with Dr. John Rock, says it has yet "to be proved that there is a cause-and-effect relationship" between use of the pill and subsequent ill effects suffered by some.

* * *

Scientists recognize, however . . . that evidence is in a gray area, that it is relative, that it boils down to sufficient data on relative risks. This is the kind of data on which persons charged with protecting the public health must judge the

relative safety of all drugs. With a small chance of being wrong, they must decide whether the occurrence of adverse reactions is significantly more than would have arisen under normal conditions.

To insist upon certainty rather than compelling evidence of lack of safety is to risk the public health.

Dr. LeRoy E. Burney, while Surgeon General of the Public Health Service, has said that to wait for "proof" is "to invite disaster, or at least to suffer unnecessarily through long periods of time."

* * *

Has FDA been adequately protecting the public health—has it been reverent of life and scientifically responsible—in taking the position that it must wait in such problems as clots and strokes for the kind of proof of a "cause-and-effect relationship" that is available for migraine?

In the labeling of oral contraceptives, has FDA promptly given physicians full information about all of the known factors in the benefit/risk ratio so they can make informed, intelligent decisions about whether to prescribe the pills?

* * *

Last Oct. 25, the *Journal of the American Medical Association* published a report on all methods for AMA's eight-member Committee on Human Reproduction.

None of the authors was an endocrinologist, although the oral contraceptives involve the endocrine system. And the article makes no clear, specific mention of the possibility of strokes in pill users.

Dr. Lasagna, asked for comment, said he believed the article, "in its concern for the benefits to be obtained from effective contraception, neglects what I consider to be all too definite warning signals on the horizon in regard to the ability of the oral contraceptives to cause vascular catastrophe."

Vascular catastrophe includes serious or fatal clots in the bloodways. Those that block brain arteries are called strokes. Those that reach the lungs are called pulmonary embolisms.

In a recent interview, the chairman of the AMA Committee, Dr. Raymond T. Holden of Washington, said frankly of the article, "Maybe it wasn't strong enough. . . . It's possible we didn't stress the side effects," although "we thought we were being emphatic."

Relying on the theory that the safety of the pills, if used as directed under medical supervi-

sion, has been assured by FDA, the article emphasizes their effectiveness ("virtually 100 percent") and says that their acceptability is "of prime importance."

* * *

While the kind of faith put in FDA by the AMA Committee has been commonplace in organized medicine, it has not been held by the chairman of congressional committees that have investigated the agency's performance.

Last summer, Rep. L. H. Fountain (D-N.C.) was so disturbed by the findings turned up during his inquiries that he felt impelled to remind top FDA officials that their responsibility is "not to the drug companies, not to the doctors, but to the consuming public that may live or die as a result of your decisions."

* * *

The Wright committee was convened after FDA and the manufacturer of Enovid had received, by late December, 1962, reports of thrombophlebitis—an inflammatory vein-clotting condition—in 272 women who had taken the pills. Thirty died after pieces of the clots broke loose and reached the lungs. By July 1963, the reported total had increased to 400 cases, with 40 deaths.

For the moment, the major point about the Wright committee is that it did *not* eliminate the possibility of a relation between the use of Enovid and the occurrence of clots in the legs, pelvis and lungs.

The committee felt that the data it had to work with required it to be cautious in drawing conclusions. In the 27 months since the committee made its report, its restraint has not always been mirrored by others, who have tended to assume that there is no reason for worry about a possible relation. Such an assumption has been nurtured in many places.

In March, 1964, for example, Dr. Robert Kistner, a Harvard gynecologist, said that "scrutiny of the available data by experts . . . has completely exonerated the drug" as the causative factor.

This defies an axiom followed by expert statisticians: that no data ever warrant a declaration that a drug has been "completely exonerated." They say that the most that can ever properly be said is that the data permit a cautious conclusion: that there is a high or low *probability* of a causal relation.

* * *

A few weeks ago, FDA said that a computer was "memorizing" more than 10,000 instances of "adverse experiences" with oral contraceptives. The agency said it had a "crash program" to catalogue every scrap of information connected with the pills.

Perhaps inadvertently, the agency thus acknowledged that, despite the gravity of the problems involved, its surveillance of adverse effects had to be strengthened by a crash program.

In explaining the program, FDA said it was about to convene a special Advisory Committee on Obstetrics and Gynecology "to look at broad, overall problems of adverse experiences with all contraceptive drugs," including discrepancies in labeling of identical and similar products that the committee is expected to ask be made uniform.

In its initial meeting Nov. 22-23, the committee said that its preliminary review "finds no evidence of a cause-effect relationship" between the pills and reports of eye damage, strokes and other injuries associated with blood clotting.

The committee did not include in its statement the usually expected counterbalance: that it has no evidence that a causal relation does *not* exist. Yet by adopting a resolution endorsing FDA's request for an interim eye-damage warning in the labeling, the committee clearly indicated that a causal relation might indeed exist.

The committee is scheduled to meet again Jan. 20-21 and to issue its final report after a third meeting next March. Its chairman is Dr. Louis M. Hellman of the State University of New York College of Medicine.

* * *

Today's concern is most intense not about nausea and other such effects associated with pill-induced pseudo-pregnancy, but about afflictions involving the circulatory system: fatal clots, disabling clots, eye damage. There are, however, other concerns, including a feared possible relation between pill use over several years and cancer.

Although his warnings about such a possible relation have been hotly and widely challenged, Dr. Roy Hertz, former chief endocrinologist of the National Cancer Institute, said in an interview that the estrogenic substances used in the pills are known to induce a wide variety of tumors in numerous species of animals.

"It is, therefore, imperative that their generalized distribution to women of child-bearing age for protracted periods of time be preceded by appropriately comprehensive epidemiologic

studies to ascertain whether such effects are to be anticipated in man," he said.

* * *

b. **FDA Advisory Committee on Obstetrics
and Gynecology
Report on the Oral Contraceptives***

The oral contraceptives present society with problems unique in the history of human therapeutics. Never will so many people have taken such potent drugs voluntarily over such a protracted period for an objective other than for the control of disease. These compounds, furthermore, furnish almost completely effective contraception, for the first time available to the medically indigent as well as the socially privileged. These factors render the usual standards for safety and surveillance inadequate. Their necessary revision must be carefully planned and tested, lest the health and social benefits derived from these contraceptives be seriously reduced. Probably no substance, even common table salt, and certainly no effective drug can be taken over a long period of time without some risk, albeit minimal. There will always be a sensitive individual who may react adversely to any drug, and the oral contraceptives cannot be made free of such adverse potentials, which must be recognized and kept under continual surveillance. The potential dangers must also be carefully balanced against the health and social benefits that effective contraceptives provide for the individual woman and society.

The oral contraceptives currently in use are probably not those that will be employed 10 or even 5 years hence. Drugs with even less potentially adverse effect, utilizable in smaller dosage, will undoubtedly be developed through continuing research. At present several such promising compounds are under investigation. The research essential to the development and testing of these compounds is carried out by the drug industry working in close cooperation with the medical profession. It would be indeed unfortunate were such research and testing to be stifled by unnecessarily complicated, unscientifically harsh, and inelastic administrative procedures. It is axiomatic that all drugs must be carefully tested on several species of laboratory animals under comparable conditions before they can be given to

human volunteers. It is equally important that the results of such experimentation be appropriately interpreted in extending their application to human beings. Particularly in reproductive functions man differs from experimental animals and other primates. To deprive a population of drugs of great benefit by overattention to adverse effects based on animal data without due consideration of clinical experience is unjustifiable. Throughout this report various types of adverse experience will be discussed. Most of them, however, occur naturally, with a definite though low incidence in our population. The data necessary to demonstrate an increase in these naturally occurring phenomena among users of oral contraceptives are not available. Most adverse reactions, including deaths, have been reported as individual cases or small series. Except in carefully controlled studies, neither the total number of people exposed to the oral contraceptives nor the number of adverse reactions in any locality is known. The crucial data are the numerator (adverse reactions) and the denominator (users) and a control made up of nonusers having the same or a different number of adverse reactions. The difficulty of obtaining such data for the oral contraceptives makes unreliable any assumption regarding a cause and effect relationship of drug and adverse reaction.

There are, however, several epidemiological approaches which can shed light on the problem. The simplest and most obvious method is a system of surveillance leading to the reporting by physicians of suspicious illness in their patients who are taking the drug. Such a system is essential because it can give the earliest warning of trouble in a situation where quick action may be imperative. It should, however, be recognized that when the physician reports a suspected adverse reaction to a drug he usually cannot know with any certainty that what he has seen is in fact an adverse reaction and not a coincidental happening. The major deficiencies of this system are:

- (a) Incomplete reporting by physicians of adverse experience for medico-legal reasons, inertia, and lack of interest or awareness of the value of such data.
- (b) Selective or biased reporting of incidents which which may reflect fashions in medical interest rather than the magnitude of a possible hazard.
- (c) The lack of a denominator population to evaluate the incidence of a possible adverse reaction.
- (d) The lack of control populations not exposed to the oral contraceptives to permit comparison of the incidence of possible complications in

* Louis M. Hellman, M.D., Chairman. Washington, D.C.: Food and Drug Administration 1-13 (August 1, 1966).

users and nonusers, to see if, in fact, any excess risks occurs in users.

- (e) The inability to detect potential long-term effects which might first appear after discontinuation of the oral contraceptives or even in the progeny of users.

Of the more formal and reliable epidemiologic methods, the one selected should depend upon the type of suspected complication and its temporal relation to the use of the drugs. Prospective studies of users and nonusers are capable of testing for each type of complication; however, they are extremely difficult and costly to perform if the suspected complication is thought to be of rare occurrence or if it is expected to occur after a latent period of many years. The prospective method has the advantages that it permits simultaneous study of all possible complications, including those which are initially unsuspected, and that certain biases are avoided. However, it does not reduce the problem that the inferences must be based on observation rather than experiment; i.e., that differences in disease frequency between the groups of users and nonusers may result from differences in their initial composition dependent on whatever determines the employment of contraceptive methods.

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Utilization

The pharmaceutical industry has estimated the numbers of women taking oral contraceptives, based on the numbers of tablets distributed in the United States. The approach is straightforward: Since each user takes 20 tablets per cycle and the average woman has 13 cycles per year, the number of tablets sold, divided by 260, gives the average numbers of users during the year. The following estimates have been prepared by this method for the period 1961-65:

1961	408,000
1962	1,187,000
1963	2,235,000
1964	3,950,000
1965	5,000,000

* * *

Thromboembolic Disease

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Of . . . concern are the deaths from thromboembolic disease. The deaths from idiopathic pulmonary embolism in women aged 15 to 44 in the United States appear to be of the order of 12 per million per year. The average annual

death rate for women of the same age group from cerebral embolism and thrombosis is about 5 per million. From these data one might expect that, of the 5 million women estimated to be taking the oral contraceptives in 1965, there should be about 85 deaths from idiopathic thromboembolic disease. Kohl's report . . . disclosed 20 such cases from all causes, only 13 of which were idiopathic. There are two possible explanations for this apparent discrepancy: (1) The oral contraceptives are protective against thromboembolic disease; (2) there has been gross underreporting. The second possibility seems to be the logical explanation, for the reported deaths fail to show the increment expected with the fivefold increase in use of the oral contraceptives from 1962 to 1965.

The present system of reporting deaths and adverse reactions relies on either the cooperation of physicians or the haphazard filtering of rumors to detail men. The latter route is patently unreliable, and the former not much better. Physicians are becoming increasingly fearful of reporting deaths or adverse drug reactions because of possible legal reprisal.

The data derived from mortality statistics are not adequate to confirm or refute the role of oral contraceptives in thromboembolic disease. They do, however, suggest that if oral contraceptives act as a cause, they do so very infrequently relative to the number of users. The committee believes, accordingly, that the only way this important question can be answered is through large, carefully designed epidemiologic studies.

Carcinogenic Potential

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It is to be emphasized that all known human carcinogens require a latent period of approximately one decade. Hence any valid conclusion must await accurate data on a much larger group of women studied for at least 10 years. Furthermore, there is not sufficient evidence to support the contention that contraceptive pills may protect against the development of carcinoma of the cervix.

* * *

Sex steroids, particularly estrogens, have been shown to produce malignant lesions and to affect adversely the existing tumors in the mouse, rat, rabbit, hamster, and dog. These neoplasms have occurred in various organs, such as the cervix, endometrium, ovary, breast, testicle, pituitary, kidney, and bone marrow. The observations

in animals given progesterone and the newer progestogens have been contradictory; however, these agents alone and in combination with other sex steroids have promoted neoplasia or metastatic growth in a few instances. A recent example is a 52-week study of six dogs that received massive doses of a combination of mestranol and ethyneron (MK-665, an experimental progestogen). Four of the dogs developed mammary lesions; one was a carcinoma in situ with early invasion; the second was a carcinoma in situ; the third represented atypical hyperplasia; and the fourth was a benign intraductal papilloma. Animal studies, in which certain susceptible strains and species are used and in which the dosage is excessive and continuous, cannot be directly transferred to human beings. There is, nevertheless, a warning that an altered endocrine environment in human tissues might result in an abnormal expression or potentiation of growth, as in experimental animals. In fact, there has always been the suspicion that experimental animal and human tissues follow the same biological laws in this regard, but conclusive data are not available. A great difficulty in obtaining a reliable answer involves the prolonged period of latency in human beings exposed to known carcinogens. Further epidemiologic studies must take full recognition of this fact.

* * *

Endocrine and Metabolic Effects

A considerable number of studies indicate that the oral contraceptives inhibit ovulation by a block at the pituitary level, specifically by inhibition of synthesis or release of LH. During such inhibition, the ovaries tend to become smaller, and changes suggestive of cortical stromal fibrosis have been described. After cessation of the medication recovery is usually prompt, with ovulation resuming in 4 to 8 weeks in most cases. Occasionally, the reappearance of cyclic ovulation may be delayed for several months. Fertility appears to be normal immediately after cessation of the oral contraceptives although a small but unknown number of patients remain amenorrheic. The outcome of pregnancy has been reported to be about the same as in the untreated population with regard to abortion, prematurity, abnormality, and anomaly. There are, however, no prolonged followup studies to ascertain the growth and development of infants born after cessation of therapy. There is no evidence that prolonged suppression of ovulation in nulliparas or multiparas will impair future fertility. The effects of

prolonged suppression of ovulation, however, are unknown and require further investigation.

* * *

Increased thyroxin-binding globulin has been noted in the majority of women on oral contraceptives. Most, but not all, investigators report a rise in PBI and a decreased T_3 -RBC uptake. . . . The level of PBI may be in the hyperthyroid range but there is no clinical evidence of hyperthyroidism. If TSH is blocked at the pituitary level, it may be masked by increased protein binding. No precise data are available on this point.

Data regarding effects on carbohydrate metabolism in experimental animals and in women are contradictory. Recent studies in women taking oral contraceptives suggest a possible diabetogenic effect of these medications. Abnormal glucose tolerance tests have been observed in as many as 40 percent of women taking oral contraceptives; in women with diabetic family histories, abnormal tests were even more frequent. . . . Whether oral contraceptives can induce diabetes in normal women or even in those predisposed is not known, nor is it clear to what extent the induced changes in carbohydrate tolerance are reversible.

Liver Function

Many women on oral contraceptives show abnormalities of some liver function tests, especially the BSP and transaminase. A few develop clinical jaundice and evidence of mild hepatic damage, demonstrated by biopsy. . . .

Effect on Lactation

Oral contraceptives in high doses (5 and 10 mg. of progestogen) tend to decrease or stop lactation in many women in the first or second cycle of use. These compounds appear in breast milk but in minimal amounts (0.004–0.1 percent of the administered dose). Despite the small quantities of the steroids appearing in breast milk, mammary enlargement may occur in nursing infants. Administration of the androgenic steroids to newborn experimental animals at crucial periods can affect sex differentiation and behavior and result in sterility. No data on human beings are available.

Masculinization

Oral contraceptives have not produced serious masculinization in women taking these agents although all large series have reported some indi-

viduals with mild masculinizing symptoms. The 19-nor-compounds appear to have somewhat more masculinizing effect than other synthetic progestogens. These effects are mild, including acne and hirsutism. These changes regress with cessation of medication. The effect on the fetus is of greater importance. Synthetic progestogens, in doses used in the treatment of threatened or habitual abortion, may produce superficial masculinization of the genitals of the female fetus. These anatomic abnormalities are correctable, but the effect upon subsequent reproductive functions and psychosexual development is unknown.

Efficacy

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The efficacy of the combined agents is exceptionally high. The more recently introduced sequential regimens are also highly effective in controlling fertility, although to a slightly lesser degree. Present evidence indicates that the frequency of pregnancies occurring with the patients on sequential medication remained unchanged over the 2½-year period, thus supporting the contention that tolerance to or escape from the medication probably does not occur.

The efficacy of oral contraceptives in the treatment of amenorrhea could not be readily ascertained from the material available to the committee because of the endpoint used. . . .

The comments pertaining to efficacy of the drugs in the management of patients with dysmenorrhea were similar to those cited in the previous paragraph. . . . Statistically, the submitted material was considered unsatisfactory because of the small number of patients in the individual series. It was surprising to find that a very small sample had been utilized in the study of such a common phenomenon. The members were aware of the difficulties in designing controlled studies, since placebos do not provide contraception, a fact that cannot remain undisclosed to the patient.

* * *

The committee found no data to indicate that any of the oral contraceptives are effective in altering the natural history of patients with habitual abortion. . . .

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Recommendations

In making the following recommendations, the committee has given careful consideration to

this problem, which is unique because of the large number of healthy women taking the oral contraceptives over very long periods of time, the low incidence of serious side effects, the metabolic changes induced, the paucity of requisite statistical and scientific data, and, finally, the health and social benefits to be derived. These factors have imposed the requirement for unprecedented standards of safety; they have demanded the detection of sequelae that are often remote and infrequent; they have opened to question the existing methods of surveillance and retrieval of data; and they have required the design of highly refined epidemiological experiments.

As our case is new and unique in the history of therapeutics, so have we had to think anew in framing these recommendations.

- I. A large case-control (retrospective) study of the possible relation of oral contraceptives to thromboembolism.

* * *

- II. Continuation and support of studies such as the ones being carried out by the Kaiser Permanente group in California and the University of Pittsburgh group in Lawrence County, Pa.

- III. Support of additional controlled population-based prospective studies utilizing groups of subjects that are especially amenable to long-term follow-up, such as married female employees of certain large industries and graduate nurses.

* * *

- IV. Continuation and strengthening of the present surveillance system of the FDA.

- V. Review of the mechanism of storage, retrieval, and analysis of surveillance data.

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- VI. A conference be held between FDA and the respective drug firms concerning uniformity and increased efficiency of reporting.

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- VII. Priority be given to support laboratory investigations concerning all aspects of the hormonal contraceptive compounds.

- VIII. Uniformity in labeling of contraceptive drugs.

- IX. Discontinuance of time limitation of administration of contraceptive drugs.

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- X. Simplification of administrative procedures to allow reduction in dosage of already approved compounds. Once safety has been established, reduction in dosage should require only minimal proof of efficacy, say 3,000-4,000 cycles without a pregnancy.

Conclusion

The foregoing considerations have been brought together to direct the attention of the medical profession and the Food and Drug Administration to those aspects of our knowledge, as well as our ignorance, that seem pertinent to our evaluation of the safety and risks involved in the use of these compounds.

The committee finds no adequate scientific data, at this time, proving these compounds unsafe for human use. It has nevertheless taken full cognizance of certain very infrequent but serious side effects and of possible theoretic risks suggested by animal experimental data and by some of the metabolic changes in human beings.

In the final analysis, each physician must evaluate the advantages and the risks of this method of contraception in comparison with other available methods or with no contraception at all. He can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data.

NOTES

NOTE 1.

TESTIMONY OF DR. LOUIS M. HELLMAN,
CHAIRMAN, DEPARTMENT OF OBSTETRICS
AND GYNECOLOGY, STATE UNIVERSITY OF
NEW YORK, DOWNSTATE MEDICAL CENTER,
BROOKLYN, N.Y.—JANUARY 22, 1970

* * *

Adverse reaction reporting has a lot of pitfalls. In the first place, at that time, there was no uniform reporting sheet from the drug houses. This has been corrected. The method of data retrieval in FDA was deficient. You could not get quickly the information that you needed. Some of it was computerized, some of it was not. There have been efforts in FDA to correct this. I think the system still needs a good, hard look and some correction if correction is possible.

The chief difficulty with adverse reaction reporting, both in the United States and Great Britain, comes from the reluctance of the physicians themselves to report to anybody an

adverse reaction. In this country it is easy to understand, because the physician does, to a certain extent, incur some liability, legal liability, in reporting an adverse reaction to anybody, and he is often very hesitant to do this.

Second, it is very difficult for a physician to tell whether what he actually sees in the patient is related to some event like taking the oral contraceptive or something entirely different. . . .

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NOTE 2.

TESTIMONY OF FDA COMMISSIONER
CHARLES C. EDWARDS—MARCH 4, 1970

* * *

SENATOR NELSON: We have had witnesses over the past 3 years, distinguished physicians, who deplored the state of reporting on various diseases as being wholly inadequate.

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This is from a statement of William R. Best, chief, Midwest Research Support Center, Veterans Administration, Edward Hines, Jr. Hospital, Hines, Ill. He said:

* * *

I know that in a recent study in Philadelphia, for example, five of the medical school affiliated hospitals tried to set up their own reporting system to catch all the adverse reactions occurring in all of these hospitals. People being people, the way they are, when they went back to check and see how complete their reporting system was, even though the chief of every service told all of his residents and internes to report every case that came through, I think they reported somewhere in the neighborhood of 5 percent. About 95 percent still did not get reported, even though this was the rule of the particular hospital.

* * *

Do you think in your experience, in your judgment, that figure is anywhere near in the ball park of any kind of voluntary reporting the FDA gets on side effects?

DR. EDWARDS: I do not think I am in a position to give you an absolute figure. I would say without any hesitation our reporting system is poor. As long as we continue to have a reporting system that is voluntary, as it is right now, where we have very little access to the medical records in both hospitals and in doctors' offices, I think the likelihood of our establishing a really accu-

rate, up to date reporting system is not going to be very encouraging.

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SENATOR NELSON: I bring this up just to make the point that if the Philadelphia study and the five hospitals with the chiefs of all the services cooperating produced only a 5 percent reporting result, all of your reports on the incidence of deaths and other side effects from the pill, would have to be multiplied by 20 to get an accurate figure.

DR. EDWARDS: I have some reservations as to whether this is an accurate figure. I would add if I were chief of the service in a major teaching hospital and if I could not get my residents and internes to do better than that, I think that maybe I would look at myself, not my staff.

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NOTE 3.

TESTIMONY OF FDA GENERAL COUNSEL
WILLIAM W. GOODRICH—MARCH 4, 1970

SENATOR MCINTYRE: . . . You quoted the September 12, 1963, report of the Wright Committee to the effect that "No significant increases in the risk of thromboembolic disease had been demonstrated."

Did FDA not, in fact, issue two different versions of the Wright Committee report?

* * *

MR. GOODRICH: There was a first report which was found by Dr. Wright to have some statistical errors in it and those errors were corrected.

SENATOR MCINTYRE: How did the finding of the August 4, 1963, version differ from the one you quoted, from the September 12, 1963, version?

MR. GOODRICH: The first report of the Wright Committee indicated that on the basis of the statistical figures, the statistical calculations made, that there was an increased risk of thromboembolic disorder in ladies, as I remember, age 35 or older. I would have to go back to the record, but the problem there was that statisticians that looked at the information concluded that the incidence of thromboembolic disorders in nonusers, the data on which the comparison had been made, were inadequate and therefore there was no basis on which they could find a statistically significant difference in the appearance of thromboembolic disorders in these age groups.

Dr. Wright wrote to the Commissioner almost immediately to say that the statistical error had been discovered. The first report had been sent to the *Journal of the American Medical Association*, and the error was corrected.

But the problem was identified as a statistical error by the calculation of the normal risk based on the nonuser experience.

SENATOR MCINTYRE: Well, the reason for the change was based on the lack of what was considered to be sufficiently definite statistical information on the occurrence of thromboembolic disease in nonusers?

MR. GOODRICH: Yes.

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SENATOR MCINTYRE: Because of these deficiencies in the available information, the Wright Committee recommended:

That a carefully planned and controlled prospective study be initiated with the objective of obtaining more conclusive data regarding the incidence of thromboembolism and death from such conditions in both untreated females and those under treatment of this type among the pertinent age groups.

What actions were taken by FDA to implement this recommendation in the 3-year period between the issuance of the Wright Committee report and the first report of the Advisory Committee on Obstetrics and Gynecology in August of 1966?

MR. GOODRICH: Dr. Wright did make that recommendation in the report. He also sent a letter to the Commissioner with it, in which he recognized that the preparation and execution of a prospective study would be difficult, if not impossible. . . .

Nonetheless, the problem there was that in order to do a meaningful prospective study involved thousands of ladies, under carefully controlled circumstances, by that I mean having a number of patients in the order of 10,000 examined at intervals of about 6 months, which was simply beyond our capability of financing, and the conclusion was reached about the time of the first Hellman report that the quickest and most effective way of obtaining information—reliable information about thromboembolic episodes—was to do a controlled retrospective study. That retrospective study was financed and completed.

We, in the meantime, got the retrospective experience from England. Even today, it is not possible for us within the resources Dr. Edwards has explained here, to mount a prospective study

with the numbers of patients that would be necessary. We think a prospective study is no longer necessary with respect to thromboembolic episodes, but a prospective study may very well be meaningful in some other parameters.

SENATOR MCINTYRE: [T]he Commissioner's statement . . . list[s] eight recommendations contained in the 1966 report of the Hellman Committee, and describes efforts made by FDA to implement six of them. However, you make no mention of efforts to implement the other two. One of these was the restatement of the Wright Committee recommendation to support prospective studies utilizing groups of subjects especially amenable to long-term follow-ups.

Now, your answer, I suppose, covers it, but I want to ask it for the record: has FDA as yet undertaken or caused to be undertaken studies such as these, and if so, when?

MR. GOODRICH: Again, the prospective study recommended by the Hellman Committee in 1966 was not undertaken. Instead, the retrospective study was planned and executed. . . . Dr. Edwards' statement . . . describes a prospective study at the University of Miami. I believe there is also one underway at Temple University, and the Walnut [Creek] Study.

SENATOR MCINTYRE: That is a carbohydrate metabolism study?

MR. GOODRICH: These are parameters: I thought I made it clear we had enough data from the retrospective studies to say that a cause and effect had been established for thromboembolic disorders. We have now tied the proof to that effect. These other issues are the issues that have been identified to us, which do need a prospective study, and we are trying to fund those within the limits of our resources.

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SENATOR MCINTYRE: You are telling us what FDA is doing now. My question was directed at what were you doing in 1965 and 1966 to support these programs and studies that we now have knowledge of by virtue of witnesses that have been here?

DR. SCHROGIE [of the FDA]: These studies were started at different points in time since 1966. It was in 1966 that as a result of the Advisory Committee report that additional funding was given to FDA to initiate such studies.

The Sartwell study was initiated at that time, the study on carbohydrate metabolism was initiated during 1967, and a feasibility study relat-

ing to a prospective study on carcinogenesis was also undertaken at that time. The other studies were phased in during 1968 and 1969, as they could be developed and as funds became available to support them. So the program developed in an orderly fashion over the space of 3 or 4 years.

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Dr. Spellacy has been under support from the Food and Drug Administration since 1967. . . .

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Dr. Wynn is funded by the National Institute of Child Health and Human Development. I would add in terms of timing, both Dr. Wynn's study of carbohydrate metabolism and lipid metabolism, and also the prospective multiphasic study of oral contraceptive users being conducted at the Kaiser Permanente Foundation at Walnut Creek, Calif., were initiated by NIH around 1966.

SENATOR MCINTYRE: You have now described to me all of the studies that FDA has supported among the witnesses who have appeared here and described their studies for this committee.

DR. SCHROGIE: To the best of my present recollection, yes.

SENATOR MCINTYRE: Well, to me anyway—I may be wrong, in 1960, the drug went on the market. And FDA seems to be getting into the act by 1966, in a concerted way by starting some of these studies. . . .

* * *

Mr. Chairman, at what now appears to be the conclusion of these hearings, I would like to say I am both surprised and disappointed to find that the Food and Drug Administration, which has legal responsibility for assuring the safety of all drugs on the market, after allowing the birth control pill to come on the market on the basis of questionable evidence, has also failed to take the lead in seeing that adequate studies are being done to answer the questions which have been raised about the safety of these drugs since they came on the market.

Instead, FDA's posture has consistently been one of reacting to studies done elsewhere, and in many instances, in other countries. I think these hearings have made it quite clear that there are a number of still unresolved questions about

the safety of the birth control pill. I hope that in the future FDA will be more aggressive and will take the lead in seeing that adequate research is undertaken to answer these questions.

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NOTE 4.

SYNTEX LABORATORIES, INC.

"DEAR DOCTOR" LETTER—JANUARY 22, 1968*

The Food and Drug Administration has asked us to call your attention to the fact that certain statements in recent advertising for our oral contraceptives, NORQUEN® and NORINYL®-1, may be misleading.

In the NORQUEN advertisement, the paragraph headed "Low incidence of side effects" emphasizes the low incidence of certain less serious side effects such as spotting, breakthrough bleeding, nausea, vomiting and other gastrointestinal disturbances, but fails to give adequate emphasis to the more serious known side effects such as cholestatic jaundice, rise in blood pressure in susceptible individuals, and mental depression which also occur in low incidence. Further, although a cause and effect relationship has neither been established nor disproved, the advertisement does not give adequate emphasis to the possible occurrence of thrombophlebitis, pulmonary embolism, and neuro-ocular lesions which have been observed in users of oral contraceptives.

The advertisements for both NORQUEN and NORINYL-1 state that "careful observation and caution are required for patients with symptoms or history of . . . cerebrovascular accident, psychic depression. . . ." The ads should have been more specific in stating:

Oral contraceptives should be used with caution in patients with a history of cerebrovascular accident and should be discontinued if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine, or if examination reveals papilledema or retinal vascular lesions, since these may be symptoms of cerebrovascular accident.

The advertisements disclose that careful observation and caution are required for patients with symptoms or history of psychic depression but do not specifically state that oral contracep-

tives should be discontinued if psychic depression recurs to a serious degree. Also, the ads fail to disclose that a decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives.

We are modifying all future advertising to reflect these changes.

c.

FDA Advisory Committee on Obstetrics and Gynecology Second Report on the Oral Contraceptives*

Since the publication of the last Report on the Oral Contraceptives in 1966, scientific as well as public interest in this method of family planning has remained high. The reservations of the first report appear to have been justified. Concern about the immediate and long-range side effects of the hormonal contraceptives has increased as scientific investigations have uncovered a host of diverse biologic effects, and as the drugs have become available to increasingly large segments of the world's population.

Adverse reactions are continually reported in the scientific literature and the lay press. Since the vast majority of the reported adverse experiences are conditions which occur spontaneously in women of reproductive age, identification of an etiologic relation has been difficult and slow.

An increased risk of thromboembolic disease attributable to the use of hormonal contraceptives has now been defined in both Great Britain and the United States. Other risks, such as those of hypertension, liver disease and reduced tolerance to carbohydrates, have not been quantitated with the same precision. Some of the risks have been recognized by isolated clinical observations, whereas others have been predicted on the basis of experiments with animals or merely on theoretical grounds.

Controversy has centered about two areas: the scientific data required to establish an etiologic relation and the balance between acceptable risk and potential benefit. The voluntary submission of reports by individual doctors to scientific journals, to the pharmaceutical industry, or directly to the Food and Drug Administration is fragmentary at best. Since the data on the natural incidence of the disorders in question are not available, it is impossible to ascertain whether the

* This is an example of letters sent by drug companies to physicians throughout the United States to correct prior advertisement. It is not taken from the Nelson hearings.

* Louis M. Hellman, M.D., Chairman. Washington, D.C.: Food and Drug Administration 1-9 (August 1, 1969).

haphazard voluntary reporting of an adverse reaction in fact represents an increase in the suspected complication. The limitations as well as the value of a voluntary reporting system for providing an initial warning of serious complications have been noted frequently. There is no easy escape from this dilemma. The current aggregate pharmacological experience with the oral contraceptives is unique, however, in that large numbers of healthy young women are using potent drugs for a purpose other than the control of disease. An improvement in national reporting of some of the alleged complications is therefore merited. If the annual national rates of incidence of the various complications thought to be associated with hormonal contraceptives were known, trends presently unsuspected might be quickly uncovered.

This pharmacological experience is unique also in the attention it has received by the press throughout the world. Particularly in Great Britain and the United States the press has attempted to keep the public informed of each discovery and each reported difficulty. Such reporting is the quickest way to satisfy the public's right to know.

* * *

The risk of thromboembolism associated with the oral contraceptives has been compared with that from pregnancy, cigarette smoking, and automobile accidents. Such comparisons are probably irrelevant, contributing little to evaluation of the relative risk. The task of balancing the risk against the benefit to the individual and to society must eventually be met. As contraceptive practices spread to all segments of our society, it becomes virtually essential that the requirements of effectiveness and safety, and the desirability of inexpensiveness and lack of association with coitus be satisfied. Oral contraceptives have proved to be highly acceptable to many couples who had found other methods inconvenient or impractical.

* * *

All available evidence indicates that the continuation rates of oral contraceptives are higher than those of traditional methods of contraception, such as the diaphragm, and lower than those of intrauterine devices. In its previous report the committee indicated an anticipated use of 6 million cycles monthly in the United States in 1970. If the present estimate of 8.5 million cy-

cles is correct, the committee's projections were conservative.

Efficacy

The theoretical effectiveness of the combined hormonal contraceptives is reflected in a pregnancy rate of approximately 0.1 per hundred women per year. The theoretical effectiveness of the sequential oral contraceptives appears to be somewhat lower as indicated by a pregnancy rate of 0.5 per hundred women per year. The usually given pregnancy rates, reflecting "use-effectiveness," average 0.7 per hundred women per year for the combined regimen, and 1.4 per hundred women per year for the sequential regimen.

Effectiveness, judged by the total number of pregnancies, is significantly higher with oral contraceptives, combined or sequential, than with intrauterine devices or any of the traditional methods. The pregnancy rates among users of diaphragms with contraceptive paste thus appear to be 10 to 30 times higher than those among users of oral contraceptives; those among users of intrauterine devices are 2 to 4 times higher.

Methods under evaluation

Since the committee's last report, pharmaceutical firms have continued to investigate synthetic progestins and estrogens in an effort to reduce side effects while maintaining maximal efficacy. For example, the most recently approved combination product contains one-third the dose of estrogen and about one-tenth the dose of progestin as was present in the original contraceptive. Steroids that are stored in and slowly released from adipose tissue after oral ingestion are currently under study with the aim of creating a pill that may require administration only once a month. Unpredictable uterine bleeding remains a problem, however.

Intramuscularly injected steroids with a prolonged effect that may last for one or more months have been widely studied. Although these compounds may suppress ovulation, uterine bleeding is often an unpredictable complication. The delay before resumption of ovulatory cycles often lasts from 12 to 21 months. There is considerable variation among patients. To regulate the uterine bleeding some investigators have administered oral or parenteral estrogen. Doing so, however, detracts from the simplicity of this purely progestational regimen.

Low-dose continuous progestin therapy has been investigated in several countries. Drugs of

this kind exert their contraceptive effect without the addition of estrogen and without the inhibition of ovulation. The pregnancy rate appears to be approximately 2 per hundred women per year. Approximately two-thirds of the women studied have some cycle irregularity.

* * *

Thromboembolic disorders

An etiologic relation between oral contraceptives and an increase in some thromboembolic disorders has been disclosed by several groups of investigators using retrospective methods of inquiry and studies of mortality trends. In 1967 the Royal College of General Practitioners in Great Britain undertook interviews of young women with vascular disease. By comparing patients with superficial thrombophlebitis with a suitably matched series of controls, it could be shown that the risk of developing thrombophlebitis was tripled in women who used oral contraceptives. In a second study, Vessey and Doll investigated young women admitted to several hospitals in the northwest of London with a diagnosis of idiopathic thrombophlebitis. These patients also were matched with suitable controls. A third study involved all the deaths that occurred in England, Wales, and Northern Ireland during 1966 in women between the ages of 20 and 44 whose death certificates referred to thrombosis or embolism of the pulmonary, cerebral or coronary vessels. . . .

According to these British investigators, in the absence of other predisposing causes the risk of developing deep vein thrombosis, pulmonary embolism, or cerebral thrombosis is increased about eight times by the use of oral contraceptives, while the risk of developing coronary thrombosis is apparently unchanged. The results of these three studies led the Food and Drug Administration to order the following change of labeling for the oral contraceptives:

The physicians should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Studies conducted in Great Britain and reported in April, 1968 estimate there is a seven to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. . . .

The conclusions reached in the studies are summarized in the table [which follows]:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain

Category	Mortality rates		Hospitalization rates (morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of oral contraceptives	1.5/100,000	3.9/100,000	47/100,000
Nonusers	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be directly applied to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may be different.

Since that time Vessey and Doll have continued their retrospective study to include a larger group of patients matched with controls. The results of this study confirm the findings of the previous investigation.

* * *

Carcinogenesis

Much indirect evidence suggests that steroid hormones, particularly estrogen may be carcinogenic in man. These data are derived from experiments on laboratory animals in which long-term administration of estrogen resulted in cancer in five species. Although all physical and chemical agents that are carcinogenic in man produce malignant tumors in experimental animals also, evidence of the carcinogenicity of estrogen in other species cannot be transposed directly to man. Suspicion lingers, however, that the results in laboratory animals may be pertinent to man. Many difficulties arise in the epidemiological elucidation of this suspected relation. The principal obstacle is the long latent period between the administration of a known carcinogen and the development of cancer in man. Thus far, no properly devised prospective or retrospective studies have provided an adequate solution to this problem.

The committee has focused its attention on three target organs: cervix, endometrium, and breast. Estrogens may produce a variety of epi-

thelial changes in the human cervix of uncertain prognostic significance. A study of women attending the Planned Parenthood Clinics in New York City has revealed a higher prevalence of epithelial abnormalities that the investigators considered to be carcinoma *in situ* among women using oral contraceptives than in those who use the diaphragm. The committee believes that this study does not prove or disprove an etiologic relation between the oral contraceptives and these cervical changes. . . .

Although estrogen causes epithelial changes in the human breast, its carcinogenic effect on that organ has never been proved. Even in women with frank mammary carcinoma, estrogen produces variable changes in the clinical course of the disease. For example, ovariectomy leads to regression of metastatic breast carcinoma in approximately half of premenopausal women. Exogenous estrogens cause either regression or stimulation of similar tumors in menstruating women but induce regression in about half of post-menopausal women. The reasons for these paradoxical effects of estrogen on breast cancer are not clear.

In accordance with suggestions in the last report, the Food and Drug Administration has required mandatory testing for all currently licensed and investigational hormonal contraceptives on monkeys throughout their lifetimes and on dogs for 7 years. Thus far the presently licensed compounds have not produced tumors in these two groups of laboratory animals. Two estrogen-progestin combinations have, however, induced mammary tumors in beagles. Because these two compounds offered no clear therapeutic advantage over previously available hormonal contraceptives, clinical investigation was discontinued. This decision still leaves unresolved the question of similarity in hormonal induction of mammary tumors in a highly susceptible canine strain and in man. Continued testing of the presently available drugs is indicated.

Currently available data on death rates from genital and mammary cancer in women in the United States do not clarify the problem of association between steroids and carcinoma. The long latent period of action of known carcinogens (10 years) and the length of time between diagnosis and death eliminate vital statistics as a source of information about this association until the mid-1970's or later.

The massive program of prophylaxis launched against cervical cancer in this country has accomplished a steady decline in deaths

from the disease. The common practice of repeating cervical smears, annually or semi-annually, in women taking oral contraceptives has contributed to the decline, but it has clouded the question of the effect of oral contraceptives on cervical cancer.

Since there is no method of early detection of mammary carcinoma comparable in efficacy to that of the cervical Papanicolaou smear, the problem of the possible carcinogenic effect of oral contraceptives on the breast remains unresolved. . . .

Lacking conclusive information about the applicability of existing animal data to women and sufficient observations of human disease, the committee concludes that potential carcinogenicity of the oral contraceptives can be neither affirmed nor excluded at this time. Clinical surveillance of all women taking oral contraceptives must be continued. A major effort to resolve the questions about steroid-induced neoplasia in human beings should be undertaken.

Metabolic effects

Hormonal contraceptives produce numerous effects on many organs, for example, the liver, the thyroid, and the adrenal. They also affect some of the body's homeostatic mechanisms; for example, they produce changes in salt and water metabolism and occasionally induce hypertension. Recently morphologic changes in blood vessels have been described. In many areas where alteration in function or structure has been noted, basic information is lacking. Little is known, for example, about the effects of the oral contraceptives on water metabolism or renal function.

Observations that large doses of estrogen hasten epiphyseal closure in girls has created fear that oral contraceptives may limit growth. Such concern is unjustified, however, because these drugs are usually prescribed only after the growth spurt and in doses far smaller than those required to stunt growth.

There is no evidence at this time that any of these drug-induced metabolic alterations pose serious hazards to health. The systemic effects of the drugs are so fundamental and widespread, however, that continued medical surveillance and investigation is required.

* * *

Conclusion

Although the Kefauver-Harris Amendments of 1962 indicate that the term "safe" has reference to health of man, nowhere do they define

safety. Discussing this subject before the Subcommittee of the Committee on Government Operations of the House of Representatives, the Commissioner of FDA pointed out that no effective drug can be absolutely safe. Therefore, evaluation of safety of a drug requires weighing benefit against risk.

The Advisory Committee on Obstetrics and Gynecology has continued to assess the risk of oral contraceptives in this light, weighing knowledge of potential hazards against benefit. It has periodically reviewed the labeling of these compounds, repeatedly advocated strict surveillance by physicians, and recommended the accumulation of additional information about biological action and clinical effects. This report states the benefits of these compounds compared with those of other contraceptives.

Specific risks as well as requisite practices for follow-up of patients have been detailed in the labeling of all hormonal contraceptives. When these potential hazards and the value of the drugs are balanced, the committee finds the ratio of benefit to risk sufficiently high to justify the designation safe within the intent of the legislation.

NOTES

NOTE 1.

TESTIMONY OF DR. LOUIS M. HELLMAN—
JANUARY 22, 1970

* * *

In the first report [in 1966] we had to make some statement about safety. This was at the request of the Commissioner, and as you know, he is charged with both the efficacy and safety of drugs. It is quite apparent, if you read the report, even the first report, that the committee recognized certain very serious problems with oral contraceptives. They, however, were unwilling, and rightly, I believe, to say these things ought to come off the market. And they were faced with the dilemma, you have to make the statement.

Now, the statement we made in the first report said that these compounds are not unsafe for human consumption, which may not be the exact words, but that is what was said. That is a cute statement, more than a good statement, because we use the double negative to imply doubt. I never was very happy with that statement. I think it is kind of like the Delphic Oracle. You ask him what did you say, we did not understand it, and it is just about like that.

I always, in discussing that, said what this means is there [is] a yellow light of caution being exhibited by this committee.

Now, in discussing the . . . second report with the committee, I said to them that a more forthright statement has to be made. We cannot just hide behind rhetoric. We are going to have to say something. And we had options. "These are not safe," and then the Commissioner might have to take them off the market if he believed us. We can say "these are safe," and our scientific data did not really permit that kind of statement.

I took it upon myself to look into, as I am sure you have, the Kefauver-Harris amendments that regulate the actions of the Food and Drug Administration at the present time. As I indicated here, although those amendments are specific when they talk about food additives and were made much more specific by the Delaney amendment, which talks to this point. When they talk about safety of drugs, they face the same kind of dilemma that the committee faced.

* * *

. . . I take full responsibility for writing the sentence, "Safe within the intent of the legislation." But I did have consultation in writing that sentence. I did not just dream it up sitting up in Maryland. It was read to the committee and discussed. They approved it. . . .

* * *

I do not know anything other than I could have said about the oral contraceptives. I think it implied that there are problems with these drugs. And if you read this report, you cannot escape the fact that there are problems. I think, though, that you have to look at benefits.

Now, benefits are of two kinds when you are discussing a drug. There are benefits to the population as a whole. I do not want to go into the population problem, but I will say that the introduction of modern contraceptive methods has made the problem of population control immeasurably easier. With the traditional methods of contraception, it is very difficult, as you must have seen in India, to get any response out of the impoverished people. They have neither the time nor the privacy nor the motivation to use diaphragms, condoms, or whatever you will.

* * *

SENATOR NELSON: This question of what the word "safe" means in the 1962 act is a difficult one, and I do not know the answer to it. But I

wonder if, in talking about weighing the risks versus the benefits, the word "safe" in the statute contemplated that the benefit of general population control was contemplated. I would guess, it would seem to me you would come up with risk-benefit vis-à-vis that particular patient. I would doubt whether anybody contemplated that you could put on the balance side on the scale the question of the fact that the control of the population is a benefit to that patient in any direct way. I think the rapid growth of the world population is disastrous. But it seems to me, and I raised this question the other day, that when we talk about risk, we are concerned about safety of an individual patient.

* * *

DR. HELLMAN: I think you put it very well, and it is quite unlikely that the hearings in 1963, or whenever they were, really considered population as a threat.

* * *

Then the argument comes up, do you really have at this moment a satisfactory alternative to these compounds for the number of people you have to treat and the actual conditions for which you are treating them? And I think I would say to you, and this is a judgment statement and not a factual statement, that we really do not.

You can argue about the effectiveness of the diaphragm and you can argue about intrauterine devices, but when you treat the people that I am treating, and these are the economically deprived individuals, you have a problem of quite considerable magnitude over what you can give them that will work for what they want to do.

SENATOR NELSON: I would remind you of your statement that many of the people you are treating, 55 percent are on the IUD and 40 percent are on the pill.

DR. HELLMAN: I think that here again, you can not expect a governmental regulatory agency to act as "big brother" to the physicians in the United States. . . .

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NOTE 2.

TESTIMONY OF FDA COMMISSIONER
CHARLES C. EDWARDS AND FDA GENERAL
COUNSEL WILLIAM W. GOODRICH—
MARCH 4, 1970

* * *

DR. EDWARDS: . . . In categorizing this drug as safe, I do not want to imply, by any stretch of

the imagination, that this is an innocuous drug. It is a very potent drug, and when arriving at this decision to call it a safe drug we had to utilize the same standards we use for all other drugs.

As you well know, most of the other "safe" drugs, the powerful drugs, have certain contraindications. There are certain dangers in taking any drug, and they have to be taken under the conditions which are stated very clearly in the labeling.

So again, I would like to emphasize that in establishing this classification, we applied the same standards for the oral contraceptives as we have for all other drugs in categorizing them as safe.

SENATOR NELSON: The use in this context, then, was not in the ordinary dictionary use of the word—

DR. EDWARDS: It certainly was not. It was a Food and Drug Administration description of the word "safe," which really is "safe under the conditions of labeling," and which perhaps is a more accurate definition.

SENATOR NELSON: . . . If it had been my responsibility, I might have come to the same conclusion, but it does raise a question about the intent of the law and its meaning.

In 1938 Congress passed the statute requiring that, to market a drug, proof of safety must be submitted, adequate proof of safety or proof of safety acceptable to the FDA must be presented.

I would just like to ask Mr. Goodrich what he thinks was intended at that time. Let me state it this way:

In 1938 there were no oral contraceptives. In 1938, I would assume that the Congress was thinking of a drug for treatment of a specific target organism in a specific disease situation. In fact, it was in response to a particular safety problem that arose at that time respecting sulfanilamide, and maybe Mr. Goodrich will have a different view—and correct me if you do—that Congress was thinking then of a drug in which the issue was, is it safe for the particular disease situation which it is being used for, that is, the drug does have side effects, we are well aware of that; however, under the circumstance the illness of the patient indicates that on balance the risks of the side effects from the use of the drug are far outweighed by the benefits that the patient would get from the use of the drug for the particular disease situation that exists.

* * *

MR. GOODRICH: Yes. My understanding is

that all safety decisions have to be made in the context of the conditions for which the drug is prescribed, recommended or suggested.

Now, going back to what Congress had in mind in 1938 when they focused on an acute episode of poisoning, it happened to be due to the vehicle and not the drug itself. But as soon as we began passing on safety from the very first drug, the sulfanilamides, that were involved there, those drugs were not safe in any absolute sense of the term but they were quite safe treating infectious disease at that time, because many of those were life threatening.

Now, in that class of drugs, of course, it is relatively easy to balance benefit to risk, which is the test here. But there are other types of drugs that we have had to deal with over the years, drugs used for prophylaxis, or that type of drug, and in each instance it is essential that the agency balance benefit to risk, because there are very few drugs that have no side effects whatever, if they do anything.

* * *

SENATOR NELSON: Let me ask this question, though. Is it not correct when using the word "safe" that you do not mean safe in general, you mean safe for this particular patient who has a particular disease situation which the doctor decides that this drug will effectively treat, that is, target organism is subject to control by this drug, and on balance it is better that the patient risk whatever side effect this drug has rather than risk letting the disease run its course untreated by any drug.

It is an individual case, an individual disease, an individual prescription under an individual circumstance; is that not what we mean by "safe"?

MR. GOODRICH: That is the decision for the individual prescriber, but the decision for the Food and Drug Administration has to take into account different circumstances in which the drug will be used, some in private practice, others in university medical centers.

It has to take into account the total experience with the drug in the total prescribing population, and make a judgment there on all of these circumstances, this drug will be reasonably safe, that is, its benefits outweigh its risk under the circumstances in which it enters the market.

There have been a few instances in which drugs were allowed to enter the market only for use in university-type hospital settings, but in others the drug is permitted for widespread prescribing in most instances. But the Food and Drug

decision has to take into account all of these circumstances in reaching a safety decision.

SENATOR NELSON: Maybe I am not making myself clear. When you say "safe within the meaning of the law" are you not saying that we mean safe for the appropriate use of that drug under an appropriate circumstance in a specific disease situation?

MR. GOODRICH: Certainly.

SENATOR NELSON: Now, then, how do we bring the word "safe" to bear in the circumstance here of the oral contraceptive when: (1) there are alternative methods; (2) when, let us say, you are dealing with an intelligent, healthy well-motivated prospective user? How does the word "safe" apply in that respect?

The person has available medical care and a good hospital, has a good physician, has all of the facilities of the medical profession available as contrasted with the situation in which the patient has diabetes, or the patient has a history of high blood pressure, or carcinoma in the immediate family, something like that. How do you evaluate that specific case, the healthy patient with the finest medical facilities available with respect to the phrase "safe within the intent of the law"?

MR. GOODRICH: As you pointed out, that individual evaluation is for the prescriber, but as I approach it, as I see the responsibility of the Food and Drug Administration, it is to make sure that that prescriber has before him the information that is necessary for the safe, effective use of this drug.

* * *

The issue balancing benefit to risk in reaching a safety decision came to the Food and Drug Administration very shortly after the enactment of the first new drug provision in 1938. We could never have approved a number of classes of drugs, such as the corticosteroids, without balancing benefit to risk.

When Dr. Hellman called me, he asked if there was in the legislative development anywhere that I knew of a discussion of this point. It happened that there had been a very comprehensive discussion of this before the Intergovernmental Relations Subcommittee of the House and before the Committee on Interstate and Foreign Commerce and before the Antitrust Subcommittee at the time of the enactment of the 1962 Drug Amendments.

* * *

SENATOR MCINTYRE: . . . Actually, in 1938,

the law was just absent of any legislative history explaining the intent with respect to the statutory meaning of the word "safe."

MR. GOODRICH: And the reason was that the revision of the Federal Food, Drug and Cosmetic Act started in 1933. It was practically at the end point in 1937. The bill, indeed, had passed both Houses of Congress, when the elixir sulfanilamide episode occurred. This focused on the need for new drug provisions.

These provisions were proposed as separate legislation and were added on to that legislation at the very end, and there was no real discussion of the legislative intent there, other than to be sure that we protected the public from episodes of acute poisoning, which was what had been involved in the elixir sulfanilamide case.

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NOTE 3.

TESTIMONY OF DR. VICTOR WYNN—
JANUARY 22, 1970

I appreciate particularly the fact that you have invited me here to give testimony, because I come from another country, Great Britain. As I am sure you are aware, far more women are taking oral contraceptive medications abroad than are taking them in this country, and they are doing so in imitation of the American woman, and they are doing so with the confidence which is inspired by the very high standard not only of American medicine, but also of the American regulating agencies, and especially the Food and Drug Administration.

* * *

In this book [a *Textbook of Contraceptive Practice* published in 1969, and acclaimed by members of the Family Planning and International Planned Parenthood Federations as being an extremely good textbook] a statement appears that under certain circumstances oral contraceptive medication would be acceptable, if they had several hundred times greater mortality than that which is already understood to be the case with this medication.

This implies that in certain communities at any rate according to these authors, and they are intelligent men, dedicated men, men who have the interests of the world at heart, but according to this statement, the oral contraceptive medication would still be acceptable if something like two out of every hundred women were to die every year of its use, and scores of others to be admitted to hospitals every year of its use,

leaving the surviving women to care for those who were hospitalized.

* * *

Now, it is my purpose merely to try and draw attention to some of those chemical changes which occur as the result of the use of these compounds. At least in this field we do have data. At least in this field we need not speculate. We can present evidence which one can inspect, and we have done so.

What we still cannot do with any degree of certainty is to interpret the evidence to you. We cannot tell you in what precise way, in how many years, and in what numbers women are going to have their health impaired by these metabolic changes, if indeed they are going to suffer such disadvantages, but it has always been and it still is and it must remain a condition of medical practice that medication must not be used unless it can be proved to be safe, and that the onus of proof is not on those who are investigating the medication. The onus of proof is on those who wish the medication to be used.

* * *

The first point I would like to make is this. That when contraceptive medication was introduced, the possibility that the biochemistry, the chemistry of the body, would be modified in very many ways was not fully understood.

Now, it is all very well for doctors to say "Of course we understood it. We anticipated it. Pregnancy does the same thing." This is not true. I refer to Dr. Gregory Pincus' book published in 1965 and called *The Control of Fertility*.

Dr. Pincus, as you know, was a very great man, a great experimenter, endocrinologist, and the originator with others of this form of fertility control. But in his book, which is very comprehensive he barely refers to the metabolic effects of the contraceptive medication.

Why is this? It is because when the book was published the metabolic effects were either inadequately understood or not understood at all. Now Dr. Doar and I had the opportunity of discussing this point in great detail with Dr. Pincus in the following year. He visited us in our laboratory, and we discussed the metabolic findings which we had made, and it was apparent to us that Dr. Pincus was unaware of a wide-ranging nature of metabolic intervention which follows and which must follow from the use of this type of chemical.

When I say these changes occur, I mean

they occur in everybody, more in some than in others, but no person entirely escapes from the metabolic influence of these compounds. It is merely that some manifest the changes more obviously than others.

* * *

... The glucose tolerance of the women taking the pill was impaired. And using criteria which are generally acceptable, using the criteria of the British Diabetic Association and the criteria of the American Diabetic Association, we came to the conclusion that in about 15 to 18 percent of women using this medication, the degree of impairment was such as to justify the term "chemical diabetes."

Now, what do we mean by chemical diabetes? Do we mean diabetes? The answer is "No, we do not." Chemical diabetes is defined as an abnormal glucose tolerance, and nothing else. Diabetes implies that there is also a clinical manifestation of this abnormality in the terms of, let us say, weight loss, or thirst, or passing a lot of urine, and so forth. The difference probably resides in the fact that diabetes is a more severe form of disorder than chemical diabetes, but is chemical diabetes insignificant? It is not.

* * *

Abnormalities of glucose tolerance, impairment of glucose tolerance, and elevation in lipid value and an alternation toward the male pattern lead one to suppose that there may be a risk of the development or the accelerated development of hardening of the arteries or atherosclerosis as it is more correctly known.

The studies we carried out were called cross-sectional in the sense that we had a group of women who were users and another group of women who were nonusers. We decided to repeat these studies using the same women as the controls. We investigated them before they started taking the medication, and then at intervals after the medication had been administered.

* * *

To be brief, what we found was that the impairment of glucose tolerance, which we had observed before, was reproduced in these women, and in addition we found that the insulin levels, the hormone which normally controls glucose metabolism, that the insulin values were higher in these women than when they were users.

Insulin-glucose interrelationships and their interrelationships with fat metabolism and the

relationships of these three to the accelerated development of atherosclerosis are one of the main medical topics of our time.

* * *

I do not know what the significance of the data is. I repeat this, that I am concerned, and every reasonable physician that I have spoken to on the subject is concerned. The Food and Drug Administration and the experts at the National Institutes of Health are equally concerned. We are not alarmed, and there is no reason why women should be alarmed at the results of my pronouncements.

We have to examine this situation. I listened very carefully to your words yesterday, when you were looking at the same proposition: Should we in fact be sitting here, with television cameras, and the world press, to discuss such an important subject?

I have had to ask myself this question, and I have no doubt that you have also seriously asked yourself this question, and I have no doubt about the answer, and the answer is this: We must discuss it. We must discuss it as rational, intelligent beings, as unemotionally as we can, and we must examine the evidence.

If the evidence is there, let us examine the evidence. If the evidence is not there, let us do everything we can to obtain the evidence. But on no account can we put this subject completely behind not an Iron Curtain but something which is substantially much worse.

* * *

It gives me no pleasure to give such an account on this subject. I derive no satisfaction from having to give a detailed description of events which we all would prefer not to be occurring in women, but it is my duty to do so.

The metabolic changes are there. It is necessary that those with responsibility examine the health of women in such a way that they can detect in good time whether these changes are deleterious or not, and if so what is the order of magnitude of the risks, but there is no time to be lost. Far too much time has already gone by without these relevant studies having been carried out.

* * *

SENATOR MCINTYRE: Dr. Wynn, the statement has been made here several times that the British findings regarding increased risk of thromboembolic disease with use of the pill can-

not be applied directly to women in other countries including the United States. In fact, a statement to this effect was allowed in the official labeling of the oral contraceptives by FDA in 1968.

Moreover, the Sartwell study did come up with a different finding regarding the magnitude of the increased risk in the United States as opposed to Great Britain.

Do you know, Doctor, of any reasons why the British and the American female population should be any different with respect to the increased risk of thromboembolic disease resulting from use of oral contraceptives?

DR. WYNN: Taking the women by and large, I think the answer to that question is no. I would not expect there would be substantial differences between British and American women so far as risk of thromboembolism is concerned.

What the data reveal is the very great difficulty of carrying out epidemiological studies. You see, you take the Sartwell study. It was not identical to the British study.

They identified over 2,500 cases—I am speaking from memory—2,500 cases of thromboembolism, but they excluded all but a small fraction, 176, for one reason or another. Now some of the reasons for exclusion were in my view unreasonable.

They excluded women with varicose veins and family histories of diabetes, and so on. Now in conversation with Dr. Sartwell, he has agreed with me that some of the reasons for exclusion were not really those which he would advocate at the present time. Be that as it may, it merely gives some indication of the great difficulties in this type of study.

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NOTE 4.

TESTIMONY OF DR. HUGH J. DAVIS,
ASSISTANT PROFESSOR OF OBSTETRICS AND
GYNECOLOGY, THE JOHNS HOPKINS
UNIVERSITY SCHOOL OF MEDICINE—
JANUARY 14, 1970

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The fundamental problem with the oral contraceptives can be readily understood by anyone: It is medically unsound to administer such powerful synthetic hormones in order to achieve birth control objectives which can be reached by simple means of greater safety. This view was expressed by prominent gynecologic endocrinolo-

gists prior to the approval of the pill for contraception 10 years ago, and subsequent history has shown that it is even more true today.

Meanwhile, 9 million women are consuming these compounds almost automatically and without much information about the hazards. The impression has been given the public that the oral contraceptives are nothing more than innocent natural female hormones. Yet milligram for milligram the synthetic chemicals used in these pills are 20 to 40 times as potent as the natural estrogenic substances. To think of them as natural is comforting but quite false.

The synthetic chemicals in the pills are quite unnatural with respect to their manufacture and with respect to their behavior once they are introduced into the human body. In using these agents, we are in fact embarked on a massive endocrinologic experiment with millions of healthy women.

* * *

One can argue that this is an acceptable risk since it is safer to take the pill than for 1 million women to become pregnant, but I do not believe this is relevant since there are safer alternatives available for either spacing pregnancies or for permanent contraception, and even if 1 million women commenced taking the pill, experience has shown they will not achieve the 100 percent protection they are often promised.

The effectiveness of the pill has been greatly overrated. Between 20 percent and 50 percent of women who start the pill abandon the method by the end of the year. Whether they abandon the method because of side effects or because of human failure to get their prescriptions renewed is, in my view, irrelevant. The fact is that failure to take the pill, just as surely as failure to insert a diaphragm, results in pregnancies. But these failures never appear in the glowing reports about the efficacy of the steroid hormones. . . .

Even among the patients who continue using the pill for birth control, pregnancies occur in between 1 and 3 percent, either because of omission of one or two tablets—that is human error—or because the method itself failed. It is very difficult to discriminate between these types of failure.

In our experience, some modern intrauterine devices provide a 99 percent protection against pregnancy and can be successfully worn by 94 percent of women, to cite but one alternative. Very similar results can be obtained with a

properly used diaphragm in a well motivated population.

It is especially tragic that for the individual who needs birth control the most—the poor, the disadvantaged, and the ghetto-dwelling black—the oral contraceptives carry a particularly high hazard of pregnancy, as compared with methods requiring less motivation. The pill is less than ideal as a contraceptive among these women for precisely the same reason that the diaphragm often leads to unwanted pregnancy—both methods require a sustained repetitive act for continued protection. For many women, the diaphragm is too messy and inconvenient and the pill too complicated. Yet these women, who desperately need birth control services the most, are frequently offered the pill as if it were the only effective contraceptive. Because of these factors, it is the suburban middle class woman who has become the chronic user of the oral contraceptives in the United States in the past decade, getting her prescription renewed month after month and year after year without missing a single tablet.

* * *

Public policy with respect to oral contraceptives has been unsound in other respects. Is the consumer—the woman—aware of, or even capable of fully understanding all of these complex questions which have puzzled and concerned some of the best brains in medicine for the past decade? Again, as Senator Nelson has brought out, I think certainly little attempt has been made either to inform her or to protect her. In many clinics, the pill has been served up as if it were no more hazardous than chewing gum. The colorful brochures, movies, and pamphlets which are used to instruct women about the pill say next to nothing about possible serious complications. The same can be said for the veritable flood of articles in popular magazines and books which have convinced many women that there are few satisfactory alternatives to these steroids and that careful studies have proved that there is little risk to life or health in the pill.

Does the woman receive the same warnings and information about contraindications to the pill as the doctor? She does not. Is she privy to the fact that her risk of thromboembolism is greatly increased if she is taking the pill and is also over the age of 30? She is not. Is she aware that prolonged use of these compounds entails a completely unknown hazard of diabetes, harden-

ing of the arteries, and possible breast cancer? Not if she must depend on the brochures prepared for her information by the drug companies.

* * *

[I]f the oral contraceptives were an article of food there would be sufficient evidence on the basis of the animal experiments to consider seriously removing them from the market. We are in a curious situation with the oral contraceptives because they are classified as a drug although they are taken chronically by many people almost as if they were an article of diet. It is chronic use beyond 2 to 3 years that is particularly disturbing from a long range point of view. The numbers of women involved, and the unknown nature of the hazard, and the very disturbing evidence we have from the animal experiment, all of these things taken together, I think, should incline us all to be extremely cautious about long-term use of these agents.

* * *

SENATOR NELSON: I noticed that Dr. Kistner states in his book that a user of the pill should have a physical examination, in his judgment, every 6 months and that, therefore, he did not give a prescription that would exceed that period so that the user would have to come back to him, at which time Pap smears and various appropriate examinations would be made.

* * *

The estimate is that there are 9 million women using the pill in this country, is that right?

DR. DAVIS: The Food and Drug Administration estimate was approximately 8½ million women at this time.

SENATOR NELSON: Supposing that figure was doubled, supposing it was 20 million, are we prepared, from a laboratory standpoint and from the standpoint of availability of the physician, in fact, to examine 20 million women every 6 months, in addition to all other demands upon the laboratories and physicians?

DR. DAVIS: It would be a pretty massive undertaking. Let's hope it doesn't happen. I think there are other reasons for wishing it not to happen, but it surely would tax the capacity of the existing facilities if you double the patient load with the existing medical manpower situation. I think it could partly be overcome by using paramedical personnel for taking blood pressures and

streamlining some of our rather archaic practices in handling people.

* * *

NOTE 5.

TESTIMONY OF J. HAROLD WILLIAMS,
M.D., LL.B., BERKELEY, CALIFORNIA—
JANUARY 22, 1970

* * *

We all recognize that drugs are essential to modern medicine, but the power of the doctor's prescription prerogative sometimes is a serious intrusion into the doctor-patient relationship. Indeed, that power is so awesome that I fear many physicians do not fully comprehend its ramifications when they put pen to pad.

Sometimes the physician is unsuspectingly caught in the middle, between his conscientious desire to serve his patients and intensive promotional pressure by drug manufacturers. The sad saga of the pill is one of the most phenomenal examples of such an entrapment of our medical profession.

* * *

As I point out some of the things that have happened in the advertising and promotion of the pill, please bear in mind that the average practicing physician relies upon the drug companies for much, if not all, of his information about the drugs. He may read some of the articles in medical journals which report adverse reactions to certain drugs, but by and large he does not have time, nor is he motivated, to read all journals, to sift the poor articles from the good, and to correlate all the information.

Obviously, he cannot repeat the research that has been done on drugs in his own practice. Usually he looks to the most convenient central source of information, the *Physicians Desk Reference*, a compendium of drug company advertising. Most of us here in this room, I think, understand that the PDR is no more than a compendium of drug company advertising. The doctor assumes that the drug companies are honest and that the FDA has been a vigilant watchdog to protect him and his patients. This is true sometimes; sometimes it is not.

* * *

Advertising of the pill to the medical profession has been characterized by many statements that tend to be misleading. . . .

* * *

. . . In *Enovid Bulletin No. 20*, published in 1964, under a section headlined "The responsibility of leadership" is this statement:

"... [F]ew drugs in any category have ever been subjected to clinical tests as exhaustive as those already undergone by Enovid."

The reader was expected, no doubt, to understand that statement as applying to safety as well as to efficacy. I think much of the testimony that has been heard before this committee in the last 2 weeks underscores the fact that research as to safety has been a long time in coming and that it had not been exhaustive by 1964 and certainly has not been exhaustive even today.

* * *

Ambiguous language has been employed many times to take away the sting from information which should have had a warning impact on the physician. For example, in *Physicians' Product Brochure No. 62*, printed March 16, 1964:

"There is no direct evidence that Enovid alters the diabetic state. However, in a few instances some degree of difficulty in the management of diabetic patients has been reported in connection with Enovid therapy. . . . They may be expected to return to their pretreatment manageability on discontinuance of the drug."

It does not alter the diabetic state but they return to their pretreatment manageability on discontinuance of the drug.

* * *

Obsolescence of statements in advertising, amounting to untruthful misrepresentation, has occurred from time to time, as newer knowledge superseded older. Such were not restricted to the early days of aggressiveness, however, an outstanding example of this practice appeared in the past year. This was at a time when past events and warnings should have made everyone, everyone on the side of promotion, more vigilant than ever to be promptly forthright with physicians and their patients. This relates to the British statistical data, first published in 1967 as preliminary findings on thromboembolism then in 1968 as firm conclusions, about the increased risk of thromboembolism in pill users.

In May 1968 those data were added to the labeling on the pill, all brands, as an emergency measure by the FDA. However, the manufacturers successfully persuaded the FDA to allow a neutralizer in the material.

* * *

"No comparable studies are yet available in the United States. The British data, especially as

they indicate the magnitude of the increased risk to the individual patient, can not be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ."

* * *

In November 1968, Drs. Markush and Siegal of NIH disclosed that their study of mortality rate "indicate[s] an association of oral contraceptives with an increase in mortality from diseases of the veins. . . ." Although that study was not comparable in technique, it was certainly comparable in conclusion—it did indeed exist. It seems to me it may not have been included up to the present time because it would have helped debunk sooner than this January some of the language quoted in this "no comparable studies" paragraph.

The results of the Sartwell study, reported in the Second Report on Oral Contraceptives by the Advisory Committee, were known in the spring of 1969, if in fact not sooner, were circulated widely in mimeographed form in August, released to the press in September, but as late as the issue of JAMA for December 29, 1969—which was the last issue I got before I left home—had not been incorporated in the labeling.

This "no comparable studies in the United States" was still there for doctors to read and get whatever reassurance they could get out of it.

. . . At the very least, this represents a 5-month delay in disseminating the new information. I submit, gentlemen, it does not take that long to revise the wording or do the new printing required in the advertising for the *Journal of the American Medical Association*.

The tone of much of the advertising has been to suggest to the doctor that he is indeed in a supreme position to order and manipulate life with his prescription pad.

Let me show you what I mean. On a number of occasions in the *Journal of the American Medical Association* has appeared this ad for Enovid-E. A photograph of a beautiful child on the lefthand side, and on the righthand side in big bold letters "Just what the doctor ordered."

Now, how God-like can you get, gentlemen?

In smaller print, "And spaced just right in the family plan, worked out years before by the physician," and oh, yes, "the baby's parents."

. . . If the pill is as good as they say it is, and if it is as safe as they say it is, that kind of advertising would not be necessary.

* * *

NOTE 6.

TESTIMONY OF DR. ALAN F. GUTTMACHER,
PRESIDENT, PLANNED PARENTHOOD/WORLD
POPULATION—FEBRUARY 25, 1970

* * *

Now, I need not extol the competence of the Food and Drug Administration Advisory Committee, because I think you know full well that it was picked from the most representative and competent people in this whole area. It is made up of very respected physicians, other scientists, and statisticians, and no doubt you know, but I would like to emphasize once more, their final statement in their recent report, which says when these potential hazards and the value of the drugs are balanced, the committee finds the ratio of benefit to risk sufficiently high to justify the designation safe within the intent of the legislation.

In mid-January, the American College of Obstetricians and Gynecologists made the statement that it "considers that the oral contraceptives are accepted therapeutic methods," and they deplored the inaccurate and sensational reports concerning the drugs.

At the January 28th meeting of my own very distinguished medical committee, which forms the National Medical Committee of the Planned Parenthood Federation, our physicians went over the data and they came up with the report that the committee continues to recommend the prescription of oral contraceptives.

Of course, the reason I quote these authorities is not to whitewash the pill, but I have a compelling interest to place this matter in proper perspective, in the hope, which I am sure you will agree with, of stemming unwarranted and dangerous alarm.

The pill, in my opinion and that of my colleagues, is an important prophylaxis, perhaps the most important, against one of the gravest socio-medical illnesses extant. That, of course, is unwanted pregnancy.

I would like to tally the results of unwanted pregnancy, a condition which is tragically common in our country. First, experts estimate that between 200,000 and 1,000,000 illegal abortions are performed each year in this country, with a death rate estimated to be 100 per 100,000 illegal operations when performed by nonmedical persons.

* * *

I think that pregnancy, in good hands—that

means excellent facilities, in a well-nourished woman who has had excellent prenatal care—carries with it a relatively minimal risk. But I think that anyone would state that if you took a thousand women—you would have to take them in terms of 100,000 women—who were so fortunate as to have this type of care, this type of nutrition, I think you would find you have a higher maternal mortality of more than 3 per 100,000. It may not be the 20 that we find in our American white population; it may not be the 30 which we find in our American black population.

* * *

SENATOR NELSON: I . . . have a pamphlet that discusses a particular oral contraceptive. The cover says, "So Close to Nature." . . . it is the pamphlet of one of the drug companies, explaining the use of the drug. . . .

* * *

So close to your natural feminine pattern. Your doctor has prescribed this newest kind of fertility-control tablet for you. Unlike others available for the same purpose, this preparation follows the principles and system of nature itself. Its actions closely resemble those of your natural menstrual pattern, and it works without upsetting the delicate balance of your normal body function.

Would you agree with that statement?

DR. GUTTMACHER: No, sir; I do not.

* * *

SENATOR NELSON: Well, this is one of the reasons for the hearings, the fact that all the data included in the FDA-sponsored study have not been widely disseminated. Although they have been published, they do not go to the user. Instead, the information in this pamphlet is what goes to the user.

This is the sort of thing being widely run in women's magazines, with an exception or two. Now, do you think that the patient who gets this, or even the doctor, is aware of the Salhanick report on "Metabolic Effects," etc.; this is the one from the workshop sponsored by NIH. Do you think the women of America are aware of what is said there?

In fact, do you think that most of the doctors—I would like the answer to both of those questions—I mean doctors who are not professionals in this field, such as you are, the gynecologic phase of it—do you think doctors are

aware of what this report says? I shall read to you from it.

Until recently the metabolic effects of the sex steroids have been inadequately investigated or ignored. These accumulated data and others suggest that no tissue or organ system is free from a biological, functional and/or morphological effect of contraceptive steroids. Many of these changes appear to be reversible after short periods of treatment, but it is impossible to form judgments on the reversibility of some of the changes resulting from prolonged administration. This question becomes more important daily for the many patients who have already had long-term contraceptive steroid treatment.

* * *

Nevertheless, the consistency of such reports on such findings reject the possibility that they are of no consequence and require that certain questions be answered.

Does the user of the pill in America know this?

DR. GUTTMACHER: No, sir; she would not get much if she read that, either. That is the difficulty. I have been in active practice for 25 years as a private practitioner, and in addition, a full-time chief of service for 10 years. I have had contact with thousands of patients in my long medical life. Unfortunately the physician has to make the decisions for patients. You may discuss this with the patient at considerable length, and usually, when the discussion is over and you are talking about a particular therapy or operation, the patient will look at you and say, "What shall I do?"

Now, I do not think that you are going to be able to educate the American woman as to what she should or should not do with regard to the pill. . . . I think that the average doctor certainly has not read this volume of Salhanick, and I think that much of the information which is in there might be new to the American physician.

I think on the other hand the American physician is a conscientious man. I do not think that he willfully threatens the life of his patient. I think he probably is so overwhelmed by his medical practice and the normal activities of making a living that he tries to get his medical information in capsule form and he is very likely to take the particular throwaway literature which comes across the desk, not seldom, from the pharmaceutical firms.

* * *

Now, I certainly feel that the more we can instruct the American physician about the intricacies of the birth control pill, the wiser the effort. My feeling is that when you attempt to instruct the American womanhood in this, which is a pure medical matter which I am afraid she has not the background to understand, you are creating in her simply a panic reaction without much intellectual background. And this is what I think has been unfortunate.

I do not accuse these hearings of any diabolical purpose, but I must say that the reaction of the American public, parading this across the news media, particularly with the news media picking out those portions which are inflammatory, has done a great deal of harm.

I think educating the American physician is absolutely commendable and important and necessary, and I think perhaps the American physician has been remiss in not trying to educate himself about the intricacies of the pill.

* * *

SENATOR DOLE: Doctor, we all recognize that you indicate it is difficult to inform the patient by setting forth a list of the possible risks involved. Is the pill in this respect different from any other medication?

Is there anything different about the pill and hundreds of other medications? Is there anything about oral contraceptives where the problem of communication is any greater?

DR. GUTTMACHER: I suppose not. Certainly, when it comes to aspirin, we know that we have gastric hemorrhages for aspirin. We have fatal cases of aspirin, even in people who are not taking a vast amount. But I feel that the pill probably is a pretty special kind of medication.

Of course, other drugs have reactions. Certainly, we know of death from penicillin, one of the most widely used drugs, or virtually any drug you can name. Whether the rate from penicillin is higher than from the pill, I cannot answer; I do not know that.

On the other hand, as Senator Nelson has pointed out, this is a drug given to women who are in a state of good health. My reaction to those remarks is that this is a powerful combination of drugs given to women to prevent a most serious illness, and that is unwanted pregnancy. From my point of view, it is justified.

Now, you asked me whether special things should be done in, I suppose, packaging and la-

beling. I have the feeling that most patients do not read what is put into their pill packages or medicines, and, if they do, they have some difficulty understanding it.

Again, my thesis goes back to the fact that your target should be the education of the American physician and that he has to take the responsibility of whether or not to prescribe the pill for Mrs. A or Miss B. This has to be his judgment. I would like to give him, equip him, with all the knowledge possible so that he can make his judgment correctly and authoritatively.

I am all for educating the American medical profession. I have rather dim enthusiasm for attempting to educate the recipients of therapy. I think that the dispenser of the therapy is the person who must be educated and not the recipient.

* * *

SENATOR NELSON: I want to just finish the discussion of this pamphlet. One of the issues we are concerned about is informed consent. The question raised here is, as a matter of public policy, are we entitled to withhold information that is known about a prescription drug which gets the stamp of approval of the Federal agency under a statute passed by Congress? . . .

* * *

. . . Do we have a right not to have public hearings and not to make the information available on the ground that all the press may not carry it the way some people think they ought to carry it? Or that it is too complicated for the public to understand? Is this the kind of decision that we have a right to make, to withhold knowledge developed by the Federal government itself through research and studies and conferences like the NIH, or should these matters be made a matter of public knowledge, counting, as it seems we always have to do, upon the ultimate good judgment of the public to come to a reasonable conclusion?

* * *

Now, let us assume that when the FDA report came out, the findings in that report had been put on the front page of the papers? Would not your reaction have been about the same as it is now?

DR. GUTTMACHER: I think people would have read it and then come to the final conclusion, which I admit is framed in verbiage which

is difficult to define. But at least it is verbiage which does create a certain sense of complacency in the user. I think that if this committee has the power and the wisdom to perhaps issue a statement at the end of the hearings to put this whole thing in proper perspective, to grant the fact that the pill has magnificent and necessary use for many segments of the population, that there are other birth control methods for some which may be substituted with equally good effect, perhaps this will help a great deal.

I think that the American public is leaning on this committee for guidance. My hope is that if you agree with me that there has been a lot of material which perhaps has been misinterpreted and has become inflammatory, you will attempt in an honest and perhaps even cautious way to undo this, I think it would be a great service.

* * *

SENATOR NELSON: I at least do not have the qualifications to draw up a summary of what the experts have said and conclusions on it, and present it to the public as a valid position respecting the pill, its side effects, and its uses. I have no such qualifications. That is the reason we have called upon distinguished experts such as yourself and many others to state the case for the record.

DR. GUTTMACHER: . . . I have not attacked the hearings, sir. I do not think I have. I am unhappy about the results on our patients in my clinics. This distresses me because I do not think that anything has changed materially.

I think they could wait a little longer, but I think there has been a very sudden kind of stampede. This, of course, I regret.

Now, whether the hearings could have been differently tailored so that this was not the result, it is certainly not within my competence to tell you. You are much more experienced at this than I am.

I am not attacking the hearings. I believe in free speech. I believe everybody has a right to be heard. But unfortunately, when it comes to medical matters, the negative is so often more clearly understood than the positive by lay people. This is just the nature of the problem, sir. I have not the solutions to it.

* * *

The fact that our clinics have grown so magnificently since the pill was introduced, I am sure, is not due to the fact that other social factors have made deep impact. The fact that we now

have a product which is extraordinarily acceptable to our type of patient, and if we did not have this product and if we deny them this product or scare them to death from using it, unfortunately, we are going to revert back to situations which are most unhealthy in America.

SENATOR JAVITS: Has anything happened in the testimony or otherwise to change your view as an authority that this is a landmark and historic development in population control?

DR. GUTTMACHER: I think that the two methods, the pill and the intrauterine device, have been significant contributions. I think we are still in the horse-and-buggy day of effective contraception. I am optimistic in feeling that in 5 years, we shall have methods that are infinitely superior and safer than either.

* * *

I think the only influence we have not covered by question is the influence these hearings are leaving in their path throughout the world. I state in my testimony that Professor Alvarez from Montevideo and Professor LaVergne from Panama actually came to the United States because they are members of the Medical Committee of the International Planned Parenthood, to talk with me and others about these hearings because they are so terribly upset and because patients throughout Latin America are upset.

* * *

SENATOR NELSON: I am puzzled as to why they would come to the United States to find what was fact and what was fancy when you have testified that everything that was presented here was in the FDA Report. Did they not have that report?

DR. GUTTMACHER: I am not sure they have had it.

As a matter of fact, I received from London an editorial in one of the Pakistan papers, in which the editorial ends with the admonition that they should discontinue the pill in Pakistan. This, of course, is a very serious problem, because I know you, Senator Nelson, are among the great protagonists of world population control. Unfortunately, the pill is being depended upon more and more throughout the world for population control, and I feel that this setback has been most unfortunate.

Now, I am not blaming you. I think you are taking it for granted that I am trying to levy a certain amount of blame, and I am not blaming you at all. I just cannot help but decry that this

has gotten so much adverse publicity in the press. I cannot help but say that nothing really has materially changed. Millions of people were on the pill before the hearings were held, and nothing has happened, really, to their knowledge about the pill.

Facts and conjectures have been ventilated to physicians who had less knowledge of the pill and ventilated to a lay public which is allergic to all kinds of scare propaganda. I feel our task is to try to put the thing in perspective so that people realize that the pill is still, to me, a magnificent therapeutic agent which has tremendous necessity, until, as Senator Javits says, this 5-year span can be passed and we have much better and safer methods.

SENATOR NELSON: There is no use going back into that. It is just a question of whether you believe the people of the United States should have all the facts or whether they should not. In my view, I think they should. Many people concerned about the question are concerned that the facts are out: some people may decide not to use the pill and therefore raise the problem about population control. I do not think we ought to use individual persons for sociological purposes.

Would you agree with the letter sent out by Dr. Edwards, Acting Commissioner of Food and Drug Administration, sent about the 18th of January . . . to 324,000 doctors. The last sentence reads:

In most cases, a full disclosure of the potential adverse effects of these products would seem advisable, thus permitting the participation of the patient in the assessment of the risk associated with this method.

Do you agree or disagree?

DR. GUTTMACHER: I have not seen it, but we have discussed it before. I think it places a great burden on the patient. I think it is impractical, sir. I think the physician has to make the decision.

* * *

NOTE 7.

TESTIMONY OF DR. JOSEPH W. GOLDZIEHER,
DIRECTOR, DIVISION OF CLINICAL
SCIENCES, SOUTHWEST FOUNDATION FOR
RESEARCH AND EDUCATION, SAN ANTONIO,
TEXAS—JANUARY 22, 1970

* * *

. . . Given the uncertain information about side effects, given the probable but certainly not

unequivocal information regarding thromboembolic deaths, given the serious question of metabolic disorders (which in my opinion at the moment must remain within the realm of scientific inquiry and supervision, and not in the realm of decisionmaking), given these circumstances—how can one give women a proper set of facts so that they can make an intelligent decision as to whether to use the pill or not?

Human beings are generally not impersonal decisionmaking machines. Emotions tend to color thinking, especially when life or safety is at stake. There are innumerable sayings, like, "The doctor who treats himself has a fool for a patient." How coolly and objectively can a lay person, a woman or her husband, weigh information and make a sensible decision if they know that there is a risk of life or death, no matter how small, in the decision they make?

Aside from all emotion, making a sound decision requires having the necessary information and being able to evaluate this information correctly. It is certain that these hearings have produced one piece of information about which no one can quarrel: that even the experts on this subject disagree as to the interpretation of many of the available data. Literally centuries of experience have paraded before this committee, and there is no consensus. Is it then reasonable to suppose that a discussion between the physician and his patient, no matter how careful and well intentioned will, in 10 or 20 minutes, so well orient that individual so that she can now make a truly informed decision for herself?

On occasion I have had patients who have discussed with me the various methods of contraception and then came back with PDR in their hand, and quizzed me about the side effects of the pill like a trial attorney. Such a patient needs, and deserves, every bit of cooperation and information the physician can give her, so that she can make a psychologically and intellectually acceptable decision.

But how many women like this do you suppose there are? Many women have heard that the pill is the most reliable of all contraceptives, and they want to be certain as possible that they do not get pregnant, and that is all they are interested in. Is the doctor serving her best by trotting out a long list of statistical uncertainties, and making her anxious about a course of action she is already content to take?

There are other women, on or off the pill, who have been frightened by misinformation and distortion of facts. They deserve to have all

the information they can understand and utilize. Unfortunately, few physicians have the power of communication, as well as the exact information, to carry out this task as well as one would wish.

Finally, we must recognize that there are vast numbers of women who simply do not have inquiring minds like those that fill this room, and do not have enough education to comprehend much more than the simplest facts of biology. A misguided effort to "inform" such women leads only to anxiety on their part, and loss of confidence in their physician. They did not come for a lecture on statistics; they came for help in not having the 10th baby. The doctor is the man who is supposed to know such things, and they want him to tell them what to do, not to confuse them by asking them to make decisions beyond their comprehension. The sound physician, by judicious questioning, can determine which contraceptive method is most likely to be acceptable and effective in that particular woman. This is the prime consideration. Then it remains to be determined if there are any medical contraindications to that particular method, and we have discussed this at great length. But the idea of informing such a woman is not possible. It depends on the woman herself. It depends on her socioeconomic status. It depends on her education. It depends on her cultural pattern.

One final point I would like to address myself to, and that is the question of who should give the information to the inquiring woman. To make this point briefly: I feel, as a practicing physician, that it is my responsibility and all other physicians' responsibility. If a doctor wishes to use teaching aids in the form of pharmaceutical pamphlets, charts, sketches he makes on his prescription pad, so long as he gets the message across, this is the important thing. In no way can that responsibility be delegated to anyone else.

* * *

NOTE 8.

AMERICAN ASSOCIATION FOR MATERNAL AND
CHILD HEALTH, INC.

PRESS RELEASE ON THE PILL*

* * *

Summarizing the responses, 3,240 (97 percent) physicians believe oral contraceptives are

medically acceptable; 61 (2 percent) believe they are not, and 51 (1 percent) are undecided. This vote of confidence for The Pill is the result of a careful balancing of the risks and benefits involved. The survey asked physicians to rank contraceptive modalities, considering pregnancy risk, general user health, and patient convenience. The results of the process appear below: oral contraceptives, with a ranking of 1.6 on a scale of 1 to 9 (where 1 indicates high desirability and 9 indicates low preference), are still the preferred method of birth control. Next, with a ranking of 2.7, was sterilization, followed by the intrauterine devices at 3.0.

Physician Rankings of Birth Control Methods

Oral Contraceptives	Sterilization Intrauterine Device Diaphragms	Foams or Gels Condoms	Rhythm	Douches Coitus Interruption
1 2 3 4 5 6 7 8 9				

1—Medically most desirable

9—Medically least desirable

Though practicing physicians continue to endorse oral contraceptive use, many women have reacted to the recent publicity about the safety of The Pill. Obstetrician/gynecologists report that new patients asking for oral contraceptives have declined by 20 percent since the recent publicity. Further, established patients using oral contraceptives asking about safety tripled in the same period. Usually these patients are just seeking reassurance. After a discussion with their physician about the comparative risks and benefits of all the available birth control methods, 82 percent elect to remain on The Pill.

Despite current observations of a 20 percent drop in oral contraceptive use among new patients and 18 percent among especially concerned patients, these physicians report that when all patients under their supervision are considered, the decline in The Pill's use is much smaller. A year ago, 72 percent of their patients desiring contraception were using The Pill. Now they estimate this level at 65 percent, a drop of 7 percent.

* * *

* Chicago: American Association for Maternal and Child Health, Inc. (April 29, 1970). Reprinted by permission.

NOTE 9.

TESTIMONY OF DR. ROBERT W. KISTNER,
DEPARTMENT OF OBSTETRICS AND
GYNECOLOGY, HARVARD MEDICAL SCHOOL—
JANUARY 15, 1970

* * *

Although the pill was declared safe in 1969 by the advisory committee on obstetrics and gynecology to the Federal Food and Drug Administration, strangely divergent views continue in the medical and lay press. The pill is either blessed or damned; a valuable therapeutic tool or a potential killer. The medical profession seems to me to be undergoing a schism into "those for" and "those against" the pill. The proponents are largely clinicians who have used the pill day in and day out, over many years, in thousands of patients and have not been impressed by the newspaper scare stories. The opponents are usually physicians or investigators who have not, for one reason or another, been in contact with patients or who have chosen not to prescribe the pill even if they are. The year 1969 did not, unfortunately, bring forth a verdict; neither a winner nor a loser was chosen. Only one decision stands or stood: The pill is safe. Safer than what? Safer than pregnancy on the basis of mortality figures but not as safe as continence.

Almost without exception the consequences of contraception are beneficial and contribute significantly to the health and well-being of the community. In contrast, many societies permit drugs and other practices which are of questionable value or are demonstrably harmful. The ill effects of alcohol and tobacco, which are tolerated for no better reason than that they provide comfort and pleasure, add appreciably to the mortality and morbidity rates of many societies, but they are inadequately regulated by civil law and social custom and do not fall within the sphere of medical prescription. John Peel and Malcolm Potts, in their recently published book, *Textbook of Contraceptive Practice*, state:

Thirty thousand deaths from lung cancer occur yearly in Britain, the majority due to smoking. By the end of the century more British men will have died from smoking-induced cancer than in two world wars. For every pill-induced death in Britain there are at least 1,500 cigarette-induced deaths; based on the total sales of the two products during 1967 one cigarette is three times as dangerous to life as one pill.

MR. GORDON: Dr. Kistner, may I interrupt

for just one moment? Since you compared the risks of smoking with that of the pill, do you know of any cases where smoking three packages of cigarettes has caused either serious illness or death? Three packages?

DR. KISTNER: Smoking three packages?

MR. GORDON: Right.

DR. KISTNER: Obviously the answer to that question is no.

MR. GORDON: I have here the proceedings of a conference held on September 10, 1962, at the headquarters of the American Medical Association sponsored by G. D. Searle and Co. In the back of that, appendix 3, there are case reports, and several reports where people have either died or have become seriously injured taking the pill for only 3 months, in other words, three packages of pills.

DR. KISTNER: Is there a cause and effect relationship demonstrated or proved?

MR. GORDON: Well, it just says "Case reports: Thrombosis and embolism in patients taking the pill."

DR. KISTNER: There is no cause and effect relationship so far as I understand.

MR. GORDON: They said the same thing about tobacco.

* * *

SENATOR MCINTYRE: . . . Doctor, I agree to a certain extent with your observation that the medical profession seems to be undergoing a schism into those for and those against the pill although none of those who have thus far testified about the danger of the pill have advocated that it be completely removed from the market. However, I am afraid that I cannot agree at all with your identification of the proponents as clinicians, who have used the pill daily, and the opponents as physicians or investigators who have not been in contact with patients or have chosen not to prescribe the pill.

Each of the four witnesses we had yesterday might be considered opponents of the pill to some extent. However, three of the four do have regular contact with patients and have prescribed the pill.

A more accurate description, I think, would be that the proponents are largely those who were involved in the development of the pill or in the promotion of its use or who have never observed a serious adverse reaction in their patients.

The opponents appear to be largely those who have observed potentially serious side ef-

fects either through research or medical practice. Do you agree?

DR. KISTNER: I will accept that.

* * *

SENATOR MCINTYRE: Dr. Kistner, the labeling of all oral contraceptives now contains a long list of side effects of varying severity and a listing of certain conditions under which the drug should not be used. In your own practice do you regularly inform a woman of these potential side effects and question her concerning any of these preexisting conditions before starting her on the pill?

DR. KISTNER: Yes.

* * *

MR. GORDON: Let me read from testimony that you gave [in a legal action for damages against a pill manufacturer].

* * *

You were asked the question "What do you tell them about Enovid when you prescribe it?" Then you said, "Well, my routine is and I hope I may be able to give my routine" and you talk about taking a thorough history, do a complete pelvic examination and so on and so forth, and then you say "in addition to this I will usually give her one of the prepared booklets that all of the pharmaceutical houses have in order to have her better understand exactly what is going on in the physiology, in her basic physiology. I like my patient to know what is going on and how the drug she has taken is effective in preventing pregnancy," and so on.

The question is then asked "To what extent do you go over with your patients the information contained in the package insert?" Your answer "I don't relate the package insert to the patient. The package insert is related to me"; then the next question, "When you give Enovid to your patients in the manner which you prescribe, do you discuss with them the reports that appear in the Searle literature?" And then "Did you tell your patients about the reports that appeared in the Searle literature in the package insert regarding the occurrence of thromboembolic phenomena of takers of Enovid?"

"[A:] Are you asking me whether I initiated the conversation?"

"Q: Yes, whether you told your patient about it, . . .

"[A:] Well as an initiation, no. I did not."

"[Q:] How would it come up if it came up?"

Your answer, "If the patient asked me that she had read there was some problem with blood clotting then I would reply to the question."

"Then what would you reply?" So on and so forth.

This was on direct examination. Then in the cross-examination the counsel asked "But you never tell your patient there is a risk of this oral contraceptive pill?" Your answer "No, I do not."

"Q: Isn't that correct?"

"A: That is correct."

You are asked later, then, "Why don't you tell them?" And you say "Well, they might get, if you tell them they have headaches then they have headaches," and so on and so forth.

Then the counsel asked, "Well, if you warn them they may get blood clots, would that warning induce them to get blood clots?"

This testimony indicates that you have not, at least as of that time, warned your patients of the risks.

* * *

DR. KISTNER: . . . But the testimony just read here has to do with complications. If you ask if I sit down and I take this out and I say "Now, I want you to know that you may die of blood clotting or you may get hepatitis or you may get this, that or the other thing," and besides that the only thing that has been said today as far as ipso facto evidence is that of blood clotting, then I would say no. I don't believe it is good medical practice with any medication to go through the list of possible complications.

If I prescribed this particular tranquilizer I wouldn't read off this list of complications. I would tell the patient, "Now, you may get dizzy from taking this. I don't want you to drive," but I wouldn't list to her the total list of complications, and the testimony was in regard to complications, and my direct reply to the interrogator was that if the patient asked me about the risk then I would tell her about that.

* * *

NOTE 10.

TESTIMONY OF DR. HAROLD SCHULMAN,
ASSOCIATE PROFESSOR, DEPARTMENT OF
OBSTETRICS AND GYNECOLOGY,
ALBERT EINSTEIN COLLEGE
OF MEDICINE, NEW YORK, N.Y.—
MARCH 3, 1970

* * *

There is little doubt that the reporting of these hearings by the press, radio and television

has created widespread alarm among women, and many have stopped taking oral contraceptives because of this. Tragically, it is once again the poor who are discriminated against in this type of situation, because they stop their method of birth control, and do not have easy access to a physician to obtain other methods.

We have already seen several women seeking abortion because of these developments. If hearings such as this are going to be held, I believe the committee must carefully plan and screen all individuals who are invited to testify as to the content of their testimony.

MR. GORDON [Committee Staff Economist]: Doctor, doesn't that sound something like censorship? Are you saying that the testimony of a witness should be examined thoroughly before he be allowed to testify?

DR. SCHULMAN: No, I am certainly not advocating the suppression of minority opinion.

MR. GORDON: Or majority opinion? What kind of opinion are you referring to?

DR. SCHULMAN: I think opinion expressed in a responsible way, and I amplify this statement in the remaining paragraph.

MR. GORDON: Who would make the decision whether it is responsible or not?

DR. SCHULMAN: I think in years past, newspapers and magazines have hired science writers and deliberately trained them so they would have some ability to present information in a way which does not alarm the public, regardless of what the content might be.

MR. GORDON: You are saying that the committee must carefully plan and screen all individuals who are invited to testify, as to the contents of their testimony. Do you think that the content of the testimony of various witnesses should be screened before it is allowed to be presented to the public? Is that what you are saying?

DR. SCHULMAN: I think in an area such as this, I think that is necessary, yes. Because you screen it does not mean you would not allow it to be heard.

MR. GORDON: But the committee, you say, should determine what should be stated publicly?

DR. SCHULMAN: No, I think it should determine how it is said publicly.

MR. GORDON: You do not think that is a type of censorship?

DR. SCHULMAN: Well, I do not see it as a type of censorship. It is conceivable that it could be, but if a committee has broad representation, presumably there would be a majority opinion or at least another opinion expressed where it would not be censorship. The committee does

not have a uniform viewpoint towards this issue, either, I would presume.

MR. GORDON: Thank you very much.

SENATOR DOLE: Perhaps the hearings should have been held in executive session because of the somewhat sensational nature of the publicity they generated. If we were concerned only with the problem, we may have been able to explore it more quickly and perhaps have a more detailed examination of witnesses in executive session.

Certainly, no one here suggests censorship, but it does seem we are dealing with a very delicate medical problem, one we Senators are not at all well qualified to deal with. We can ask questions, we can enlist the witnesses, and we can listen to their statements, but we really do not understand the problem. We have had no experience at all with the problem, except in the work we have done—I cannot speak for Mr. Gordon, because he does have great knowledge in this area—that is in the record.

DR. SCHULMAN: Well, I am certainly not advocating censorship, but freedom also implies responsibility and I think the minority [opinion] should be responsibly expressed.

As I mentioned, reputable newspapers and magazines have employed science writers to ensure that the public gets accurate information without unduly alarming the public. Furthermore, the committee must use its legal skills to question and deliberately point out to witnesses and the public at the time of testimony when inflammatory statements such as "mass experiment," and a number of others that have been made today, are being used.

NOTE 11.

POLL ON THE PILL*

* * *

Largely because of all the recent publicity, 18 per cent of the 8.5 million U.S. women on the pill—nearly one in five—say they have stopped it altogether. In addition, 23 per cent say they are giving serious consideration to quitting.

What makes the proportion of women who are defecting even more remarkable is the fact that many of them also say that they have had entirely satisfactory experiences with the pill. Fully 76 per cent of users say they have been "very satisfied" with oral contraceptives, and another 11 per cent were "fairly satisfied." Moreover, two-thirds of U.S. users continue to believe

* *Newsweek* 52-53 (February 9, 1970). Copyright Newsweek Inc., 1970. Reprinted by permission.

that the advantages of oral contraceptives outweigh the risks. Forty-one per cent of the women say they have had no side effects or complications, and 38 per cent attribute their approval of oral contraceptives to their unquestioned effectiveness.

* * *

The influence of the recent bad news about the pill is easy to understand. An astonishing 87 per cent of American women have heard or read about the Senate pill hearings, a degree of awareness rare on public issues or events. And no matter what their own personal reaction, more than a third, on the basis of the reports, are prepared to believe that the pill is linked to cancer, blood-clotting problems, diabetes and heart trouble. There remain, however, a good many women who are not particularly frightened by what they have heard. Twenty per cent of the users believe that the relationship between the pill and cancer, or between the pill and blood clotting, has yet to be established, and another 14 per cent believe that conflicting testimony has made it impossible to reach positive conclusions about the hazards. "It seems to me most of the people who testified stressed the detrimental effects," said a wary housewife in Morristown, N.J. "You could die in childbirth just as easy as taking the pill," noted the wife of a Hastings, Neb., laborer.

One of the main purposes of the Nelson hearings was to determine whether women are being adequately informed by their doctors about the suspected dangers of oral contraceptives. And in the light of the survey, the sub-committee's concern was well founded. A startling two-thirds of pill-taking women say they have never been told about possible hazards by their physicians. On the other hand, only 16 per cent of women have taken the trouble themselves to discuss the dangers of the pill with their doctors as a result of the Senate investigation. Most of these were reassured by their physicians that the pill is safe and that they have prescribed it for a considerable time without noting serious side effects. An Omaha woman quoted her doctor as saying that he had prescribed the pill "long before they were called birth-control pills and never had any patient get cancer or anything else."

Less than 1 per cent of women have found their doctors to be totally against the pill. A Norfolk, Va., woman reported that her physician told her oral contraceptives were "not natural." And still other physicians seem evasive to their uneasy patients when asked about the risks of the pill. A 26-year-old Denver woman reported that

her physician "couldn't be tied down to an answer."

* * *

NOTE 12.

L. L. COLEMAN, M.D.
"PILL" SCARE STORIES*

A most terrifying article on birth control pills appeared in a ladies' magazine. It was filled with terrible tales of disabling injuries to the brain and the uterus. I am certain my doctor would never suggest that I take these drugs if they are as harmful as this article says they are. Are we really risking death or permanent injury by taking these pills?

—Mrs. C.W.T.

Dear Mrs. T.: I happened to see the article you referred to and am distressed by the unnecessary fears it highlighted. Unfortunately, some eager writers, with little or no scientific knowledge, find that the greatest impact can be made by emphasizing fear rather than hope in their writing. I disagree completely with this destructive attitude.

Before contraceptive pills were distributed to the general public, untold control studies were done to be sure of their safety. This is one of the great responsibilities of government health agencies which constantly protect the American people from the "overenthusiasm" for new drugs by their manufacturers.

All drugs may have some potential danger. Even the most innocuous drugs can call forth an unusual reaction in the highly sensitive or allergic person. It is with this understanding that your doctor prescribed the birth control pills. The advantages and disadvantages are carefully weighed in the choice of these pills. You can be certain that all these considerations were appreciated by him for you. There are some risks in everything we do. We must not permit ourselves to be terrified into believing that our health and lives are in jeopardy every time we read scare statistics that have no solid basis in scientific truth.

d.

Testimony of FDA Commissioner Charles C. Edwards—March 4, 1970

* * *

Under the present system we try to keep the physician abreast of adverse reactions as we be-

* *The San Francisco Examiner* (June 12, 1969). Copyright 1969, King Features Syndicate. Reprinted by permission.

come aware of them. This is certainly true with regard to the oral contraceptives. There is no question that it is vitally important to communicate this information to the physician, but there is also corresponding need to keep the patient well informed. I believe that the patient should receive as much accurate information as is necessary for her to make certain decisions.

Let me examine for just a moment how women are currently being informed as regards the oral contraceptive.

They get a good deal of information and misinformation from sources other than the physician—through newspapers, pamphlets, books, television, and from discussion with others. This additional information is reaching a large number of people in a short period of time. While we can control the prescribing information which goes to the physician and any printed or graphic matter that may ultimately reach the patient through him, we have no such opportunity to see that other presentations are accurate, balanced, and properly informative.

I have come to the conclusion that the information being supplied to the patient in the case of the oral contraceptive is insufficient and that a reevaluation of our present policies is in order.

Accordingly, I have asked our Bureau of Drugs to examine this area of consumer information and to give me their recommendations.

I have with me today, which I will submit to you, a statement which we are going to publish in the *Federal Register* so that all interested parties will have an opportunity to comment on it. This statement is the proposed language for a reminder leaflet of uniform content which will be placed by the manufacturer into each package of oral contraceptives produced.

This leaflet is designed to reinforce the information provided the patient by her physician. I emphasize the word "reminder" as its purpose is to recall to the patient her discussion with the physician when she made her decision to begin taking an oral contraceptive.

* * *

What You Should Know About Birth Control Pills (Oral Contraceptive Products)

All of the oral contraceptive pills are highly effective for preventing pregnancy, when taken according to the approved directions. Your doctor has taken your medical history and has given you a careful physical examination. He has discussed with you the risks of oral contraceptives, and has decided that you can take this drug safely.

This leaflet is your reminder of what your doctor has told you. Keep it handy and talk to him if

you think you are experiencing any of the conditions you find described.

A WARNING ABOUT "BLOOD CLOTS"

There is a definite association between blood-clotting disorders and the use of oral contraceptives. The risk of this complication is six times higher for users than for non-users. The majority of blood-clotting disorders are not fatal. The estimated death rate from blood-clotting in women *not* taking the pill is one in 200,000 each year; for users, the death rate is about six in 200,000. Women who have or who have had blood clots in the legs, lung, or brain should not take this drug. You should stop taking it and call your doctor immediately if you develop severe leg or chest pain, if you cough up blood, if you experience sudden and severe headaches, or if you cannot see clearly.

WHO SHOULD NOT TAKE BIRTH CONTROL PILLS

Besides women who have or who have had blood clots, other women who should not use oral contraceptives are those who have serious liver disease, cancer of the breast or certain other cancers, and vaginal bleeding of unknown cause.

SPECIAL PROBLEMS

If you have heart or kidney disease, asthma, high blood pressure, diabetes, epilepsy, fibroids of the uterus, migraine headaches, or if you have had any problems with mental depression, your doctor has indicated you need special supervision while taking oral contraceptives. Even if you don't have special problems, he will want to see you regularly to check your blood pressure, examine your breasts, and make certain other tests.

When you take the pill as directed, you should have your period each month. If you miss a period, and if you are sure you have been taking the pill as directed, continue your schedule. If you have not been taking the pill as directed and if you miss one period, stop taking it and call your doctor. If you miss two periods, see your doctor even though you have been taking the pill as directed. When you stop taking the pill, your periods may be irregular for some time. During this time you may have trouble becoming pregnant.

If you have had a baby which you are breast feeding, you should know that if you start taking the pill its hormones are in your milk. The pill may also cause a decrease in your milk flow. After you have had a baby, check with your doctor before starting to take oral contraceptives again.

WHAT TO EXPECT

Oral contraceptives normally produce certain reactions which are more frequent the first few weeks after you start taking them. You may notice unexpected bleeding or spotting and experience changes in your period. Your breasts may feel tender, look larger, and discharge slightly. Some women gain weight while others lose it. You may also have epi-

sodes of nausea and vomiting. You may notice a darkening of the skin in certain areas.

OTHER REACTIONS TO ORAL CONTRACEPTIVES

In addition to blood clots, other reactions produced by the pill may be serious. These include mental depression, swelling, skin rash, jaundice or yellow pigment in your eyes, increase in blood pressure, and increase in the sugar content of your blood similar to that seen in diabetes.

POSSIBLE REACTIONS

Women taking the pill have reported headaches, nervousness, dizziness, fatigue, and backache. Changes in appetite and sex drive, pain when urinating, growth of more body hair, loss of scalp hair, and nervousness and irritability before the period also have been reported. These reactions may or may not be directly related to the pill.

NOTE ABOUT CANCER

Scientists know the hormones in the pill (estrogen and progesterone) have caused cancer in animals, but they have no proof that the pill causes cancer in humans. Because your doctor knows this, he will want to examine you regularly.

REMEMBER

While you are taking _____, call your doctor promptly if you notice any unusual change in your health. Have regular checkups and your doctor's approval for a new prescription.

* * *

SENATOR NELSON: The figures that have been used frequently before the committee indicate that hospitalization from blood clotting occurs in 1 of every 2,000 users. Is there any reason for not using that figure in here?

* * *

DR. JENNINGS: . . . That was a hospitalization rate, which is one indication of morbidity. I think what we attempted to do here was not a literal translation of the information given to the physician, who is, after all, much more sophisticated and capable of handling these numbers, but to try in a simple fashion to alert the woman to the fact that there was an increased risk and then to give her some idea of the magnitude of this, especially in relation to the most important, that is, the fatality.

SENATOR NELSON: Well, all I say, as just a layman reading it, is that when you talk about the death rate being one in 200,000 for women not taking the pill and for users six in 200,000, those are very large figures. But when you get down to the more practical aspect in a higher in-

cidence and talk about almost one in 2,000 being hospitalized, which is a very high incidence, it is a figure that is much easier to understand, and does not just talk about deaths, it talks about hospitalization rates.

* * *

DR. EDWARDS: I think your point is well taken, and I would emphasize that this is not the final package. This is for discussion purposes primarily, and we certainly anticipate making changes, as requested by groups such as your committee and others.

I think your particular point is a good one.

SENATOR DOLE: Dr. Edwards, this insert has been in the making for sometime; is that correct?

DR. EDWARDS: Right.

SENATOR DOLE: I am not certain whether the average person realizes there is any great risk if it is one out of 200,000 or six out of 200,000. We have had witnesses indicate we should not include a laundry list with medication, because to do so would confuse the patient.

I am not certain where you draw the line, whether you should indicate any numbers, whether you should indicate there is some risk. The question is how to best communicate with patients, but we do not want to frighten the few people left who are not frightened as a result of these hearings.

I would hope that we do not try to rewrite the memorandum in committee hearing.

SENATOR NELSON: I hope the Commissioner did not think I was trying to rewrite the memorandum; I was just asking the question for information purposes because I thought it was a good question. I would not think of trying to write the memorandum, but I would think it is within the province of a member of the committee or any citizen in America, and there are 200 million of them, to ask a question.

* * *

NOTES

NOTE 1.

F.D.A. RESTRICTING WARNING ON PILL—
A DRAFT REVISION INDICATES ORIGINAL
IS TONED DOWN*

The Food and Drug Administration is toning down its announced package warning for 8.5

* *The New York Times* (March 24, 1970). © 1970 by the New York Times Company. Reprinted by permission.

million users of oral contraceptives after pressure from physicians, drug manufacturers, and high Government officials.

An F.D.A. spokesman and sources in the Department of Health, Education, and Welfare confirmed today that the 600-word leaflet announced earlier this month was being extensively reworded.

The original leaflet referred to such serious possible reactions to the pill as blood clots, mental depression, swelling, skin rash, jaundice, high blood pressure, and elevation of blood sugar levels. . . .

One draft revision runs less than 100 words, mentions only a single specific danger from oral contraceptive use, and deletes detailed suggestions on when women using the pill should see a physician.

"Any similarity between this draft and what the F.D.A. proposed is purely coincidental," said one knowledgeable Senate source.

Dr. Charles C. Edwards, F.D.A. commissioner, read to a Senate monopoly subcommittee on March 4 the leaflet's specific wording, which he said, "We are going to publish in *The Federal Register* so that all interested parties will have an opportunity to comment on it."

* * *

It is not unusual for an agency to revise a proposed regulation after publication and after receipt of comments. But it is unusual, informed sources said, for the regulation to be drastically reworded before publication and before formal comment is received.

* * *

Dr. Edwards ruffled bureaucratic feathers when he told the Senate subcommittee about the leaflet and its specific warning without first informing his superior, Dr. Roger O. Egeberg, Assistant Secretary of Health, Education, and Welfare.

The American Medical Association complained to Dr. Egeberg and the H.E.W. Secretary, Robert H. Finch, that the leaflet would interfere with the doctor-patient relationship and possibly could lead to malpractice suits.

The drug industry objected, contending that the leaflet overemphasized dangers and minimized benefits from oral contraceptives.

The revised draft leaflet has this to say about the pill's dangers:

"As with all effective drugs, they may cause side effects in some cases and should not be

taken at all by some. Rare instances of blood clotting are the most important known complications of the oral contraceptives."

The original wording was much sharper on clots. It said:

"There is a definite association between blood-clotting disorders and the use of contraceptives. The risk of this complication is six times higher for users than for nonusers."

The original warning offered signpost symptoms requiring immediate medical attention. It also said:

"Your doctor has taken your medical history and has given you a careful physical examination."

The revised draft said the contraceptives "should be taken only under the supervision of a physician," and users should have "periodic examinations at intervals set by your doctors."

NOTE 2.

MORTON MINTZ

PILL ADVICE STILL UNCLEAR AS FDA
SPURNS NEW WORDING—AGENCY PREFERS
SHORT WARNING, DESPITE PROTESTS*

An entirely new warning to users of the Pill has been recommended to the Food and Drug Administration by its outside advisers on birth control.

At least temporarily, however, the FDA is rejecting the recommendation in favor of a proposal of its own.

Thus it was still unclear yesterday what advice an estimated 8.5 million women eventually will get with each package of oral contraceptive pills.

The recommended new warning resulted from a hitherto undisclosed development last Wednesday—the invasion by two members of the Women's Liberation Movement of a closed meeting of the Advisory Committee on Obstetrics and Gynecology at FDA headquarters in Rockville.

After hearing the Women's Liberation protests, Dr. Roy Hertz, a committee member, wrote this draft for a sticker to be affixed to every package of pills:

"Do not take these pills without your doctor's continued supervision. Contact him if you experience any unusual symptoms, particularly the following: 1. Severe headache. 2. Blurred vi-

* *The Washington Post* (April 6, 1970). © 1970, The Washington Post. Reprinted by permission.

sion. 3. Pain in the legs. 4. Pain in the chest or cough. 5. Irregular or missed periods."

All but "5" can be symptoms of blood-clotting diseases.

The committee suggested that the FDA publish the draft in the *Federal Register* and drop a 96-word agency proposal that would tell women about the Pill in general terms, with none of the committee's emphasis on symptoms and what to do about them. A Women's Liberation member denounced the 96-word statement as "worse than no warning at all."

However, Commissioner Charles C. Edwards told a reporter last week that if the Secretary of Health, Education, and Welfare approves, the FDA soon will publish the 96-word statement "without any change." At the end of a 30-day period for filing of comments, he said, the agency will consider modifications, giving "very top priority" to the advisory committee draft.

Dr. Edwards emphasized that he was not foreclosing the possibility that the statement ultimately adopted will be stronger than the 96-word version. His primary goal is to start the legal process by which a warning of some kind will go directly to users, he said.

* * *

NOTE 3.

HEW PUBLISHES WARNING ON THE PILL*

The Department of Health, Education, and Welfare settled yesterday on a fourth version of a warning to be enclosed in every package of birth control pills.

The language is not necessarily final. After publication today in the *Federal Register* comments can be filed for 30 days. Then this language or a modification will be ordered into effect, provided there is not a court challenge.

The fourth version, announced by HEW Secretary Robert H. Finch at the end of a press conference on civil rights, follows:

"The oral contraceptives are powerful, effective drugs. Do not take these drugs without your doctor's continued supervision. As with all effective drugs they may cause side effects in some cases and should not be taken at all by some. Rare instances of abnormal blood clotting are the most important known complications of the oral contraceptives. These points were discussed with you when you chose this method of contraception.

"While you are taking this drug, you should have periodic examinations at intervals set by your doctor. Tell your doctor if you notice any of the following: 1. Severe headache; 2. Blurred vision; 3. Pain in the legs; 4. Pain in the chest or unexplained cough; 5. Irregular or missed periods."

The portion of the warning dealing generally with the pill was taken from a 96-word proposal that Dr. Charles C. Edwards had wanted to publish and which, in turn, was a watered-down version of an 800-word warning he had endorsed on March 4 at a hearing before Sen. Gaylord Nelson (D-Wis.).

The second portion of the warning—advising women to be alert to possible symptoms of blood-clotting and gynecological disorders—had been recommended by the FDA's outside advisers on the pill.

HEW overrode Dr. Edwards, who had tentatively rejected the advice of the consultants. Secretary Finch acknowledged that he now has endorsed a compromise, which he called "a delicate balance." He said he believed the shorter statement is more likely to be read.

NOTE 4.

FOOD AND DRUG ADMINISTRATION STATEMENT OF POLICY CONCERNING ORAL CONTRACEPTIVE LABELING DIRECTED TO USERS*

On April 10, 1970, there was published in the *Federal Register*, 35 F.R. 5962, a notice of proposed rule-making to establish new labeling which would assure that the user is provided information necessary for her safe use of these drugs.

The proposal was controversial and drew a substantial number of comments. . . .

* * *

[P]ursuant to the provisions of the Federal Food, Drug, and Cosmetic Act . . . the following new section is added to Subpart A of Part 130:

* * *

. . . The oral contraceptives are restricted to prescription sale, and their labeling is required to bear information under which practitioners licensed to administer the drugs can use them safely and for the purpose for which they are intended. In addition, in the case of oral contracep-

* *The Washington Post* (April 8, 1970). © 1970, The Washington Post. Reprinted by permission.

* 35 *Federal Register* 9001-9002 (June 11, 1970).

tive drugs, the Commissioner concludes that it is necessary in the best interests of users that the following printed information for patients be included in or with the package dispensed to the patient:

(Patient Package Information)

ORAL CONTRACEPTIVES

(Birth Control Pills)

*Do Not Take This Drug Without Your
Doctor's Continued Supervision.*

The oral contraceptives are powerful and effective drugs which can cause side effects in some users and should not be used at all by some women. The most serious known side effect is abnormal blood clotting which can be fatal.

Safe use of this drug requires a careful discussion with your doctor. To assist him in providing you with the necessary information,—(Firm name)—has prepared a booklet (or other form) written in a style understandable to you as the drug user. This provides information on the effectiveness and known hazards of the drug including warnings, side effects, and who should not use it. Your doctor will give you this booklet (or other form) if you ask for it and he can answer any questions you may have about the use of this drug.

Notify your doctor if you notice any unusual physical disturbance or discomfort.

Providing the patient package information to users may be accomplished by including it in each package of the type intended for the user as follows:

(1) If such package includes additional printed materials for the patient (e.g., dosage schedules), the text . . . shall be an integral part of the printed material and be in boldface type set out in a box, preceding all other printed text.

(2) If such package does not include printed material for the patient, the text . . . shall be provided as a printed leaflet in boldface type.

(3) Include in each bulk package intended for multiple dispensing, a sufficient number of the patient package information leaflet, with instructions to the pharmacist to include one with each prescription dispensed.

Written, printed, or graphic materials on the use of a drug that are disseminated by or on behalf of the manufacturer, packager, or distributor and are intended to be made available to the patient are regarded as labeling. The commissioner also concludes that it is necessary that information in lay language, concerning effective-

ness, contraindications, warnings, precautions, and adverse reactions be incorporated prominently in the beginning of any such materials, and that such labeling must be made available to physicians for all patients who may request it. Such labeling shall be substantially as follows, based on the approved package insert for prescribers of the oral contraceptives, and shall include the following points:

(1) A statement that the drug should be taken only under continued supervision of a physician.

(2) A statement regarding the effectiveness of the product.

(3) A warning regarding the serious side effects with special attention to thromboembolic disorders and stating the estimated morbidity and mortality in users vs nonusers. Other serious side effects to be mentioned include mental depression, edema, rash, and jaundice. The possibility of infertility following discontinuation of the drug should be mentioned.

(4) A statement of contraindications.

(5) A statement of the need for special supervision of some patients including those with heart or kidney disease, asthma, high blood pressure, diabetes, epilepsy, fibroids of the uterus, migraine, mental depression or history thereof.

(6) A statement of the most frequently encountered side effects such as spotting, breast changes, weight changes, skin changes, and nausea and vomiting.

(7) A statement of the side effects frequently reported in association with the use of oral contraceptives, but not proved to be directly related such as nervousness, dizziness, changes in appetite, loss of scalp hair, increase in body hair, and increased or decreased libido.

(8) A statement regarding metabolic effects such as on blood sugar and cholesterol setting forth our current lack of knowledge regarding the long-term significance of these effects.

(9) Instructions in the event of missed menstrual periods.

(10) A statement cautioning the patient to consult her physician before resuming the use of the drug after childbirth, especially if she intends to breastfeed the baby, pointing out that the hormones in the drug are known to appear in the milk and may decrease the flow.

(11) A statement regarding production of cancer in certain animals. This may be coupled with a statement that there is no proof of such effect in human beings.

(12) A reminder to the patient to report

promptly to her physician any unusual change in her general physical condition and to have regular examinations.

Optionally, the booklet may also contain factual information on family planning, the usefulness and hazards of other available methods of contraception, and the hazards of pregnancy. The material shall be neither false nor misleading in any particular and shall follow the material presented above.

* * *

Existing stocks may be shipped without the package insert for a period of 90 days, provided the labeling booklet is prepared and disseminated as promptly as possible.

Effective date. This order shall become effective 30 days from the date of publication in the *Federal Register*.

NOTE 5.

VICTOR COHN AMA PLEDGES ALL-OUT FIGHT AGAINST BIRTH-PILL WARNING*

The American Medical Association today promised a "legal and legislative battle" against a printed warning due soon in every package of birth control pills.

But Dr. Charles C. Edwards, commissioner of the Food and Drug Administration, defended the warning as a kind of "insurance policy" in the patient's interest.

The warning—ordered by the FDA this month despite AMA and other medical opposition—would tell women of possible side effects such as increased risk of blood clotting and advise "careful discussion with your doctor."

"We must remember that we are long past the medicine man times when no patient knew anything about medicine except where it hurt," Edwards told a meeting here of the Pharmaceutical Advertising Club.

At almost the same hour, the AMA house of delegates voted to oppose "any requirement that interjects a federal agency between a physician and his patient."

The resolution listed these objections:

"The proposal to supply information on side effects . . . intrudes on the patient-physician relationship and compromises individual medical evaluation. . . . The proposed statement would confuse and alarm many patients. The package

insert is an inappropriate means of providing a patient with information regarding any prescription drug; the most effective way to inform the patient is through the physician."

The resolution also stressed "the importance of making certain this FDA requirement not be extended to other prescription drugs."

* * *

NOTE 6.

TURNER V. EDWARDS F.D. COSM. L. REP. ¶ 40, 422 (D.D.C. 1970)

GESELL, DISTRICT JUDGE: This cause came before the Court September 8, 1970 on plaintiff's motion for a preliminary injunction. On the basis of the pleadings, affidavits, and documents, and upon argument of counsel, the Court denied the motion, and herein sets forth its findings of fact and conclusions of law. . . .

Plaintiffs, individually and on behalf of all women who are presently taking or are considering taking oral contraceptives, seek a mandatory injunction directing the Food and Drug Administration to require that each package of oral contraceptives contain more detailed labeling with respect to the health hazards of the pill. The F.D.A. issued a regulation on June 11, 1970, effective September 9, 1970, requiring that a short warning accompany each package of oral contraceptives, stating certain health hazards of the pill and directing users to consult their physicians for further information. The regulation required that manufacturers prepare a pamphlet for distribution by all prescribing physicians, detailing more fully the potential side effects of oral contraceptives and the symptoms of adverse reactions. For the purposes of the motion for a preliminary injunction, the adequacy of the warnings contained in the pamphlet is not challenged. Plaintiffs seek only to have this longer pamphlet placed in packages of the drug, pending final resolution of this litigation.

Plaintiffs have not shown a substantial likelihood that they will ultimately prevail on the merits. The central issue in the case is whether the labeling required by the F.D.A. meets the statutory standards of the Food, Drug, & Cosmetic Act, 21 U.S.C. § 352. These provisions require essentially that labeling of a drug not be false or misleading, that it bear adequate instructions for use, and that it include adequate warnings of potential health hazards. Following elaborate rule-making procedures, the F.D.A. determined that the labeling required by its regulation of June 11 meets each of these standards. [P]laintiffs' claim that the agency's decision was

* *The Washington Post* (June 24, 1970). © 1970, The Washington Post. Reprinted by permission.

arbitrary, irrational, or not in accordance with the relevant statute and the regulatory scheme governing other prescription drugs is not supported by the record. Upon final disposition of this case, it will be open to plaintiffs to question the premise that oral contraceptives are distributed through normal prescription channels; but such a finding is not now warranted.

[T]he Court does not believe that plaintiffs will suffer irreparable injury by the denial of the relief requested. That consumers should be informed of the dangers of oral contraceptives and adequately cautioned as to their use is unquestioned, but the Court is not persuaded that placing the longer pamphlet in packages of the drug, as opposed to the labeling scheme formulated by the Food and Drug Administration, is required to afford protection to the consumer. Indeed a preliminary injunction would delay regulated distribution of the warning pamphlets. These pamphlets at the time of hearing were in the hands of physicians for distribution, and all necessary steps had been taken to operate under the regulations effective the next day. Plaintiffs' requested injunction would change the status quo rather than preserve it pending final judgment. Only in unusually pressing circumstances, which the Court does not find present in this case, should such an injunction be issued. . . .

e.

Joyce Barrett Product Liability and the Pill*

* * *

The lion's share of the oral contraceptive market belongs to G. D. Searle & Co.—"Where the Pill Began". . . . Litigation stemming from alleged Pill-caused side effects began at Searle too. The first of such cases to come to trial was *Simonait v. Searle*, which went to the jury on theories of negligence and breach of implied warranty. Plaintiff claimed that she had contracted thrombophlebitis (formation of blood clots within the veins) as a result of taking the defendant's oral contraceptive Enovid. She charged Searle with negligence in failing to warn of the possibility that Enovid might cause thrombotic disorders. Among the battery of doctors who testified for Searle were Victor A. Drill, who headed Searle's investigation of Enovid, and Celso-Ramon Garcia, who performed Searle's Puerto Rico field trials of Enovid. The doctors

testified that they believed plaintiff's condition was caused by her varicose veins and not by her use of Enovid. The jury agreed, and after a short deliberation brought back a defendant's verdict.

Black v. Searle came to trial on May 12, 1969, and went to the jury on May 20 on counts of negligence, breach of implied warranty, and strict liability. This was an action brought by Raymond Black, as administrator of the estate of his deceased wife, Elizabeth, who had died on September 18, 1965, at the age of twenty-nine, from a pulmonary embolism allegedly caused by Enovid. Plaintiff charged that Searle had failed to adequately warn in its instruction booklets given to doctors, and, in turn, to patients, that the Pill could cause thromboembolic phenomena (clotting). The issue of warning went to the state of knowledge chargeable to Searle as of the date of Mrs. Black's death. Plaintiff maintained that at the time there were approximately 600 reports of thromboembolic phenomena, including a number of deaths, among women using Enovid. The plaintiff had a difficult time, however, proving causation. . . .

* * *

From this conflicting testimony emerged a "qualified" defendant's verdict. The jury found for the defendant on all three counts, but appended this recommendation to their verdict:

Further, it is the recommendation of this jury that, effective immediately, G. D. Searle & Company, in instruction literature both to doctors and patients, advise the dangers of the possibility of phlebitis, thrombotic, and embolic phenomena.

Judge Robert Grant, however, advised the jury that their added directive would not be legally binding upon Searle.

* * *

Attorney Paul D. Rheingold is trustee of a seventy-member Birth Control Pill Group comprised of attorneys with Pill cases who have banded together to render mutual assistance. Most of the group members have one or two cases; a few have a half dozen or more. Mr. Rheingold thinks that many more suits are imminent and will probably be joint malpractice-product liability actions.

Such a suit is *Charles Gillette, Administrator of the Estate of Alinie Gillette v. Samuel L. Friedman, M.D., and G. D. Searle and Company*. Plaintiff's decedent was twenty-two years old, had two children, and a history of rheumatic heart disease, anemia, and pulmonary con-

* 19 *Cleveland State Law Review* 468-470, 472-478 (1970). Reprinted by permission.

gestion. She had been using foam as a contraceptive when, in May of 1967, the defendant doctor started her on Searle's oral contraceptive Ovulen. During June and July Mrs. Gillette reported migraine headaches, menstrual frequency and irregularity, and small hairlike veins appearing on the lower extremities. She was hospitalized on August 27, 1967, and died two days later. The autopsy showed rheumatic heart disease, bilateral pulmonary congestion, edema, hemorrhage, and apparent obstruction of major bronchi.

The defendant doctor was charged with negligence in that he knew, or should have known, that oral contraceptives should not be prescribed for a patient with the medical history of plaintiff's decedent; that he assured her that Ovulen was safe; that thereafter he negligently examined, treated, and advised her and failed to observe and investigate the cause of certain warning symptoms and continued her on Ovulen until the date of the last treatment on August 5, 1967.

* * *

As regards the failure-to-warn count, the plaintiff must establish the state of medical knowledge of oral contraceptives as of and prior to August 29, 1967, the date of his wife's death. In the year 1966, the *Index Medicus*, for the first time under its general heading "Oral Contraceptives" listed a subheading called "Adverse Effects." Reports of vascular problems are prominent in this list. Numerous other medical articles reporting adverse Pill effects had been published prior to August 29, 1967. As early as 1964, the *Physician's Desk Reference*, the chief source of drug information that is available to physicians, reported "thromboembolic phenomena with some fatalities" among women on the Pill.

Was Searle disseminating information about these side effects to prescribers and/or users of Ovulen? The package insert in the Ovulen-21 Compact "warns" of the following "adverse effects":

1. Spotting or breakthrough bleeding.
"Such irregular bleeding seldom occurs with Ovulen. . . ."
2. Nausea.
"A mild nausea may come and go for several days of the first cycle or two. The vast majority of women never experience this."
3. Feeling of fullness and weight gain.
"A few women, once they no longer fear pregnancy, feel better and actually eat more, which, of course, will result in weight gain."

Searle's final "warning" is: "Unusual changes in your health should be reported to your physician—just as they should if you were not on Ovulen."

Were Searle's detail men "bringing the warning home" to physicians about the Pill's harmful side effects? Searle's suggested presentation of Ovulen by detail men to doctors went like this:

Dr. _____:

Searle is happy to present a chemically new, clinically unique oral contraceptive—OVULEN—offering at the lowest dosage, positive prevention of pregnancy, with the lowest incidence of side effects—at the lowest price. The safety of OVULEN has been well established by world-wide experience including 4 million women's cycles. Ovulen has no additional contraindications or precautions to those that apply to all oral contraceptives.

* * *

[T]he chief roadblock to the argument for strict liability to the drug manufacturer is found in Comment *k* to §402A of the Second Restatement of Torts, which provides:

There are some products which, in the present state of human knowledge, are quite incapable of being safe for their intended and ordinary use. These are made especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable degree of risk which they involve. Such a product, properly prepared and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk. (Emphasis added.)

The question then to be considered is what

constitutes a "defective condition." Comment g to § 402A defines it as a "condition not contemplated by the ultimate consumer, which will be unreasonably dangerous to him," and Comment h goes a step further by suggesting that where a defendant has reason to anticipate a possible danger from a particular use, and it fails to give adequate warning thereof, a product sold without such warning is in a defective condition.

* * *

. . . With the sword of legal responsibility for the Pill harm hanging over the prescribing physician's head as well as the manufacturer's, one insurance company, providing malpractice coverage for some 18,000 physicians, sent out on May 14, 1969, the following "Dear Doctor" letter:

Dear Doctor:

Contraceptive Pills

Because of the increasing awareness of potential complications from contraceptive pills, and because we are already handling lawsuits dealing with some of these complications, we are advising physicians to obtain signed statements from their patients which acknowledge requests for these pills despite awareness of the serious risks involved.

We offer the enclosed form which can be used in most instances.

Sincerely,

The suggested form:

CONTRACEPTIVE DRUGS

Read Carefully Before Signing!

The prescription for contraceptive drugs on this date and for every refill hereafter is at my request. In making this request, I am aware that such drugs can cause serious reactions and complications, both known and presently unknown.

Date: _____ Signature of patient: _____

The great social value of the Pill in this era of the population explosion has been stressed. As the simplest and most effective form of contraception available, the Pill has enjoyed a "diplomatic immunity" from criticism. However, in light of the Senate hearings into the Pill and other reports of its adverse effects, the Pill's halo is rapidly tarnishing. Also ending is the immunity from liability enjoyed by Pill manufacturers for the past five years.

On April 15, 1970, after a five-week trial, a Brooklyn, New York jury returned a \$250,000.00 plaintiff's verdict in *Meinert v. Searle*. Mrs. Meinert developed a mesenteric thrombosis in 1962 after taking Enovid for eight months, necessitating an operation to remove

portions of her intestines. Plaintiff proceeded on the bases of express warranty, implied warranty, strict liability, and common-law negligence; the latter theory being subdivided into failure to properly test before marketing and failure to warn of dangers known or which should have been known. The court rejected the express warranty theory, but submitted the other three to the jury, along with interrogatories asking the jury to specify on which theory it made its findings. The jury brought back a verdict for the plaintiff on all three submitted counts.

Lightning struck again on April 24, 1970, when a Federal District Court jury in Detroit brought back a plaintiff's verdict in *Tobin v. Searle*. Mrs. Tobin was awarded \$225,000.00 (her husband received \$50,000.00 for the loss of her consortium) for clotting in the deep veins of her right leg following the use of Enovid. Plaintiff was hospitalized eight times from 1963 through 1965, and underwent surgery twice—once to sever a nerve in an attempt to end severe pain in her groin and right leg, and a second time to replace her destroyed long thigh bone with artificial tissue. Bolstering plaintiff's case was testimony from plaintiff's own prescribing physician that he had relied on data sent to him by Searle, which were incomplete, and some 350 case reports of other clotting incidents obtained from Searle by discovery.

* * *

f.

Placebo Stirs Pill "Side Effects"*

The least serious but most common problems associated with oral contraceptives are those discomforting side effects noted, discussed, and catalogued since the earliest pill trials. . . .

"What we've shown is that a vast majority of reported side effects can also be found in a placebo group, and may indeed reflect the symptomatology of everyday life," says Dr. Joseph Goldzieher of San Antonio's Southwest Foundation for Research and Education. In a randomized, double-blind study . . . he and his associates recorded, after the first treatment cycle, only small differences in the incidence of headache, nervousness, nausea, vomiting, depression, and breast tenderness in women taking oral contraceptives and those on a placebo pill.

The trial—sponsored by Syntex Labs and the Agency for International Development—in-

* *Medical World News* 18-19 (April 16, 1971). Copyright 1971 by McGraw-Hill, Inc. Reprinted by permission.

volved 398 women and a total of 1,523 cycles. Besides the placebo, it included a commercial high-estrogen sequential, a high-estrogen combination, a low-estrogen combination, and an investigative progestin preparation, chlormadinone acetate. . . .

[T]he San Antonio test subjects . . . were multiparous women, almost all of them Mexican-American and poor, who had come to the foundation's research clinic—which is associated with Planned Parenthood—seeking contraceptive assistance.

In a crossover procedure, the 76 women in the placebo group were switched to active agents after the first four cycles. The changeover came too late to entirely nullify the hazards of placebo use, though. Despite warnings about the need to apply vaginal cream, one major side effect showed up in ten women on the dummy pill, plus one on chlormadinone: They became pregnant.

Some of those randomly assigned the placebo may have been lax about the precaution, comments Dr. Goldzieher. But he also concedes that the pregnancy ratio turned up in his study is entirely consistent with results of trials with vaginal cream or foam. "It just doesn't always work all that well," he says.

* * *

Says Dr. Goldzieher: "The words 'dummy pill' were not mentioned to the women. However, they did have to agree [all of the placebo group and some of those on the pill] to use a vaginal cream 'until we're sure your pill is effective.'"

* * *

What about the 11 pregnancies? "We could have aborted them if the abortion statute here in Texas weren't in limbo right now," replies Dr. Goldzieher. "A court here overturned the law and the case is awaiting Supreme Court review. If we had a liberalized law, we'd abort them."

None of the women selected had used the pill before. All the capsules given out were identical in appearance and packaged in 28-day strips. Before the study was to be completed, the federal government—basing its action on studies in beagles—banned all further investigation with chlormadinone; since the Texas trial was double-blind, it had to be discontinued at that point—after only six cycles.

* * *

The investigator stresses that his findings in no way prove that any of the symptoms do not

occur in association with oral contraceptives. But he feels they do indicate that "the true incidence is far less than generally supposed" and less than suggested by previous uncontrolled testing.

* * *

g.

Barry Kramer

Chemical Offers Hope for a New Approach to Population Control*

The claims sound like they're coming from a pitchman pushing his magic snake-oil elixir at an old medicine show: A "morning-after" contraceptive and yet also a cure for male infertility, a palliative for asthma and a treatment for ulcers and high blood pressure.

These claims aren't being made by hucksters, however. Rather, they're being discussed by medical researchers who are seriously studying the possibility of such future uses for a new family of chemicals into whose secrets they are now delving. Called prostaglandins, the substances are found in minute amounts in the body, where they perform an amazing variety of jobs.

The results of recent experiments are astonishing even the most skeptical researchers, and some scientists are classing the prostaglandins in the same "wonder-drug" category as antibiotics.

Considerable excitement has been generated over the use of prostaglandins in the whole field of fertility and birth control. Researchers know that prostaglandins are closely involved in the reproductive process, including the induction of labor. Thus, trials are under way on using the prostaglandins to bring on childbirth.

More intriguing, however, are the findings that if used earlier in pregnancy, prostaglandins cause abortions. Indeed, some early trials in women indicate that prostaglandins can end pregnancy only a few days after conception. Thus, there's promise of the frequently discussed morning-after birth-control drug.

* * *

"Much work remains to be done to establish the efficacy and safety of the prostaglandins and their therapeutic role," cautions a British scientist, Mostyn P. Embrey of the University of Oxford. Echoing other scientists, he says in a letter to the medical journal *Lancet* that extensive testing will have to be completed before prostaglandins can be safely used.

* *The Wall Street Journal* 1, col. 1, 21, col. 3 (December 11, 1970). Reprinted by permission of The Wall Street Journal.

And the research director of a major American pharmaceutical concern says that although the compound's ability to induce abortions and clear asthmatic lungs has been shown, "the rest of the uses haven't been proved yet."

Part of the excitement over prostaglandins' possible use in fertility control stems from research by a 35-year-old Ugandan, Sultan M.M. Karim. Last September he announced findings that could open the way for a birth-control method women could administer without clinical supervision. This is considered a must in lesser-developed countries, where present methods of birth control aren't denting population growth.

* * *

Several years ago Mr. Karim, who is a pharmacologist at Makerere University in Kampala, Uganda, identified prostaglandins as the substance that clamps shut the severed umbilical cord, preventing newborn babies from bleeding to death. After noting that prostaglandins had an apparent role in labor, he reported in 1968 the first use of the compound, by intravenous infusion, to induce labor in several women when they were due.

Mr. Karim then went on to test the anti-fertility effects of prostaglandins on more than

1,000 women. Such tests wouldn't have been possible in the U.S., where the Government rigidly controls human experiments with new drugs. The Ugandan's work has probably shaved years off the development of the compound as a useful medical tool, some scientists believe.

Since Mr. Karim began his work, other researchers have used the compound on pregnant women to induce labor and abortion, refining dosages and methods of application. Drs. Marc Bygdeman and Nils Wijkvist of Sweden, for example, have experimentally induced abortions using intrauterine infusions.

Side effects have been limited to diarrhea, nausea and vomiting, not uncommon with abortifacients. Researchers say such effects can be ameliorated by using other prostaglandins and altering the method of administration and the amount used.

* * *

If prostaglandins prove effective, their use to control pregnancy will raise difficult moral and religious questions. The most obvious: Are prostaglandins contraceptives or abortifacients? No one knows for sure. One determinant is the debatable one of when pregnancy actually begins.

* * *

C.

Medical Innovation and the Profession—A Case Study of Mitral Valve Surgery*

1.

Therapy, Experimentation, and Failure— The First Phase (1902–1929)

a.

Sir Lauder Brunton Preliminary Note on the Possibility of Treating Mitral Stenosis by Surgical Methods†

Mitral stenosis is not only one of the most distressing forms of cardiac disease, but in its

* Grateful acknowledge is made to Judith P. Swazey and Renée C. Fox whose article on "The Clinical Moratorium—A Case Study of Mitral Valve Surgery" was invaluable in identifying much of the original source material which appears in this section.

† 1 *The Lancet* 352 (1902). Reprinted by permission.

severe forms it resists all treatment by medicine. On looking at the contracted mitral orifice in a severe case of this disease one is impressed by the hopelessness of ever finding a remedy which will enable the auricle to drive the blood in a sufficient stream through the small mitral orifice, and the wish unconsciously arises that one could divide the constriction as easily during life as one can after death. The risk which such an operation would entail naturally makes one shrink from it, but in some cases it might be well worth while for the patients to balance the risk of a shortened life against the certainty of a prolonged period of existence which could hardly be called life, as the only conditions under which it could be continued might to them be worse than death. I was much impressed by the case of a man under middle age whom I had under my care at St. Bartholomew's Hospital. For no fault

of his own, but simply because of his disease, this man was really exiled from his family and one might almost say imprisoned for life inasmuch as he could only live in a hospital ward or a work-house infirmary. Whenever he left the hospital or infirmary with an amelioration of his distressing symptoms and returned home the exertion brought on an exacerbation and he had to leave home again in a few days to return to the hospital or infirmary. It occurred to me that it was worth while for such a patient to run a risk, and even a very grave risk, in order to obtain such improvement as might enable him at least to stay at home. But no one would be justified in attempting such a dangerous operation as dividing a mitral stenosis on a fellow-creature without having first tested its practicability and perfected its technique by previous trials on animals. Accordingly I obtained a licence and certificate a year ago in order to make the necessary experiments, but unfortunately other calls upon my time have not allowed me to do more than to make trial experiments of dividing stenosed valves in diseased hearts from the post-mortem theatre and on healthy valves in the hearts of cats, and also to try the proposed operation in the dead animal. It may be some months longer before I can get anything more done, and I therefore think that it may be worth while to write this preliminary note, especially as, after all, if the operation is to be done in man it will be surgeons who will do it, and they must, of course, make their own preliminary experiments, however fully the operation may be described by others, and each must find out for himself the method which he will employ in each particular case.

The first question that arises is whether the mitral orifice should be enlarged by elongating the natural opening or whether the valves should be cut through their middle at right angles to the normal opening. I think there can be little doubt that the former would be the better plan, but the latter is the more easily performed, and it might be sufficient to effect the desired purpose of facilitating the flow of blood from the auricle into the ventricle. The knives which I have used have been like tenotomy knives, but some which I have had made of ladies' bonnet pins were too thin and flexible for stenosed valves although they were sufficiently strong to divide the normal valves in the hearts of cats. The cutting edge of some of these was only a quarter of an inch, but this is too short and a cutting edge of one-half an inch to an inch is really required. The main part

of the valve can be divided with comparative ease, but the thickened edge is firm and it resists the knife. I have not yet decided on the best form of knife, and its form will depend to some extent upon whether the surgeon decides to operate from the auricle or from the ventricle. The latter is less likely to bleed as the knife need not be much thicker than a needle, and a needle wound of the ventricle rarely gives rise to any bleeding. . . .

* * *

The good results that have been obtained by surgical treatment of wounds in the heart emboldens one to hope that before very long similar good results may be obtained in cases of mitral stenosis.

NOTES

NOTE 1.

EDITORS OF THE LANCET

SURGICAL OPERATION FOR MITRAL STENOSIS*

A NOTE by Sir LAUDER BRUNTON published in our columns last week contains a sufficiently heroic therapeutic suggestion. It calls attention to the grave effects of stenosis of the mitral valve and to the possibility that relief might be obtained by a surgical division of the diseased valve. With an ambition to bring relief to these patients Sir LAUDER BRUNTON obtained a licence and certificates a year ago to enable him to test on animals the validity of his suggestion. We gather that he has proceeded no further than the table of the dead-house in making his investigation, and having many other claims upon his time he now publishes the suggestion in the hope that others will complete what he has begun. This is a somewhat unusual course to pursue and we think that Sir LAUDER BRUNTON would have been better advised to have himself completed his experiments, even at considerable inconvenience, rather than to incite others to pursue a path into the unknown which must be beset with very grave difficulties and responsibility. The experiments on animals which he advocates require considerable delicacy and skill on the part of the experimenter, and we have a strong feeling that the man with whom the idea originated is certainly the most fitted to cope with the initial difficulties and to bring the experiments to a satisfactory conclusion, if that be possible.

* 1 *The Lancet* 461-462 (1902). Reprinted by permission.

Having taken this preliminary objection to the form in which the proposal has been published, let us consider the proposal itself. As it is only a suggestion and the operation has never been performed we can only fall back upon *a priori* arguments. And we are all aware how fallacious such arguments are. How many of the great advances which have raised surgery to its present exalted position have been ruthlessly condemned on *a priori* grounds? The surgery of the brain, the stomach, the spleen, the liver, and the uterus has all been advanced and almost perfected in spite of weighty *a priori* reasons against the procedures which are now known to be useful. So that, as a general rule, we deprecate such a line of reasoning. Experiment and observation are the "weapons of our warfare," and the only ones in which we have much confidence. But Sir LAUDER BRUNTON's proposal challenges criticism in two directions—the difficulty of the operation and the doubt as to its efficacy, even if successfully carried out. On a dead and motionless heart the division of the mitral valve through a fine puncture in the ventricle is a difficult and very delicate step. But when the operation is complicated by the rapid movements of the auricle and ventricle and the respiratory movements of the chest it is plain that the operation is beset with very grave difficulties—difficulties that only the boldest surgeons, with the best-balanced sense of the limitations of their science, could for a moment face. We think that these difficulties have been under-estimated and that the very technique of the operation will prove fatal to its adoption. The introduction of a fine knife through the ventricular wall would have to be done rapidly, and then the manipulation of the knife into the orifice between the deformed cusps of the mitral valve and the section of the valve would also have to be accomplished very rapidly; and all this in conditions most embarrassing and most destructive of that entire self-control which is the chief secret of success in rapid and exact surgical manoeuvres. But were this difficulty overcome and the safety and feasibility of the operation established, a further doubt arises in our mind. If the narrowed valve is divided, what hope is there that the incision in the valve will heal without renewing the contraction? The incision in such a valve would show a great tendency to unite directly and the state of the valve would then be worse than before. . . . It has also to be borne in mind that the operation might convert the valvular lesion from a mitral stenosis into a mitral regurgitation with very

doubtful benefit to the patient. For the difficulties of the procedure must be enormous.

* * *

NOTE 2.

W. ARBUTHNOT LANE

SURGICAL OPERATIONS FOR MITRAL STENOSIS*

Referring to the preliminary note on the possibility of treating mitral stenosis by surgical methods by Sir Lauder Brunton . . . it may interest your readers to know that this suggestion was made by me to my colleague, Dr. Lauriston Shaw, some years ago. I then went into the matter fully, both as to the surgical measures to be adopted and the physical conditions of the valve which seemed most suitable for such interference, and was quite prepared to act as soon as Dr. Shaw succeeded in finding a case likely to derive benefit. It was entirely due to his perhaps wise caution that the operation has not yet been performed by me. The method by which I proposed to divide the contracted valve through the ventricle was practically identical with that described by Sir Lauder Brunton. Personally I believe that the operation is feasible and, under certain circumstances, justifiable.

NOTE 3.

THEODORE FISHER

SURGICAL OPERATIONS FOR MITRAL STENOSIS†

In your leading article upon the suggestion by Sir Lauder Brunton that it may be possible to operate upon some cases of mitral stenosis you give several reasons why such an operation is likely to fail. It seems to me that another may be added. Marked fibrosis of the cardiac muscle is found after death in many cases of mitral stenosis and it is probable that the prognosis in this variety of valvular disease depends as much upon the condition of the heart wall as upon the size of the mitral orifice. If the cardiac muscle remains healthy it is possible not only for life to be prolonged, but for the man or woman in whom the mitral orifice is narrowed to live an active life. For example, in an ostler, aged 64 years, who was busy at his work to within a few days of his death, which was caused by acute bronchitis, I found a mitral orifice which would only admit one finger.

* 1 *The Lancet* 547 (1902). Reprinted by permission.

† 1 *The Lancet* 547–548 (1902). Reprinted by permission.

NOTE 4.

LAURISTON E. SHAW

SURGICAL OPERATIONS FOR MITRAL STENOSIS*

In reference to the correspondence in your columns with regard to Sir Lauder Brunton's preliminary communication upon the above subject, I can corroborate Mr. Arbuthnot Lane's statement that he and I fully discussed the matter at least 12 years ago. Mr. Lane introduced the subject to my notice and satisfied me that he probably could without any immediately harmful result temporarily enlarge, by surgical means, the orifice of a constricted mitral valve. Lest however, it should appear from Mr. Lane's letter that I am still hoping to succeed "in finding a case likely to receive benefit" therefrom, I shall be obliged if you will allow me to state that the *a priori* arguments against the probability of any patient deriving benefit from this operation seemed to me so conclusive that I deliberately decided against regarding it as a justifiable therapeutic measure. These arguments are so clearly summarised in your leading article of Feb. 15th that your readers will, I think, agree with me that Sir Lauder Brunton's chief task is not to show his surgical colleagues that it is possible to enlarge the stenosed mitral orifice, but to persuade his medical colleagues that such a proceeding is useful. It is possible to do many things that are useless and some things that are harmful.

b.

Elliott C. Cutler and S. A. Levine

Cardiotomy and Valvulotomy for Mitral Stenosis—Experimental Observations and Clinical Notes Concerning an Operated Case with Recovery†

During the recent decennial celebration of the former and present members of the nursing and professional staff of the Peter Bent Brigham Hospital, we presented (May 24, 1923) a case of mitral stenosis upon which we had operated four days previously in an attempt to alleviate the condition by diminishing the degree of stenosis of the valve.

... So far as we can determine, this is the only case on record of such a surgical attack upon a mitral stenosis being completed. Doyen

previously attempted a similar case, but his patient did not survive the operation.

Ever since Sir Lauder Brunton in 1902 suggested the possibility of the surgical treatment of valvular disease of the heart, investigators have studied the experimental creation of valvular lesions. Papers by McCallum, Cushing and Branch, Bernheim, Schepelmann, and Carrel and Tuffier from 1906 to 1914 describe fully the experimental methods in use. All of these methods were only successful in creating defective valves resulting in regurgitation. The most successful methods consisted in inserting a knife-hook (valvulotome) into the apex or down the aorta and cutting or tearing out valve cusps. Carrel and Tuffier added a new method of creating an insufficiency by the use of an endothelial transplant over the region of valves, the ring at the base of the valve then being cut, thus permitting a bulging at that point. In 1922 Allen and Graham reported investigations of a similar nature with the addition that they used a cardioscope in which a small knife was carried, and by inserting the instrument *via* the left auricular appendage they were able to cut the mitral valve under direct vision.

For over two years we have sought to clear up by experimentation some of the points still left unanswered by all this work. The chief difficulty has always been to create a stenosis. Obviously until this can be produced further animal investigation will not tell us what benefits accrue when such a lesion is converted into an insufficiency. Temporary, but purely temporary, stenoses can be made by placing a thread in the ring about the base of the valves and tying it snugly. We attempted to improve on this by various methods of partial ventriculectomy, by plicating, and by plastic operations at the region of the valves. None of these methods proved successful in our hands. The experience gained, however, proved of great value, chiefly educating us in the ability of the heart muscle to stand trauma, in the methods of restoring an injured heart to renewed function, and in our ability to locate and "feel" valves in a writhing, pulsating organ.

We had reached a point where it appeared to us that further knowledge could only be gained by an attempt in an actual case, and, much as we feared the difficulties, our experimental work gave us the courage to carry out what must appear as a hazardous trial. Our experimental work with the cardioscope left us with the impression that the greater intricacy of the

* 1 *The Lancet* 619 (1902). Reprinted by permission.

† 188 *Boston Medical and Surgical Journal* 1023-1027 (1923). Reprinted by permission.

operation and the greater amount of time consumed with this method was such that it seemed wiser to use the simpler and more speedy route through the ventricular wall with the valvulotomy in the first human case.

The opportunity arrived through the interest and vision of Dr. Maurice Fremont-Smith, who asked us to see in consultation with him a child in the Good Samaritan Hospital. The history is as follows:

The patient is a girl 12 years old, whose chief complaints are dyspnea and bloody sputum. . . .

* * *

During the past six months repeated attempts were made to get the patient out of bed, but each time the pulse would become rapid—120 to 140—and the dyspnea would increase. During this time there were frequent pulmonary hemorrhages. She would raise from 20 to 300 cc. of pure bright blood at a time and would seem desperately sick, so that for a while she was on the danger list.

On May 15, when we saw her, the patient presented the following picture: She was sitting up comfortably in bed, but could not lie flat. . . .

* * *

In general, the picture presented was one of mitral stenosis in a child who had no cardiac reserve. She could be fairly comfortable in bed except for the repeated attacks of severe hemoptysis. It proved to be impossible to get her out of bed. Our studies indicated that the heart muscle was still in fair condition and that the stenosis was sufficient to be an important factor from a purely mechanical point of view.

* * *

[The operation was performed on May 20, 1923.] Towards the end of her third postoperative day, the temperature and pulse and respiratory rates fell, the signs in the right apex rapidly cleared except for some sticky râles, and after a comfortable night the patient seemed in as good general condition as before operation.

Indeed, we felt so sanguine of her ultimate recovery that she was brought down to the large amphitheater and presented before the reunion group of doctors and nurses the fourth day after operation (May 24, 1923). From this time on her recovery was rapid, as it is in most children once the period of convalescence becomes well

established. Her appetite, spirits, strength, and general condition responded marvelously. . . .

* * *

At this stage of our observations we cannot with accuracy define just what has occurred nor what benefits may have accrued, if any. It is true that we do not feel very sanguine about the latter, although, should any improvement occur in the patient's vital capacity, that might be taken as a definite indication that some alleviation of the stenosis had resulted. The experience with this case, however, is of importance in that it does show that surgical intervention in cases of mitral stenosis bears no special risk, and should give us further courage and support in our desire to attempt to alleviate a chronic condition, for which there is now not only no treatment, but one which carries a terrible prognosis. Unquestionably further attempts will be made, and our own experience in this instance has shown us technical improvements that should render a subsequent attempt both less hazardous as well as more hopeful for success.

* * *

NOTE

THE EDITORS OF THE BRITISH MEDICAL JOURNAL
OPERATIVE TREATMENT OF MITRAL STENOSIS*

The ambitious efforts of surgery to remove conditions which physicians are unable to cure has been extraordinarily successful in the comparatively recent past, but hitherto valvular disease of the heart has remained outside the sphere of those who have been described as "physicians who can use their hands". . . .

A milestone has . . . been reached by the recent publication of a paper by Drs. E. C. Cutler and S. A. Levine. . . .

[T]he authors, who must be sincerely congratulated on this brilliant operation, are cautious in avoiding any statement as to the benefit that the patient has received, but they feel that the experience gained in this operation, now for the first time successfully accomplished, has provided technical improvements which should render any subsequent attempt both less dangerous and more likely to be followed by a satisfactory result.

* 2 *British Medical Journal* 530-531 (1923). Reprinted by permission of the editor of The British Medical Journal.

c.

**Elliot C. Cutler, Samuel A. Levine,
and Claude S. Beck**
**The Surgical Treatment of Mitral Stenosis—
Experimental and Clinical Studies***

* * *

It is difficult to analyze at this time the stimuli that led us to begin this investigation in 1920. Certainly, we were increasingly impressed with the inadequacy of medical treatment in many cases of mitral stenosis. The suggestion of Sir Lauder Brunton had been brought to our attention. . . . The proposal and useful methods for its study were at hand, and the technical improvements in surgery had advanced to the stage in which difficulties from this aspect alone no longer assumed the dominant role. The cranial chamber having been successfully brought into the province of safe surgery, chiefly through the technical methods of Professor Cushing and his pupils, it appeared that the heart alone remained as a field for the almost unchallenged labors of the internists. That this state of affairs was not to continue long was evidenced by the developments already stated.

Fortunately, one of us had already conducted experimental studies involving exposure of the heart of the cat. In these experiments, levers had been sutured against the walls of the heart, and cannulas had been inserted into the various chambers without much disturbance of function, so that we began with no particular trepidation concerning the inability of the heart to withstand trauma and manipulation.

From the beginning, we set out to develop a surgical method for the treatment of mitral stenosis. It seemed to us . . . that the medical treatment of chronic cardiac valvular disease, and especially that of mitral stenosis, was inefficient. It was hoped and expected that the technical difficulties could be surmounted. This could only be accomplished by means of animal experimentation.

* * *

A series of experiments were conducted on cats and dogs, with the purpose of developing a technic to be used in the surgical treatment of certain heart affections in human beings.

* 9 *Archives of Surgery* 689, 712, 723-724, 769-770, 812, 814 (1924). Reprinted by permission.

It was learned that the heart could withstand considerable trauma and yet recover normally. The use of hot salt solution applied directly over the exposed heart, manual massage and epinephrin solution was found of great value in restoring proper cardiac contraction.

The entire circulation to and from the heart could be clamped off from two to eight minutes with recovery of a satisfactory circulation; but when the circulation was stopped in this way for more than two or three minutes, although the heart could be made to recover properly, the animals died in a few hours or a few days in opisthotonos or marked rigidity. It seemed that the cerebral centers, unlike the heart, could not tolerate the standstill in the circulation. Experiments were successfully performed in which the circulation was clamped; during this procedure, the left ventricle was opened and the mitral valve cut under direct inspection. This operation as a general procedure had to be given up because of the damage to the higher nervous centers.

An attempt was made to produce mechanical mitral stenosis by a puckering stitch in the heart in the region of the auriculoventricular ring, and by excising wedge-shaped portions of musculature in this region. These experiments failed because, although insufficiency of the valve lasting a few weeks would result, the valves would always return to a normal condition. Attempts to create stenosis were made by implanting radium emanation seeds about the base of the mitral valve.

An approach to the mitral valve through the left ventricle proved to be successful in cutting valve leaflets without clamping the circulation. Such animals could recover good health and manifest a mitral systolic murmur for many months. When finally examined, the hearts would show that the rent in the valve did not close up, and that there was no tendency to thrombus formation either at the site of the incision through the left ventricle or on the cut valves.

These experiments enabled us to feel that enough had been learned to warrant an attempt to relieve the obstruction in man.

* * *

[The] four cases constitute the first attempts to enlarge the stenosed mitral orifice in human patients. A preliminary report of Case 1 appeared in the *Boston Medical and Surgical Journal* of June 28, 1923, one month after the operation. . . .

These cases are not, however, the first at-

tempts to operate on man for valvular disease. In 1912, Tuffier operated on a young man with a marked aortic stenosis. He states that he would have liked to attempt division of the valve, but that he thought that the experimental data justifying this were insufficient. Instead, he attempted to dilate the orifice by the insertion of his little finger. He reported that there was temporary improvement, and that in 1920 the man was still living. Tuffier also reported that Doyen attempted to operate on a patient considered to have mitral stenosis, but that the operation disclosed an interventricular communication. The patient did not recover.

. . . It seems best, however, to call to your attention at this point that the experimental and clinical work, except for the early investigations . . . were going on simultaneously. Thus, in the first three cases, the knife method was used in the dividing of the valves. However, after the post-mortem examination in Case 2, we became convinced that this method would not prove satisfactory, and we began at once the development of the cardiovalvulotome. . . . The principle of excising a fragment of the valve had been in our minds for at least a year. The new and powerful valvulotome was actually sterilized and on the table in Case 3, but as this case was complicated by an adherent pericardium, we felt it unwise to use it when the opportunity to do so arrived. An hour's struggle with the pericardial adhesions had unfortunately dissipated much of our courage. The new instrument, however, was used in the last case and proved effective. With each clinical attempt, new questions arose which could only be answered by fresh laboratory investigation. The experience in such work enabled us to approach each new patient with both better instruments and an improved procedure. Carrel once stated that many of the questions put to him regarding the possibilities of the surgical treatment of valvular disease could only be answered by experience obtained in human cases. It is our hope that we have obtained as much benefit as our capacities enable us to obtain from the following attempts in human cases.

* * *

From such a limited experience no final deduction can be drawn either for or against the proposal or the procedure. We feel, however, that much has been learned that should be of value in the consideration of such cases and in subsequent operations. Certainly, there can be no

doubt that the method of exposure used is satisfactory, simple in execution and that it apparently produced no especially harmful effect on our patients. The fact that there were no operative deaths, or any indication that the procedure per se was a factor in the subsequent fatalities, is comforting.

A mortality of 75 percent is alarming, but to those who will analyze the full reports of the separate cases it may not appear so disastrous. The three fatalities seem fully explained by causes not inherent in the procedure itself, except in Case 3, in which the slight but continuous oozing from the divided cardiopericardial adhesions added to the burden of an already diseased heart. Death in Case 2 was obviously due to cardiac failure. We might in retrospect think that this type of case, in which fibrillation gave evidence of considerably advanced myocardial damage, was too poor a risk to be considered for such a procedure. But even our judgment here may be faulty because, if we could have produced in such a case a real decrease in the mechanical obstruction, great relief might have occurred. Of course we do not know how the diseased auricle would have borne the increased regurgitation, or how the damaged ventricle would have tolerated its increased amount of blood. In Case 4, a common, and often serious, pulmonary complication was apparently a factor in the fatal issue.

Indeed there are so many questions, obviously unanswered before the first and even after the last operation, that we feel that our mortality rate should be judged, if one wishes to use this as a criterion, only in comparison with figures obtained in the early surgery of other parts of the body, when similar important questions were still unanswered. May we recall the mortality figures in the early surgery of such a relatively simple field as that of the stomach, collected by Dr. W. W. Keen for his Cartwright lectures. Of the first twenty-eight gastrostomies, collected in 1875, all the patients died, and in a series of thirty-five gastroenterostomies in 1885 the operative mortality was 65.7 percent. Moreover, it took years for these figures to improve. In 1884, the mortality for gastrotomy was still 81.6 percent.

* * *

We feel that the proposal that certain cases of mitral stenosis may be relieved by surgery has not been contradicted by our experiences, and

we hope that similar opportunities in other cases will prove that the proposition is well founded and desirable.

NOTE

J. S. GOODALL AND LAMBERT ROGERS
SOME SURGICAL PROBLEMS OF CARDIOLOGY—
TECHNIC OF MITRALOTOMY*

Disheartened by the distressing nature, the progressive character, and the frequent inefficacy of the medical treatment of certain cardiac lesions, enterprising workers have from time to time endeavored to develop a surgical aspect to the treatment of heart disease, their prevailing idea being not to supplant medical treatment by surgery but to introduce the latter in a more radical attempt to relieve pain or prolong life.

* * *

The tragic death of the young sufferer from mitral stenosis, whose systemic circulation is starved of oxygenated blood because of the obstruction at the mitral valve, is well known. "Desperate diseases need desperate remedies," and desperate though an attempt at relieving the obstruction by surgical means may seem, it would appear that in the hands of an operator who has developed and sufficiently practiced an efficient technic, the operation may afford a ray of hope for the future.

It has been well said that in order to decide upon the justification for operating, a surgeon should endeavor to put himself in his patient's place and imagine the operation applied to himself. With death imminent from mitral obstruction who of us would not clamor for something to be done, could we but place our faith in an operator and a technic sufficiently sound to give at least a chance of life?

It should be obvious in the first place that so highly a specialized technic as is required for any intracardiac operative procedure can be carried out only by the specialist who has devoted much time and patience to perfecting his methods of operating upon the heart, and however expert an operator a general surgeon may be, he would be quite unjustified in attempting such an operation without first developing this technic by experimenting upon the cadaver and upon animals.

* * *

* 38 *American Journal of Surgery* 108 (1924).
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d.

H. S. Souttar The Surgical Treatment of Mitral Stenosis*

There can be no more fascinating problem in surgery than the relief of pathological conditions of the valves of the heart. Despite the consecutive changes to which these lesions may have given rise in the cardiac muscle, the relief of the lesions themselves would undoubtedly be of immense service to the patient and must be followed by marked improvement in his general condition. Expressed in these terms, the problem is to a large extent mechanical, and as such should already be within the scope of surgery, were it not for the extraordinary nature of the conditions under which the problem must be attacked. . . .

* * *

. . . I have been interested for some time in the development of a suitable technique for reaching this valve, and I owe to Dr. Otto Leyton the opportunity . . . for putting my ideas to the test. A description of the case itself will give the clearest indication of the method of approach I adopted and of the technique which I devised.

L. H., aged 15, was admitted to the London Hospital in January, 1921, suffering from chorea and mitral stenosis. Her subsequent history was one of many relapses, with steadily increasing failure of compensation. In September, 1924, she was admitted with haemoptysis, vomiting, and severe dyspnoea. She was cyanosed, her feet were swollen, and her liver was enlarged and tender. After three weeks in hospital she had greatly improved and was sent to a convalescent home, whence three weeks later she was discharged.

Early in March, 1925, she appeared at the London Hospital with cough, dyspnoea, and pain in the limbs. She was sent home to bed and given digitalis and aspirin, but she did not improve. After a severe attack of epistaxis and precordial pain she was again admitted as an in-patient.

* * *

In view of her many relapses it appeared that her heart was unable to establish compensation for the combined stenosis and regurgitation from which she suffered, and it was therefore

* 2 *British Medical Journal* 603-606 (1925).
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decided to attempt to relieve the stenosis by surgical means.

* * *

The auricular appendage was . . . drawn forward, a soft curved clamp was applied to its base, and it was incised in an antero-posterior direction with scissors. Into this opening the left forefinger was inserted, the clamp was withdrawn, and the appendage was drawn over the finger like a glove by means of the sutures. The whole of the inside of the left auricle could now be explored with facility. It was immediately evident from the rush of blood against the finger that gross regurgitation was taking place, but there was not so much thickening of the valves as had been expected. The finger was passed into the ventricle through the orifice of the mitral valve without encountering resistance, and the cusps of the valve could be easily felt and their condition estimated.

The finger was kept in the auricle for perhaps two minutes, and during that time, so long as it remained in the auricle, it appeared to produce no effect upon the heart beat or the pulse. The moment, however, that it passed into the orifice of the mitral valve the blood pressure fell to zero, although even then no change in the cardiac rhythm could be detected. The blood stream was simply cut off by the finger, which presumably just fitted the stenosed orifice. As, however, the stenosis was of such moderate degree, and was accompanied by so little thickening of the valves, it was decided not to carry out the valve section which had been arranged, but to limit intervention to such dilatation as could be carried out by the finger. It was felt that an actual section of the valve might only make matters worse by increasing the degree of regurgitation, while the breaking down of the adhesions by the finger might improve the condition as regards both regurgitation and stenosis.

It was now decided to withdraw the finger and close the appendage. . . .

* * *

She made an uninterrupted recovery, the freedom from pain or any disturbance which might have been expected to result from the operation being remarkable. Her general condition appeared to be greatly improved, but the physical signs showed little or no change. She was sent to the country and kept in bed for six weeks, but as at the end of that time her pulse rate had remained constant at about 90 she was

gradually allowed to get up. At the end of three months she declared that she felt perfectly well, although she still became somewhat breathless on exertion.

I believe that this is the first occasion upon which an attempt has been made to reach the mitral valve by this route in the human being, or to subject the interior of the heart to digital examination. The value of the method cannot possibly be judged on a single case, but I think that I may claim to have shown that the method is practicable and that it is reasonably safe. Indeed, the features which most struck all who were present at the operation were the facility and the absolute safety of the whole procedure, while even on a first attempt the amount and precision of the information to be gained by digital exploration were very remarkable. I had intended to divide the aortic cusp by passing a thin hernia bistoury along my finger and thus to relieve the stenosis, and this could have been done with perfect facility had it been considered advisable.

* * *

It appears to me that the method of digital exploration through the auricular appendage cannot be surpassed for simplicity and directness. Not only is the mitral orifice directly to hand, but the aortic valve itself is almost certainly within reach, through the mitral orifice. Owing to the simplicity of the structures, and, oddly enough, to their constant and regular movement, the information given by the finger is exceedingly clear, and personally I felt an appreciation of the mechanical reality of stenosis and regurgitation which I never before possessed. To hear a murmur is a very different matter from feeling the blood itself pouring back over one's finger. I could not help being impressed by the mechanical nature of these lesions and by the practicability of their surgical relief.

NOTE

HARRINGTON SAINSBURY
THE SURGICAL TREATMENT OF MITRAL
STENOSIS*

I have read with the greatest interest Mr. Souttar's description of his operation for the relief of mitral stenosis. It shows triumphantly the accessibility of the interior of the left auricle, and

* 2 *British Medical Journal* 818 (1925). Reprinted by permission.

of its passage of communication with the ventricle, to surgical measures.

My object in writing is to draw attention to a danger which must attend an operation such as that described, but to which no reference is made. . . . The danger arises from the fact that these cases of pronounced mitral stenosis are so often the seat of recurrent attacks of acute endocarditis (Mr. Souttar's case was admitted with pain in the limbs, though the temperature is not recorded). In such cases fresh vegetations are a common pathological feature, and the risk of the detachment of these in passing the finger through the auriculoventricular orifice, with embolism as a necessary consequence, is plain. I need not dilate upon this peril, which even very delicate manipulation might involve. . . .

* * *

e.

Elliot C. Cutler and Claude S. Beck
The Present Status of the Surgical Procedures
in Chronic Valvular Disease of the Heart—
Final Report of All Surgical Cases*

[It] seems opportune to review the cases of valvular disease in which surgical treatment has been used. In summarizing these cases, we shall attempt to evaluate the general idea of subjecting such disorders to surgical therapy and we shall also attempt to emphasize the problems that must in the future be overcome to make surgical procedures on the cardiac valves useful and beneficial.

Operation has been performed in twelve cases of chronic valvular disease of the heart. . . .

* * *

[The cardiac abnormalities included] one case of pulmonic stenosis, one case of aortic stenosis and ten cases of mitral stenosis. We have not had any personal experience with pulmonic stenosis and aortic stenosis. It seems that mitral stenosis offers greater promise than do any other of the valvular lesions, and for this reason we shall confine discussion to the cases of mitral stenosis.

Of the ten patients with mitral stenosis who were operated on, only one is living, giving a mortality of 90 per cent. Eight of the ten patients died so soon after operation that the changes brought about in the mechanics of the circulation could not be adequately studied. One

patient lived four and a half years after the operation. It is difficult to say definitely whether in this case the enlargement effected in the mitral valve by the operation was followed by an improvement in the circulation. We believe, however, that there was an improvement in the patient's condition. If it be true that the mechanics of the circulation were improved by reduction of the stenosis, a definite advance in this subject has been brought about. It will require, however, a number of cases in which operation is successful to determine definitely whether an improvement in the circulation can be expected by enlarging the orifice in the stenosed valve. Such physiologic observations have not been produced in animals. Unfortunately, it seems that the basic idea underlying this development will have to be established by attempts on human patients.

If it be taken for granted that the mechanics of the circulation become more compatible with life when the degree of mitral obstruction is decreased, there remain the technical problems of the operation. . . .

* * *

[T]hree kinds of procedures were utilized in the attempts to enlarge the stenotic orifice. These methods were finger dilatation, incision of the stenotic valve and excision of a segment of the stenotic valve. We have not had any experience with dilation of the stenosis. We feel, however, that the method may be worthy of trial. A small instrument . . . could be devised, and this instrument could be inserted into the stenotic ring and the latter stretched and dilated. It will be seen that the only two patients of the series living are those on whom dilatation was done. Incision of the stenotic valve was carried out in four cases. From our experience in cases 5 and 6, we felt that the enlargement effected by a simple incision of the stenotic valve was inadequate. We then devised an instrument which could excise a segment from the valve and remove it from the blood stream. This instrument was used in five cases. In each of the four patients that we operated on, some difficulty was experienced in orientation within the heart. We feel at the present time that that is one of the most serious problems in cardiac surgery. The cardioscope devised by Allen and Graham affords a slight degree of visualization of the endocardium at the point of contact with the instrument. The examination that can be carried out with this instrument, however, is so slight that we have not used it in any human cases.

* 18 *Archives of Surgery* 403, 413-416 (1929). Reprinted by permission.

Finally, it may be that we already have the evidence that the success in the finger dilatation method and the success in our first case are due to the fact that only a slight change was made in the size of the orifice of the valve. It may be that the cardiovalvulotome with its actual removal of a piece of valve creates a too sudden change. We know that all the changes created by nature are slow and gradual; could we return a stenotic valve to the insufficient type by a gradual procedure, we might well achieve success. This question unfortunately cannot be answered until we can experimentally produce stenosis similar to what occurs in man, and then suddenly change this to an insufficiency. We have convinced ourselves that a simple knife cannot enlarge a typically stenosed, thickened and often calcareous valve; we do not know whether the actual removal of a piece of the valve by the powerful cardiovalvulotome is deleterious or not. And we have not yet available evidence as to what excision of a segment of a stenosed valve will result in when the operative procedure is simplified (as performed in our last case), and the post-operative course, therefore, less of a strain on the already lowered vitality.

It may seem that the information obtained from the twelve cases of chronic valvular disease in which operation was performed is so meager that further attempts are not justified. However, in view of the preceding discussion, we feel that a few more attempts are necessary in order to answer certain questions already mentioned. Should it be possible to produce experimental stenoses, these questions could be answered in the laboratory. Unfortunately, our own attempts for seven years along this line have been as unsuccessful as the attempts of other and more experienced investigators.

It is our conclusion that the mortality figures alone should not deter further investigation both clinical and experimental, since they are to be expected in the opening up of any new field for surgical endeavor.

NOTE

ELIZABETH H. THOMSON

HARVEY CUSHING—SURGEON, AUTHOR, ARTIST*

* * *

The story is told of Sir Victor Horsley by one of his graduate students, Dr. Ernest Sachs,

that he walked into the wards at the Queen Square Hospital one morning to see a patient at the request of Dr. Charles Beevor. He decided that the patient had a pituitary tumor and announced that he would operate the following Tuesday. Beevor, knowing the usual result of such attempts, protested, "But Victor, if you operate on that man, he will die." "Of course he will die," returned Horsley, "but if I don't operate on him, those who follow me won't know how to perform these operations."

This had to be the underlying philosophy of all who attempted surgery of the brain in the first discouraging years. . . .

* * *

2.

Experimentation and Moratorium— The Second Phase (1929–1945)

From 1929 to 1949 no further reports on mitral valve surgery were published. At least insofar as publication was concerned, a complete moratorium on such interventions had been declared. However, work in the laboratory continued.

John H. Powers

Surgical Treatment of Mitral Stenosis*

The technical difficulties and hazards of an operative procedure on the heart are great. Medical therapy in chronic cardiac valvular disease offers nothing but supportive and palliative treatment without hope of permanent relief. Consequently the surgical treatment of mitral stenosis presents a most fascinating and interesting problem to both surgeon and physician.

The rationale for the procedure has been based on the assumption that mitral insufficiency is functionally a less damaging lesion than mitral stenosis. With this hypothesis as a major premise, the first operation of election on the mitral valve was performed by Dr. Elliott C. Cutler in May, 1923. A tenotome was inserted into the mitral orifice through the left ventricle, and an attempt was made to incise each segment of the obstructing ring. The patient recovered and was definitely improved until the onset of a terminal illness four and one-half years later.

After this first intrepid effort, Allen and Graham attempted a three-stage procedure with

* New York: Henry Schuman 134 (1950). Reprinted by permission of Murnat Publications, Inc.

* 25 *Archives of Surgery* 555–557, 568–569 (1932). Reprinted by permission.

an instrument carrying an optical system, by which they hoped to cut the valve under direct vision. The patient died on the operating table.

The experience gained in their first and two subsequent cases convinced Cutler and Beck of the impossibility of enlarging the mitral orifice sufficiently with a simple knife to obtain an adequate degree of regurgitation. Consequently the cardiovalvulotome was developed, a powerful cutting instrument by which a segment of the valve could be excised and removed from the circulation.

With one exception all subsequent operations have been performed with this instrument. The exceptional, and only successful, case is that reported by Souttar, in which the mitral orifice was dilated with the finger, introduced through the left auricular appendix. This patient is living and apparently improved.

In all, ten patients with mitral stenosis have been subjected to surgical treatment. The mortality has been 90 per cent. Except for Cutler's first case, death occurred from three hours to six days after operation, and in the majority of instances was due, not to operative shock, but to cardiac failure. The mechanical difficulties of the operation have been overcome, mitral insufficiency has been created both by incising the stenotic orifice and by excising a segment of the sclerosed valve, and yet the patients have died. The question presents itself therefore: Is valvulotomy or partial valvulotomy a feasible and justifiable operation in patients with mitral stenosis?

It is undeniably true that an insufficient valve is a more tolerable valve from the patient's standpoint than a stenotic one. Furthermore, Cutler and his collaborators showed experimentally that mitral regurgitation was well tolerated by normal dogs. One may reasonably assume, however, that the physiologic alterations that take place in the circulation after the excision of a segment of normal valve do not approximate those which obtain when a defect of similar degree is made in the thickened and sclerotic post-rheumatic valve. The facts suggest that an embarrassed cardiac mechanism, laboring under the mechanical difficulties of a chronic mitral obstruction, is unable to tolerate the additional insult of a sudden, superimposed regurgitation and death occurs from cardiac failure.

The experiments presented here are offered in support of this contention.

Since the development of a method for creating chronic cardiac valvular disease in dogs,

certain phases of the problem, which previously were restricted to clinical impressions and observations on patients have become amenable to precise physiologic study in the laboratory. Four distinct procedures have been carried out:

1. Experimental stenosis of the mitral valve has been produced in dogs, a chronic, sclerosing lesion which, in its mechanical and gross pathologic aspects, is comparable with mitral stenosis in man.

2. Physiologic observations have been made on the circulation of these animals with experimental mitral stenosis.

3. The stenosis has been abruptly converted into insufficiency by partial valvectomy with the cardiovalvulotome.

4. The physiologic observations have been repeated to determine what effect this procedure has on the mechanics of the circulation, and why the sudden transformation of chronic mitral stenosis into stenosis with insufficiency should be incompatible with life.

* * *

All five dogs with experimental mitral stenosis died after the removal of a portion of the obstructing valve. Postmortem examination of each animal disclosed tremendous dilatation and engorgement of the right side of the heart, acute pulmonary congestion and edema, pleural effusion, acute and chronic congestion of the liver with central necrosis and, in one case, ascites.

* * *

From [the] results, one must conclude that although mitral regurgitation may be created in normal dogs without clinical evidence of decompensation, the abrupt conversion of experimental chronic mitral stenosis into insufficiency produces such sudden and radical alterations in the mechanics of the circulation that cardiac decompensation and death ensue.

The canine lesion was comparable in its gross pathologic aspects to mitral stenosis of rheumatic origin in man. The instrument and the operative technic were similar to those which have been employed on human beings. It seems justifiable to assume, therefore, that the physiologic alterations in the circulation that account for death after partial valvectomy on animals may explain the same result following a similar procedure on man.

Could mitral stenosis be relieved more gradually, either by repeated excision of tiny fragments of the valve, by multiple incisions into the

obstructing segments or by dilatation of the stenotic orifice, the results might be more satisfactory. The only two cases in which the operation was not succeeded immediately by a fatal outcome were Cutler's first case, in which simple incision into the segments of the valve was performed, and Souttar's case, in which the mitral orifice was dilated with the finger. In both of these procedures only a slight change was produced in the size of the orifice. Souttar's patient is living five years after operation and presents the appearance observed in a well-compensated case of mitral stenosis.

* * *

3.

Therapy, Experimentation, and Success— The Third Phase (1945–Present)

a.

Charles P. Bailey The Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy)*

Stenosis of the mitral valve has long challenged the therapeutic ingenuity of the medical profession. It has seemed unreasonable that young persons in otherwise satisfactory health should be condemned to a life of invalidism and early death. Success in treating strictures and stenoses in other organs has suggested that such a simple mechanical defect should not present an insuperable problem.

However, fear of surgical attack upon the heart, discouraging results of early attempts, and a general lack of appreciation among the medical profession of the extreme seriousness of this disease, have greatly hampered those interested in the problem. Many internists, among whom are cardiologists, feel that with proper medical management and limited activity these patients may live a normal span of life. It is true that most older practitioners know of a case or two of mitral stenosis which has survived to an advanced age. Unfortunately, these men do not have any roughly accurate idea of the much larger number of cases which have died at an early age. It is also notable that these same older patients will admit that they have not especially enjoyed their prolonged life of limited activity.

* 15 *Diseases of the Chest* 377–393 (1949). Reprinted by permission.

The author has recently been consulted by a woman of 58 and another of 62 who have been "successfully" treated medically for 25 and 28 years, respectively. They now, at their advanced age, being no more limited than they were 10 years ago, are futilely petitioning for a chance at surgical relief.

The serious prognosis of mitral stenosis can hardly be properly presented statistically, since cases vary in severity, and since death is often wrongly attributed to some other heart condition, to asthma, or to pulmonary tuberculosis with hemorrhage. This latter syndrome (mitral stenosis with serious hemoptysis) has been shown by Wolfe and Levine in 1941 to have a mortality of 66 per cent within 3 years. This has been brought home dramatically to the author, who recommended surgery in two such cases eight and six weeks ago, respectively. Both at first accepted surgery and then changed their minds because of the presumed risk. Both have already died of pulmonary hemorrhage.

With such a dismal outlook, it is time to take steps to differentiate those cases which are mild or non-progressive from those who will not have any useful existence. It then is incumbent upon the profession to learn how to alleviate the severe cases.

* * *

It is my belief that there are at least one million cases of mitral stenosis in the United States, one-quarter of which are suitable for surgery. . . .

* * *

A review of the reports in the literature by Cutler and Beck in 1929 of operations upon the aortic and mitral valves revealed that of the first 10 cases of mitral stenosis subjected to operation, one died during insertion of an instrument into the left auricular appendage, two were subjected to finger dilatation of the mitral valve after insertion through the left auricular appendage (both cases lived and were improved) three cases were treated by tenotome division of a valve cusp (one lived 4½ years and was much improved), and five cases were subjected to partial valvectomy by the cardiovalvulotome (all died).

* * *

After 1929 no more surgical attempts were made until 1945. Both Dr. Dwight Harken and Dr. Horace Smithy, as well as the author, have made recent operative attempts to improve cases

of mitral stenosis. Our clinical experience with the surgery of the mitral valve has been with five cases to date.

During the past eight years the author and his associates have performed diverse and repeated operations upon the mitral valve of some 60 mongrel dogs. Several conclusions have been reached: (1) The approach through the left auricular appendage is the most satisfactory one since there is less danger of arrhythmia, greater ease of entering the valve, and greater ease in controlling hemorrhage. . . . (2) Production of an appreciable degree of sudden mitral regurgitation is tolerated poorly by dogs. Thus extensive cutting of the anterior cusp of the mitral valve is nearly always attended by operative mortality. It would seem that regardless of the reported observation that clinical mitral regurgitation is less crippling than clinical mitral stenosis these sick human hearts will not tolerate the sudden production of a large mitral regurgitation very well. (3) The accurate placement of an instrument to divide a mitral valve depends upon actually palpating the valve and instrument from within the auricle at the time of operation. Thus, whether the cutting instrument is inserted through the ventricle or auricle, it is necessary that the right index finger be passed through an incision opening. These incisions should be extended well into the normal valve tissue margin. . . .

Case 1: Our first clinical case was W.S., a man of 37 years who had been severely incapacitated for 16 years and who had had several severe episodes of hemoptysis. On November 14, 1945 his left anterior chest was opened. . . . The patient died on the operating table of hemorrhage, no valvulotomy having been performed. We have ever since realized that the human auricular appendage in mitral stenosis is friable and entirely unlike that of a normal dog. We no longer permit a hemostat to be closed on an auricular appendage beyond the first tooth of the ratchet, and prefer not to actually close the ratchet.

Case 2: Our next case was W.S., a 29-year-old married female who had been a cardiac invalid for 11 years, and who had been in congestive failure on several previous occasions during the preceding 7 years. On this occasion she failed to respond to the usual medical measures and remained in a precarious state with engorged liver and ascites in spite of digitalis and mercurial diuretics. Since she was deemed hopeless, her physicians felt that she might be subjected to valvulotomy. At operation on June 12, 1946 the

heart was approached through a left anterior thoracic incision. . . . Up to this point the blood pressure was approximately 60/50 mm. mercury, and the surgeon began to seek an honorable way of abandoning the procedure. However, the medical consultants stressed that she would undoubtedly die from the anesthesia and exploration unless some relief of the stenosis could be obtained. . . . The mitral valve was found to be a tiny slit which would not admit the tip of the index finger. There was considerable calcification about the valve mouth. This had been palpated by the instrument, but the actual orifice was too small to admit the punch (about the size of a small lead pencil). The valve was forcibly dilated digitally, so that the finger could be inserted into the orifice to the second phalangeal joint. Care was taken not to obstruct the opening for longer than three heart beats at a time. The valve appeared to tear open at both commissures. The thrill which was prominent prior to dilating the valve, immediately disappeared. The blood pressure promptly rose to 80 systolic and the patient's condition began to improve. Because of the improvement and the desperate nature of the risk, the finger was withdrawn and the auricular appendage ligated without any attempt at incising the valve.

The patient's condition continued to improve so that the blood pressure was 130 systolic at the conclusion of the procedure. . . . Improvement was continued for 30 hours. After that the condition began to deteriorate and she died rather quickly 48 hours after surgery. Autopsy revealed a greatly dilated heart. . . . The mitral valve showed evidence of having been torn open at both commissures, but the tears had not extended into the normal marginal valve tissue. The torn surfaces had therefore not separated much, and had become agglutinated by fibrin which accumulated in the orifice and gradually reduced the effective mitral opening to probably a smaller size than that existing at the time of operation. It was difficult to imagine any degree of regurgitation through that valve orifice. No anticoagulant therapy had been employed. As a result of the autopsy findings, the idea was conceived of performing what had been later termed "commissurotomy". . . .

Case 3: The next patient was W.W., a white male 38 years of age, who had been having episodes of severe hemoptysis over a period of 1½ years. In fact, he had had a segmental resection of the right lung performed for bronchiectasis

one year previously, in the belief that his hemorrhages were of pulmonary origin. However, after 8 months his hemorrhages had returned in an exsanguinating form. Re-study then revealed that a marked enlargement of the heart had taken place during the interim and typical evidences of severe mitral stenosis were now evident. The patient was also showing early signs of decompensation. On March 22, 1948 at the Memorial Hospital in Wilmington, Delaware, the left 4th anterior rib was removed and the pericardium was opened. . . .

Because of the bitter experience with the previous patient, it was decided to use anticoagulant therapy. . . . The patient did reasonably well until the second postoperative day, when evidence of hemorrhage into the left pleura required repeated thoracenteses. Heparin therapy was discontinued. When the red blood count had dropped to 2,450,000 on the third postoperative day, it was felt necessary to transfuse him, and this was done, 2600 cc. blood being given. Unfortunately, there was a misunderstanding regarding orders pertaining to fluid balance, and a total of 7,400 cc. of fluid by mouth and parenterally on the fourth postoperative day, and 1,500 cc. on the fifth postoperative day was administered. As a result the patient became markedly edematous. At about 4 P.M. he suddenly developed pulmonary edema and expired. . . .

In reviewing this case, we considered that the following errors had been made: (1) Perhaps the use of the heparin therapy was unwise, since it had required the administration of a considerable volume of fluid, and since it undoubtedly played a major role in the secondary intrapleural bleeding. (2) The use of saline rather than glucose solution as a vehicle for the heparin. (3) Inadequate incision in the lateral commissure of the valve, partly due to the repeated disengaging of the knife blade on account of its shape. The medial commissure could not be cut because of the large calcification. (4) Unwise and excessive fluid therapy. (5) Perhaps accepting a case for surgery who had had diminished contralateral lung function from previous disease and partial lung resection. It was the consensus, however, of all physicians concerned that if we had just returned the patient to bed postoperatively, and not treated him, recovery would have followed.

Case 4: The next case was J.R., a 32-year-old white male who had had advanced mitral stenosis for 7 years. During the past 1½ years he

had been in chronic congestive failure, although ambulant much of the time. Digitalis and mercurial diuretics did not completely control the congestion. Since his prognosis was extremely grave without surgery, it was finally decided to attempt a commissurotomy. . . . The pericardium was incised. [T]he least touching of the heart, either ventricle or auricle, was followed by frequent extrasystoles and other irregularities. Because of this extreme irritability of the myocardium, no attempt at valvulotomy was made. The surgeon became worried and suggested abandoning the procedure at that time. The staff felt that this would be the last opportunity for surgery to be utilized in this man. Intravenous atropine did not relieve the myocardial irritability, nor did 50 mgm. doses of procaine intravenously. Intravenous quinidine was administered slowly by personnel experienced in its use. Before completion of the injection, the heart rate had become slow, so the quinidine was discontinued. The systoles became weaker and stopped.

Immediate manual massage restored regular contractions which ceased after a few minutes. Massage was repeated. After that, various stimulants, venesection, artificial respiration, etc., were used. After the heart had been revived by massage a number of times and had failed as many, it was suggested that he might improve if the left ventricular output was increased by opening the mitral valve. Since all was already lost, the auricular appendage was opened and the left index finger was inserted into a tight mitral orifice containing calcium deposits. It was widely dilated, and the finger withdrawn. No instruments were used. The auricular appendage was ligated. After massage had again reestablished a temporary heart beat, it was evident that the left ventricle had become considerably enlarged. However, in spite of repeated massage and all recognized forms of drug stimulation, no permanent restoration of cardiac function could be accomplished. . . .

* * *

We do not consider this a death attributable to mitral valve surgery, since death and an irreversible state had apparently become established well before a last ditch emergency dilation of the valve was performed. Undoubtedly this man was too bad a risk for mitral surgery. The pre-operative ballistocardiogram had revealed a poor cardiac output, increased only slightly on exercise.

Case 5: C.W., a 24-year-old white house-

wife, had been known to have a heart murmur for 17 years and mitral stenosis for 24 months. She had had gradual and progressive onset of dyspnea on exertion and had an attack of congestive failure in November 1947. Since that time she had been on extremely limited activity and received a daily maintenance dose of digitalis. [S]he was admitted to Episcopal Hospital in Philadelphia for study preliminary to a possible mitral commissurotomy. . . . Operation was performed on June 10, 1948. . . . The mitral valve was found to be small, just admitting the tip of the finger. It was not calcified and had a leathery feel, more like kid-skin than cow-hide. It was displaced high up anteriorly. The hooked knife was inserted through the valve orifice and engaged on the lateral commissure under direct digital guidance. The knife was then drawn backward an inch, widely dividing the commissure. The finger was now inserted through the cut valve and some fine remaining fibrous strands were broken up. The valve was now widely patent. The finger was withdrawn and the auricular appendage ligated. . . . The entire operation had taken 80 minutes. . . .

. . . . She was out of bed on the third day, and walking the fourth. Her greatest difficulty was inability to void for four days postoperatively. On the seventh postoperative day the patient had no cardiac murmur audible to the author. . . .

Because of her evident good condition she was transported without incident by train to a 1,000-mile-distant medical convention for presentation in person.

* * *

(February 1, 1949: Patient is continuing to do well 7½ months subsequent to surgery. She is now able to perform all her own housework. . . .)

* * *

February 1, 1949: Since this time, 5 additional patients have been subjected to this operation. Two are doing very well. One died 2½ months after surgery. One died of an error in technique at operation (cutting across a valve leaflet). One did very well for 6 days but died suddenly of a cerebral arterial embolus. Clotting had occurred in the sutured left auricular appendage. We now ligate the appendage at the base to prevent this.

* * *

NOTES

NOTE 1.

JUDITH P. SWAZEY AND RENÉE C. FOX
THE CLINICAL MORATORIUM—
A CASE STUDY OF MITRAL VALVE SURGERY*

* * *

Bailey's three operations had been performed at three different hospitals in the Philadelphia area, and he was informed that further intracardiac surgery would not be permitted at those institutions. Nevertheless, he scheduled two more cases of mitral surgery for June 10, 1948, at the last two Philadelphia hospitals where he still had operating privileges. Case four died during surgery in the morning, of cardiac arrest judged by Bailey to be unrelated to an attempted finger dilatation. Success finally came that afternoon, at Episcopal Hospital, when a 24-year-old housewife withstood her surgery. . . .

* * *

NOTE 2.

RICHARD A. MEADE
A HISTORY OF THORACIC SURGERY†

* * *

In 1945, Bailey operated on a patient with mitral stenosis expecting to bite out a piece of the mitral valve, but he tore the auricle and lost the patient from hemorrhage. In 1946, he operated on his next patient with the same object in view. He was planning to use a backward cutting instrument which he could pass through the left auricular appendage. During the operation, the stenosis was found to be so severe that he could not pass his instrument through the valve. Quoting from Bailey's letter to me,

At that moment my medical men became a great help to me because they urged me to go ahead, to make further efforts to relieve the valvular obstruction because the rapid deterioration of the patient on the operating room table augured ill for a survival from this exploratory operation unless something definitive could be accomplished. In desperation, remembering Souttar's report, I inserted my finger through the auricular appendage, palpated the valve and pushed my finger through the diminished slit. Although the leaflets were calcified, both commissures

* Paul A. Freund, ed.: *Experimentation with Human Subjects*. New York: George Braziller 315, 330 (1970). Reprinted by permission of the American Academy of Arts and Sciences.

† Springfield, Ill.: Charles C. Thomas 440-448 (1961). Reprinted by permission of Charles C. Thomas.

split well and I immediately appreciated three things. One was that there was now an opening many times larger than that which had existed previously. Second, the diastolic thrill, which in this particular case was very prominent in the region of the valvular structure itself, immediately disappeared. At the same time I was unable to recognize any regurgitant jet of blood from the valve. I was quite familiar with the digital feel of the regurgitant jet from my animal experimentation. I was, therefore, convinced that I had both relieved the stenosis and failed to produce any regurgitation. For about twenty-four hours post-operatively, the patient's condition improved remarkably and steadily. There was no clinical evidence of regurgitation. However, one day later, she suddenly collapsed and died. From the post-mortem examination it was clearly evident that both commissures had been split and considerable mobility of the leaflets had been accomplished. It was evident from the intact suspension of the valve leaflets that regurgitation had not been produced.

Before continuing the account of the progress of Bailey's work, it is well here to refer to the work done by Horace Smithy during 1948. In spite of his knowledge of the literature and especially of the experimental work of Powers, he revived the Cutler operation and carried out the procedure on seven patients with mitral stenosis. He differed from Cutler in that he used the auricular approach in four of the cases. One patient was operated on twice because at the first operation, when he attempted to pass the instrument through the auricular appendage, he tore the auricle and, after controlling the hemorrhage, he abandoned the procedure. Later, he used the ventricular approach with success. He concluded that the ventricular approach was the better of the two. Two of his patients died soon after operation, and one after ten months. One patient showed marked improvement during the year in which she was followed. The other three showed only slight improvement. The fact that five of the patients survived the operation was presumably due to the great improvements in anesthesia and surgical technique since the 1920's. These patients survived, and showed some improvement in spite of the regurgitation produced. . . .

* * *

[W]hile Bailey and Harken were working in this country on the problem of the surgical relief of mitral stenosis, Russell Brock in England was also planning an attack. Following his success in dividing a stenotic pulmonary valve, he decided that the same procedure could be used on the mitral valve. Remembering Souttar's article, he successfully carried out the Souttar opera-

tion on a patient with mitral stenosis in September, 1948. At this time he was not aware of the work done by Bailey and Harken. He became convinced that the operation was a sound one and carried it out on seven more patients before publishing his results in 1950. Two of his patients died after operation, but one of them died of hemorrhage, having been given heparin on the second postoperative day because of a cerebral embolus. One other patient developed a cerebral embolus but fully recovered. The other five patients had uneventful recoveries. Following this first report, he began operating on an increasingly large number of patients. He has used finger fracture in the great majority of his cases but occasionally resorts to the use of a knife to cut the commissure.

Following the reports of the work of Bailey, Glover, and O'Neil, and of Harken in this country, and of Brock in England, the operation became widely adopted. At first the mortality rates were high, but as the cardiologists changed their points of view and began referring better risk patients, the mortality rate fell. It soon became apparent that finger fracture was all that was needed in most of the cases but in some it was necessary to use a knife to open the commissures sufficiently. Harken in this country and Brock in England have made important contributions regarding the anatomy of the mitral valve, and have pointed out the relative importance of the major and minor leaflets.

* * *

Although the modern operation for relief of mitral stenosis differs very little from that done by Souttar in 1925, it is worth noting [one] . . . technical [advance], the use of special knives in those cases in which it is felt that complete splitting along the commissures has not been accomplished by the finger.

* * *

The one unexplained fact in the history of the development of an operation for mitral stenosis is the failure of other surgeons to repeat Souttar's operation until 1948. In retrospect, it seems incredible that he himself did not continue his work, and that the men in this country who had done so much work on surgery of the heart did not recognize its value.

The explanation for Souttar's failure to continue his work is simple. He had no more patients referred to him for operation. And yet, he was Director of Surgery of the London Hospital and

one of the leading surgeons in England at the time. However, Sir James Mackenzie was the leading cardiologist at that time and had a profound influence over the other cardiologists in England and even in this country. He believed that the chief feature of mitral stenosis was the diseased myocardium, and that the stenosed valve was of secondary importance. So he was opposed to operation for relief of the stenosis. And this opposition prevented Souttar from continuing his work.

In this country, there was the same general opposition to surgery for mitral stenosis. Even Dr. Evarts Graham was unable to persuade his medical colleagues of the value of operation. In Boston, Dr. Samuel Levine stood out in opposition to Sir James, and was responsible for Cutler being able to operate on some seven patients with mitral stenosis. Why then, did not Cutler and Beck follow Souttar's lead? We shall never know why Cutler failed to do so, but Beck has stated, in a letter to me and in an article in the *Journal of the American Medical Association*, his reason for not adopting the operation. He believes that there has been a change in the character of the mitral valve as a result of the use of sulfonamides and antibiotics. The hearts he studied in the pathology laboratory in the 1920's had valves that were calcified and so tough that he does not believe finger fracture could have been used. In this connection, it must be remembered that in Souttar's case he did not fracture the valve with his finger. He merely placed his finger through the valve and was assured of its patency by doing so. He probably was not aware of the possibility of actually fracturing the valve, although he was sure that the stenosis could be corrected by passing his finger through it.

It is interesting to hear the comment of Dr. Samuel Levine who worked with Cutler and with him reported the first successful case of surgery for mitral stenosis. He wrote, "the fact that no further case reports or experiences were recorded indicated that nothing very much had been accomplished. I do recall that the criticism on the part of the leading authorities at that time, particularly Sir James Mackenzie, was that it was useless to attack the valve because that was not important. Mackenzie thought that the all-important part was the myocardium and that would not be altered by surgery of the valve. In fact, he wrote me just to that effect, after Cutler and I had published our first case. I was certain even then, and have felt the same way ever since, that the valvular defect was all-important in rheumatic heart disease." He also stated that he did

not believe there had been any change in the character of the valve. He felt that our surgery was just not sufficiently advanced at the time. When one recalls that lobectomy carried a mortality rate of around 45 percent at that time, his comment seems reasonable.

Another reason for the failure of American surgeons to adopt the Souttar operation has been well expressed by Dr. Evarts Graham. He wrote, "when I heard about Souttar's case, I was, of course, much interested but felt that his procedure would never amount to very much because it lacked precision and was a blind one. It had always been my feeling that, in surgery, one of the first rules is to have exposure so that you can see exactly what you are doing."

So, for one reason or another, twenty-three years passed after Souttar's operation before it was tried again, and then within a period of three months, in widely separated places in the world, his operation was revived. The time was not ripe in 1925. It was in 1948.

* * *

NOTE 3.

FRANCIS D. MOORE

REPORT OF THE SURGEON-IN-CHIEF*

A creative science defines problems worthy of solution, and seeks their solution by every effective method available. Both parts of this definition are important.

One of the duties of science is to define problems which should be solved. The Greek philosophers defined their problems very broadly; they wanted to understand the whole universe and the relationship of its parts. The scientist of today sometimes defines his problems in a much more narrow area, as one can see by reading over a list of thesis titles at Commencement. When a field of research ceases to describe problems, it ceases to be effective.

The second part of the definition, stating that the investigator must use any techniques whatsoever to attain his ends, is also important. All is fair in love, war and research. Many fields of science have developed methods which ultimately have come to dominate and sterilize the field; they must reach out for new techniques to revitalize their search for knowledge.

In many respects surgery is an art; it is also a creative science. Let us look at [an example].

* * *

* 37th Annual Report of the Peter Bent Brigham Hospital (Boston) 48, 55-58 (1950). Reprinted by permission.

In 1940, Dr. Dwight Harken returned to Boston from his year in England with Mr. Tudor Edwards and took up a residency at the Boston City Hospital. During this time he spent many hours in the laboratory, and in August of 1942 published an article entitled "Experiments in Intracardiac Surgery." His original idea had been to invade the heart surgically through the auricular appendage to excise the vegetations of bacterial endocarditis. Again surgery had posed a question: "May we operate within the human heart and rectify major valvular disease?" Surgery also sought an answer. In this case the initial approach was to the experimental animal, that unsung hero whom a few agitators would like to remove from the scene!

During this work Dr. Harken found to his interest and surprise that the function of the two mitral valve leaflets was very different. The aortic, or major leaflet, had to be preserved intact. If it were destroyed, one wall of the aortic outflow tract was gone and the animal soon died of mitral regurgitation. This observation was of fundamental importance several years later when mitral surgery was being revitalized. It was a basic conceptual advance. Twenty years previously we had assumed mitral regurgitation to be the price of relieving mitral stenosis. Now Dr. Harken knew that stenosis could be relieved without adding such a burden to the already sick heart and lungs, providing the surgeon did not disturb the aortic leaflet.

The war intervened; the investigator found himself treating soldiers with wounds of the heart. Besides the development of operative techniques and personal facility with cardiac surgery, one further observation of fundamental interest was made. Dr. Harken saw that dislocation of the heart from its normal position in the thorax resulted in the development of sudden arrhythmias incompatible with life. If the heart were returned quickly to its position of optimum function, normal rhythm was quickly restored. Here was a guiding principle for further work and here was an explanation for some of Dr. Cutler's difficulties twenty years before: not only had he entered through the ventricular muscle—which in itself must carry some special hazard—but he had found it necessary to dislocate the rheumatic heart from its normal position, a dislocation that the hearts of well-conditioned soldiers could not tolerate.

With this background, Dr. Harken commenced his first clinical work with mitral stenosis in the spring of 1947. The basic premises were (1) to approach the mitral valve from above

rather than through the ventricle, (2) to operate on the heart without dislocating it from its normal position, (3) to remove only portions of the lesser leaflets, thus leaving the aortic outflow tract intact and avoiding regurgitation, and (4) to use the superior pulmonary vein as the port of entry.

The progress of knowledge often simplifies rather than complicates. This was true with the technique of valvular surgery. Many complex instruments were developed and used in these early operations. The results were disappointing: the instruments were hard to control. Several of the early patients failed to survive. All had been operated upon in a far advanced and hopeless stage of disease and approached their operation knowing fully its formative character and the hazards it entailed. We are apt to think of the long hours of work or difficult problems faced by the investigator. There are many occasions when we must also recognize the knowing sacrifice of those dangerously sick patients who are willing to take well-understood risks in the interest of more than personal benefit—in the assurance of benefit to others.

* * *

The problem then (early 1949) seemed to rest on the question of how to control the intracardiac manipulation which broke apart the fusion bridges of the valve. The surgeon's finger, endowed with a sense of feeling and position, was clearly more controllable than any other device. Instead of using a complicated instrument through the difficult approach of the superior pulmonary vein, the surgeon's finger was introduced through the auricle itself and the two fusion bridges were broken apart. Fracture is a good word for this procedure. The fused valve is rigid and the rigid area breaks where it is difficult or impossible to cut. With experience in a few more cases, it became apparent that the fracture of the valve made by the surgeon's finger through an opening in the auricle had made possible an entirely new evaluation of valvular surgery because it was done with a new order of accuracy.

The selection of cases was not easy. One possibility would have been to select patients who were not very ill, feeling that they might recover more easily. This would hardly yield information about the value of the procedure. A much more critical approach would be to select patients who were severely ill and whose outlook was very limited; this was the approach Dr. Harken selected. His selection was based on the studies of

his medical colleagues in the cardiac laboratory.

As testimony that this selection was realistic, we must point out that of 16 patients selected for operation but who were not operated upon, 14 are now dead, 11 within six months of the time when surgery was advised.

Forty-two other patients in exactly the same sort of situation have now been operated upon; 29 are now alive and 24 are outstandingly successful results.

The surgery of mitral stenosis has now been through its "dark days," days when the surgeon, his medical colleagues and those with whom he sought counsel were tried as to whether or not the effort should be maintained through such difficulties. It is through those dark days and into a phase where its scope should be broadened. Recently a group of six patients who were *not* in the last stages of the disease have been operated upon. All of them have done well and have showed a gratifying return to normal heart function.

NOTE 4.

DWIGHT E. HARKEN, LAURENCE B. ELLIS,
AND LEONA R. NORMAN
THE SURGICAL TREATMENT OF MITRAL
STENOSIS*

* * *

Our experience with mitral stenosis now involves a study group of twenty-five patients, eight of whom have been treated surgically. There have been three surgical deaths. The operations have been as follows: Five valvuloplasties, two interatrial septal defects, and one denervation. The deaths were all in the valvuloplasty group. The first patient of the series was lost because we did not at that time appreciate the devastating effect of tachycardia. The second death was the fourth valvuloplasty. This death was on the operating table from uncontrolled blood loss. The third death was from pulmonary edema on the fifth postoperative day, and autopsy revealed that too little valvuloplastic incision had been made. This debilitated patient was therefore subjected to a very strenuous operation without the relief of adequate correction of the fundamental mechanical handicap.

The experience to date seems to indicate that essential knowledge of the technical difficulties and the indications for various surgical procedures is being gathered.

The possibility of practical surgical relief of

* 19 *Journal of Thoracic Surgery* 1, 13-14 (1950). Reprinted by permission.

mitral stenosis calls for more complete understanding of the disease. Means must be sought to predict the probable clinical course of a given patient. Those who have a truly malignant form of valvular disease should be selected, if possible, before the pulmonary changes render the patient an inordinately serious risk for surgical intervention.

Objective evaluation before, during, and after operation must be conducted in order to determine which procedures are best tolerated and most beneficial. . . .

* * *

NOTE 5.

JUDITH P. SWAZEY AND RENÉE C. FOX
THE CLINICAL MORATORIUM—
A CASE STUDY OF MITRAL VALVE SURGERY*

* * *

. . . In the winter of 1948/49, six out of Harken's first nine patients died during or shortly after valvulotome surgery.

At this point I went home depressed and said "I quit." Some people suggested I should try my technique on better-risk patients, in order to help me get better results, so I wouldn't "ruin the reputation of cardiac surgery." But I wouldn't do that. After I lost my sixth patient, I had a call from Dr. Laurence Ellis [then President of the New England Cardiovascular Society]. I told him I wouldn't kill any more patients [through mitral valve surgery], and that no respectable referring physician would send me any more patients anyhow. Ellis asked me what I meant: didn't I realize that these patients surely would die if I didn't operate? He said he would still refer patients to me, and didn't I think he was a good cardiologist? This talk with Ellis was a turning point. I went back and operated and my patients suddenly started doing better. But I almost called a moratorium.

Early in 1949, Dr. Harken realized that he "couldn't do an operation successfully with the [valvulotome] and have the patient survive in a substantial number of cases." As he studied post-mortem specimens of mitral stenosis, seeking to improve his procedure, he became convinced that the best way to open up the fused bridges of the valve's leaflets, without unduly damaging the valves themselves, was the simple technique Souttar had pioneered: finger dilatation through an auricular entry. After a few cases it "became apparent" that this method, which Harken aptly

* Paul A. Freund, ed.: *Experimentation with Human Subjects*. New York: George Braziller 315, 331-332 (1970). Reprinted by permission of the American Academy of Arts and Sciences.

named finger-fracture valvuloplasty, "had made possible an entirely new evaluation of valvular surgery because it was done with a new order of accuracy."

Apart from some technical refinements, the operation done today for most cases of mitral stenosis differs little from that done by Souttar in 1925. . . .

* * *

NOTE 6.

DWIGHT E. HARKEN, LEWIS DEXTER,
LAURENCE B. ELLIS, ROBERT E. FARRAND,
AND JAMES F. DICKSON, III
THE SURGERY OF MITRAL STENOSIS*

* * *

The principal purpose of this publication is to present a simple surgical technic for converting . . . mitral stenosis into effective valves. It is important to realize that stenosis is not being corrected at the expense of producing mitral regurgitation. Contrariwise, minor degrees of regurgitation may be corrected by this maneuver. We have consistently found, by postoperative catheterization, that finger-fracture valvuloplasty can correct mitral stenosis without producing mitral regurgitation.

* * *

Once the exploring finger is in the auricle, the position of the stenotic funnel is determined, the character and type of stenosis is assessed. . . . Gentle pressure is then exerted in a posterolateral direction to effect fracture of the posterior fusion bridge. . . . Gentle anterolateral pressure will then effect fracture of the anterior fusion bridge with much less difficulty. . . . Having fractured the anterior and posterior fusion bridges, careful appraisal is made of the mobility of the major leaflet and of its competence in closing the mitral orifice in systole. Also, the size of the newly created orifice is determined. While every effort is made to conduct this intracardiac blunt dissection deliberately, the surgeon must avoid excessive periods of obstruction of the mitral orifice. . . .

. . . If . . . the elastic fusion bridge resists the simple efforts at fracture described above, the surgeon may then advance the exploring finger 2 or 3 cm. farther into the chamber of the ventricle, hook the finger posterior to the fused posterior chordae and then make a circular motion

from behind forward, in a counter-clockwise direction, in an effort to fracture the lesser leaflet. If this is effective, a similar maneuver will probably fracture the leaflet in the region of the anterior fusion bridge, this time catching the anterior chordae in front of the finger as it is rotated in a clockwise fashion. *Should this simple secondary attempt at fracture fail, the surgeon must not use force but, rather, gently retreat in order to resort to incisional valvuloplasty* (Bailey's "commissurotomy"). . . . On the basis of this exploration of the stenotic funnel, the surgeon is prepared to select the valvulotome best suited to the pathologic process at hand.

* * *

Initially, it was our feeling that it was morally right to accept only those patients who were dying of their disease. We felt that technical failures would inevitably account for the loss of a number of the earlier patients. We could not properly accept patients for surgery who had a reasonable chance of surviving until a better era of surgical technic emerged. That we did in fact select such a group of patients who were dying is attested by two control groups. The first control group was comprised of 19 patients who were either offered surgery or whom we considered proper candidates for surgery but who did not, for one reason or another, come to surgery (through refusal and fear on their part or their families' part or because of hospital admission details). *Seventeen of this self-selected control group of 19 patients were dead within one year and 15 of the 17 died within six months of the time that surgery was recommended.* We are dealing, therefore, with a malignant disease. Conversely, that we have not generally rejected patients because they were too ill for operation is attested by the fact that there were only six patients for whom operation was deferred because they were too ill for immediate surgical intervention. Four of the six died within two weeks and all six died within a month. They were all but moribund.

* * *

Eighty-six operations have been performed to relieve patients with mitral stenosis. There have been nine valvulotome valvuloplasties, two reservoir-shunt operations, two denervations of the heart, two interauricular septal defects and 71 finger-fracture valvuloplasties. This latter operation is vastly superior to the others. . . . Of this latter group, 20 are dead. Eighteen of the deaths were associated with the surgical proce-

* 134 *Annals of Surgery* 722, 726, 734, 737-740 (1951). Reprinted by permission.

dures and two were not related to the valvuloplasty.

In spite of the fact that we have described the original group as in a malignant phase and have confirmed this fact by the mortality rate in the control group, it is true that some were more desperately ill than others. Also, recently we have accepted patients who were even less critically ill and deserve a separate classification. It is very difficult to present an accurate, serviceable, clinical classification of a protean disease such as mitral stenosis. A preliminary effort at such a clinical classification will be made here and elaborated later.

GROUP I comprises patients whose present course is *benign*. They have auscultatory signs of mitral stenosis but few if any symptoms and minimal evidence of increase in pulmonary vascular pressure. We believe that there is no justification for operation on these patients at this time. Patients in this group may continue to run a benign course or they may develop an acceleration of their lesion which shifts them to one of the other groups.

GROUP II includes patients somewhat *handicapped* by a static degree of moderate dyspnea on effort or by infrequent attacks of acute dyspnea or other pulmonary symptoms usually provoked by an extrinsic cause such as unusual exertion, fatigue or by infection. Rarely they may have some peripheral edema but do not have evidence of right ventricular failure.

GROUP III includes patients whose disability is progressive either with increasing dyspnea on effort or with alarming and increasing and easily provoked attacks of hemoptysis, chest pain, pulmonary edema, etc. They suffer from palpitation, tachycardia, and distress over the liver on exertion. At any time they may slip into GROUP IV, or may die of an acute attack of pulmonary edema, or with peripheral or pulmonary infarctions. Their life expectancy under medical therapy is *hazardous*.

GROUP IV is a *terminal* group. They are completely incapacitated, usually with right ventricular failure manifested by chronically elevated venous pressure, considerably enlarged liver, and a marked tendency to congestion. Their pulmonary disability may or may not be greater than those in Group III. They often have poor liver function, evidence of decreased peripheral blood flow, and many have had emboli. Most of them are in auricular fibrillation.

* * *

With respect to these categories, it is particularly interesting to note that in Group III there have been 22 patients and but one death. This single death was due to a technical error incident to forcing hastily a Type II valve following cardiac arrest. Contrast this low Group III mortality with Group IV. There have been 34 patients and 16 of these have died, a mortality rate approaching 50 per cent. Furthermore, the clinical improvement of Group III is far more dramatic than Group IV. This is really not surprising in view of the fact that in Group IV the correction of the mitral stenosis follows irreversible changes in the lungs, the liver, and the heart muscle. Whereas in Group III the correction of the mechanical barrier was effected before severe or irreversible secondary damage occurred. Group III, therefore, gets more benefit and risks much less than Group IV.

* * *

With respect to future activities in this field, there would seem to be no argument about Group III. Surgery is easy and good. That we should now offer surgery to Group II has been suggested. Group IV demands further scrutiny. It is our feeling that we must continue to operate in this group if we can actually select patients who are dying. It does seem that we have been able to do this. These patients, who are suffering from a malignant disease and for whom life is a burden, do not always succumb for the same reason. Sometimes the cause is disturbed electrolyte balance; sometimes it is embolism; sometimes it is pulmonary failure. As long as there continue to be various causes for death in this group but there is salvage in life and comfort, we must continue to accept the acknowledged hazards of surgery and explore the possibilities of a reasonable method. This application of valvuloplasty to the desperate risk group must continue until such time as we have established conclusively which patients are benefited and, conversely, which patients have no salvage in life or comfort. This effort must continue until the above requirements have been fulfilled or, better still, until the time when the awareness of our medical colleagues to a useful, surgical technic brings the patient to surgical correction in an earlier phase and thereby eliminates this late and disappointing phase. The responsibility of the medical man has nowhere been more clearly defined nor the obligation of the surgeon more richly rewarding.

NOTE 7.

DWIGHT E. HARKEN, LAURENCE B. ELLIS,
LEWIS DEXTER, ROBERT E. FARRAND,
AND JAMES F. DICKSON, III

THE RESPONSIBILITY OF THE PHYSICIAN IN
THE SELECTION OF PATIENTS WITH MITRAL
STENOSIS FOR SURGICAL TREATMENT*

* * *

. . . Group II disability may justify waiting for improved surgery because the illness is static but if that static disability is unacceptable to the patient, it may constitute a reasonable justification for surgical intervention. To date, we have not felt that these patients should have operation now.

Those patients in group III are the ideal candidates for surgery now as the prognosis without intervention is bad and the risk of valvuloplasty is low (less than 10 per cent) considering the severity of the disease. . . .

* * *

Certain patients can be selected whose present course is benign (group I) but who of course may degenerate to one of the more serious categories at any time. If properly followed and observed, these patients should not have surgical intervention at this time. Some of these patients will never require surgical intervention. Furthermore, there is a real possibility that surgery can render this group a substantial disservice (a) incident to the risk and discomfort of an unnecessary operation, (b) incident to the valvular alteration itself, and (c) incident to the sacrifice of the auricular appendage in the event that subsequent operation should become necessary.

In group II, patients whose degree of disability is static, selection of cases for operation must be made on the basis of the discomfort and limitation in the individual case. The risk of operation in this group is not great; it can be carried below 5 per cent. The chance of relieving the handicap is good. On the other hand, if patients in this group are not materially discommoded by their illness, it is entirely possible that better valvuloplasty may be available within the next year or so. We have deferred surgery in this group, placing the patients on a waiting list and meanwhile insisting on careful clinical check lest they slip into group III.

Group III. The risk in this group is rela-

tively low, below 10 per cent in this series, whereas the benefits are considerable. These patients are usually restored to comfortable, useful lives. This is because they get good, functional valvuloplasty before there is irreversible damage in the lung, myocardium and liver. In short, they are treated before they have slipped into group IV or die. These patients in group III *constitute the ideal and urgent candidates for surgery at this time*

Group IV. This, like group II, again represents a borderline group but in quite another way. These patients are suffering from a malignant disease. During the early phases of this study we preferred to take our surgical candidates from the group of dying patients. A control group demonstrates how group IV patients fared without surgical intervention. The control group constituted patients in group IV acceptable for surgery but who did not have it for various reasons, such as refusal of surgery on the part of the patient or the patient's family. There were 19 of these patients and 17 died within one year, 15 within six months. Thus, it becomes apparent that it is fair to call this a terminal or malignant phase. There were 39 patients in group IV who were operated on and 14 died from this intervention. Of course, these results are far better than those in the control group and if we were discussing carcinoma of the stomach or liver we would be delighted with such salvage rates. However, in this malignant phase the results are being improved.

* * *

b.

Laurence B. Ellis, Dwight E. Harken, and
Harrison Black

A Clinical Study of 1,000 Consecutive Cases
of Mitral Stenosis Two to Nine Years
after Mitral Valvuloplasty*

The present study is a report of the clinical results in 1,000 consecutive cases with a pre-operative diagnosis of predominant mitral stenosis on whom mitral valvuloplasty was performed between the years 1949 and March 1956. . . .

* * *

. . . Because of the very small number of group-II patients in this series these have been included with group-III patients in the subsequent analyses, and whenever the expression "group

* 5 *Circulation* 349, 360-361 (1952). Reprinted by permission of the American Heart Association, Inc.

* 19 *Circulation* 803-820 (1959). Reprinted by permission of the American Heart Association, Inc.

III" is used, it denotes group II and III patients. There was 1 operative death in the group-II patients. For the purpose of this analysis "operative mortality" denotes death during the operation or during the period of the hospitalization when the operation was performed. [913 patients survived the operation.]

* * *

In spite of the great number of studies that have been made over the years on the survival of patients with mitral stenosis it is extremely difficult to obtain data on medically treated patients that are comparable to this series. Many studies are statistically invalid or are made on groups that are not easily comparable, or consider only the survival period of those who ultimately were known to be dead. . . .

[T]he series most comparable to ours which has been medically treated and followed is that by Olesen, who studied a group of patients first observed between the years of 1933 and 1949 in Copenhagen. . . . We have therefore utilized his data to compare our group-III patients with his male and female patients in class 3. . . . [I]ncluding an operative mortality of 3 per cent, 83 per cent of our group-III patients have survived over the period of observation up to 7 years, and 71 per cent to 9 years, although the numbers dealt with in the last 2 years are small. This survival is better than for the medically treated patients. In group IV 57 per cent have survived up to 9 years, which include an operative mortality of 24 per cent for the group as a whole. This survival is vastly better than for the medically treated patients of whom none was alive at 8 years. . . .

* * *

Ninety-five patients have died since operation. . . . Eleven died of conditions clearly unrelated to their heart disease. Two of these, however, were patients in which death might be considered related to the operative procedure, including 1 death 2½ months following surgery from hepatitis, which might have been homologous serum jaundice acquired from a transfusion at the time of surgery, and 1 death from a reaction occurring during the course of an intercostal block for treatment of residual intercostal pain. There were 4 sudden deaths that have been assumed to be cardiac in origin. Patients developing cerebral vascular accidents, whether fatal or not, following surgery have been considered to have had these on the basis of emboli dislodged from the heart, though some of these may have

been due to independent vascular disease of the brain. In the calculation of the survival curves all deaths have been included, whether or not they were of cardiac origin.

* * *

Sixty-nine per cent of group-II and III patients and 55 per cent of the group-IV patients have improved. . . .

* * *

Two hundred twenty-eight of the patients in this study have become worse after having been significantly improved, that is "markedly" or "moderately," for at least 1 year after valvuloplasty. For the sake of this analysis, the definition of "deterioration" is that they have slipped by at least 1 class, according to the American Heart Association classification. Sixty-two of these patients slipped only from "markedly" to "moderately" improved, and hence would still be classed in the "improved" category. The remaining 166 deteriorated from either being originally "markedly" or "moderately" improved into the "unimproved" classification; that is, they are now either only "slightly" improved, their condition is unchanged as compared to the pre-operative state, they are worse, or dead. Of these patients, 48 have died since operation, and 45 have been reoperated on for mitral valvular disease. These patients were not all personally observed by the authors at the time of their deterioration; evidence for their deterioration was obtained in some from their answers to annual questionnaires or from letters from their physicians.

* * *

NOTES

NOTE 1.

ANDREW LOGAN, CLIFTON P. LOWTHER,
AND RICHARD W. D. TURNER
REOPERATION FOR MITRAL STENOSIS*

After successful mitral valvotomy, improvement may last for several years; but thereafter many patients deteriorate. Experience has now shown that re-stenosis is the most frequent cause of this deterioration. It is also the most important cause, being the only one for which essentially satisfactory treatment is available. As soon as

* 1 *The Lancet* 443 (1962). Reprinted by permission.

stenosis is believed to be again severe, a second operation would be advised.

* * *

Of 500 consecutive patients with severe stenosis treated by mitral valvotomy in the past eleven years, 264 survivors have now been followed for more than five years and can reasonably be regarded as having been "at risk" for a second operation. Experience has shown that symptoms from re-stenosis rarely become evident in less than four years. 80 patients have now had a second valvotomy at which an important degree of re-stenosis was found, while the remaining 184 have not deteriorated in this way. . . .

* * *

Varying opinions on the incidence of re-stenosis have been reviewed by Wilcken. Doubtless these are related to differences in selection of cases, efficacy of operation, and duration of subsequent observation. Earlier in our experience we thought that re-stenosis of the mitral valve was infrequent, because after five years few patients had apparently deteriorated for this reason. Similar views were held by other observers.

Wilcken reported re-stenosis in 10 per cent of 73 selected patients considered to have had an adequate valvotomy. . . . Harken et al. (1961) repeated valvotomy in 80 of 1000 cases (8 per cent) within nine years of the first operation.

In the present series there have been 80 operations for re-stenosis among 264 patients followed for more than five years after the first operation—an incidence of 30 per cent. The rate has increased steadily from 5 per cent for patients followed for only five years to 70 per cent in the small group who have been followed for ten years, and it may be expected to increase further. . . .

* * *

NOTE 2.

LAURENCE B. ELLIS AND DWIGHT E. HARKEN
CLOSED VALVULOPLASTY FOR MITRAL
STENOSIS—A TWELVE-YEAR FOLLOW-UP
STUDY OF 1571 PATIENTS*

* * *

The question whether or not operation for patients with symptomatic mitral stenosis is

worthwhile has now become academic. It is now generally agreed that it is a very useful procedure. The questions that remain are how long lasting and how good the results are and what conditions lead to deterioration.

* * *

Is there any way that mitral surgery can be improved so that longer lasting results can be obtained? Those who advocate routine open surgery for mitral stenosis contend that adequate visualization of the valve permits more accurate and careful fracture of the commissures and relief of subvalvular stenosis as well as debridement of calcium and the correction of any insufficiency that may be present. If required, prosthetic devices of various types, including total valve replacement, can be employed. It has been claimed that the immediate postoperative results are better as far as both clinical and hemodynamic findings are concerned. Long-term results, however, are not yet available in sufficiently large numbers to have any significance. Some authors have also failed to indicate how severely disabled the patients have been before surgery. This is a critical factor in the assessment of the mortality and postoperative results of any type of surgery.

The arguments of the advocates of open surgery for mitral stenosis have obvious appeal. However, some surgeons experienced in various techniques of mitral surgery believe that it may be more difficult to assess mitral incompetence, either that occurring before surgery or that produced by surgery, unless the heart is turgid and functioning. One must also bear in mind the possibility that more late complications will follow open cardiac surgery, particularly if a prosthetic device has been inserted, than have taken place after closed mitral valvuloplasty. The two major complications of this type are late embolization and late infection, particularly bacterial endocarditis. We have previously shown, and have emphasized earlier in this paper, that postoperative emboli are infrequent after closed mitral valvuloplasty. Moreover, to our knowledge, there has not been a single case of bacterial endocarditis that has occurred in any of our patients undergoing closed mitral valvuloplasty within four months, or a time span that would make it unlikely that the operation was a factor in initiating the infection.

* * *

* 270 *New England Journal of Medicine* 643, 648-649 (1964). Reprinted by permission.

D.

Appraising the Role of the Participants

Throughout this volume we have suggested that the analysis of the role of the participants in the human experimentation process will be facilitated by focusing separately on the different stages in this process at which the authority of the participants may vary to a significant degree. We have distinguished three such stages, and the materials in this section accordingly divide the appraisal of the participants' roles into three parts. First, we are concerned with the *formulation* of policies which encompasses, most generally, the establishment of guides for decision for the entire process and, more specifically, such policy decisions as the qualifications of subjects and investigators, the determination of societal interests and priorities, and the establishment of criteria for harm and disclosure. We then turn to the *administration* of research and explore such issues as the allocation of authority to conduct and supervise ongoing investigations as well as the means and organizational structure by which the participants should arrive at their decisions. Finally, we examine mechanisms for after-the-fact *review* of the consequences of particular investigations and the entire experimentation process through congressional hearings, scholarly analysis, press coverage, or actions initiated by the government, public interest groups, the subject, or the investigator himself.

Though the focus in this section is on the professions, the state, and the public, the materials also touch on the roles of the other participants so as to facilitate the construction of a comprehensive theory of decisionmaking about experimentation. The task of the student of human experimentation is to identify those decisions which most adequately promote and protect the interests and values that he deems important. Nevertheless, concern with the ultimate outcome should not diminish the attention given to the participants and methods of decisionmaking for a number of reasons. First, the content of any decision is largely dependent on the people and institutions who make it and the procedures they follow. Since all the issues which deserve resolution cannot be anticipated, achieving "good" decisions requires designing a system which employs the means and participants most likely to advance the interests one favors. Second, the choice of decisionmakers and methods is itself a value choice which can have a greater impact, for better or worse, on the interests of science, subject, and society than that of any particular decision. Finally, the focus on "who" and "how" highlights the need to examine decisionmaking from the vantage points of both those who are given authority and those who give the authority.

In studying these materials, consider the following questions in addition to those posed at the beginning of the chapter:

1. What purposes should professional or state regulation of the human experimentation process serve?
 - a. At what stages in the process would regulation by the professions, state, or public be most effective in protecting, rather than undermining, the interests of investigators, subjects, science and society?
 - b. What specific decisions in this process should be formulated, administered, and reviewed by the professions, state or public?

c. What specific decisions at each stage in this process should be left to the investigator and subject?

2. What alternatives to present regulations of the human experimentation process by the professions, state, or public are better suited to promote the interests of all the participants?

a. Should the goal of any regulation be to encourage maximal self-regulation by the profession with minimal state and public intervention? If so, how can this be accomplished while still providing adequate safeguards for all the participants?

b. Should the goal of any regulation be to encourage maximal self-regulation by the investigator and subject with minimal interaction by the professions, the state, and the public? If so, how can this be accomplished while still providing adequate safeguards for all the participants?

1.

In Formulating Policy

a.

Deciding about Societal Interests and Priorities?

[i]

*United States Congress
Joint Resolution to Provide for a Study
and Evaluation of the Ethical, Social, and
Legal Implications of Advances in
Biomedical Research and Technology**

* * *

Resolved by the Senate and House of Representatives of the United States of America in Congress assembled, That . . .

SEC. 2. There is hereby established a National Advisory Commission on Health Science and Society (hereinafter referred to as the "Commission").

SEC. 3. (a) The Commission shall be composed of fifteen members to be appointed by the President from the general public and from individuals in the fields of medicine, law, theology, biological science, physical science, social science, philosophy, humanities, health administration, government, and public affairs.

* * *

SEC. 4. (a) The Commission shall undertake a comprehensive investigation and study of the ethical, social, and legal implications of ad-

vances in biomedical research and technology, which shall include, without being limited to—

(1) analysis and evaluation of scientific and technological advances in the biomedical sciences, past, current and projected;

(2) analysis and evaluation of the implications of such advances, both for individuals and for society;

(3) analysis and evaluation of laws, codes, and principles governing the use of technology in medical practice;

(4) analysis and evaluation, through the use of seminars and public hearings and other appropriate means, of public understanding of and attitudes toward such implications;

(5) analysis and evaluation of implications for public policy of such findings as are made with respect to the biomedical advances and public attitudes.

(b) The Commission shall make maximum feasible use of related investigations and studies conducted by public and private agents.

(c) The Commission shall transmit to the President and to the Congress one or more interim reports and, not later than two years after the first meeting of the Commission, one final report, containing detailed statements of the findings and conclusions of the Commission, together with its recommendations, including such recommendations for action by public and private bodies and individuals as it deems advisable.

* * *

SEC. 7. For the purpose of carrying out this joint resolution, there are authorized to be appropriated such sums as may be necessary, but not to exceed \$1,000,000 for each of the two years during which the Commission shall serve.

* * *

* Senate Joint Resolution 75, 92d Congress, 1st Session, introduced on March 24, 1971, and adopted by the Senate as amended on December 2, 1971, 117 *Congressional Record* S20089-S20093 (1971). It is presently before the Subcommittee on Public Health and Environment of the House Committee on Interstate and Foreign Commerce.

NOTES

NOTE 1.

SENATOR WALTER F. MONDALE
HEALTH SCIENCE AND SOCIETY*

* * *

MR. MONDALE: Mr. President, I introduce for myself and Senators Bayh, Brooke, Case, Fong, Harris, Hart, Hughes, Humphrey, Javits, Kennedy, McGee, McGovern, Moss, Nelson, Pell, Randolph, and Schweiker for appropriate reference a joint resolution to create a National Advisory Commission on Health Science and Society.

Recent advances in biology and medicine make it increasingly clear that we are rapidly acquiring greater powers to modify and perhaps control the capacities and activities of men by direct intervention into and manipulation of their bodies and minds. Certain means are already in use or at hand—for example, organ transplantation, prenatal diagnosis of genetic defects, electrical stimulation of the brain. Others await the solution of relatively minor technical problems, while still others depend upon further basic research. All of these developments raise profound and difficult questions of theory and practice, for individuals and for society.

* * *

[T]hree years ago I introduced a joint resolution which was essentially the same as the one I am introducing today. At that time, heart transplants were a startling new medical breakthrough. Since then, several hundred heart transplants have been performed. When I reintroduced the resolution in the last Congress, the first successful test-tube fertilization of a human egg had just been reported. Now, just 2 months ago, Nobel Prize winner Dr. James D. Watson told the House Committee on Science and Astronautics that we will soon see the day when a baby will be conceived in a test tube and placed in a woman who will bear the child. As you may recall, Dr. Watson's reported prediction was that when such an implantation is successfully made, "All hell will break loose."

These brief comments indicate that the need for a sober and thoughtful analysis and evaluation of biomedical advance is even more urgent

now than it was 3 years ago when I first proposed this commission.

* * *

While holding forth the promise of continued improvements in medicine's abilities to cure disease and alleviate suffering, [recent] developments also pose profound questions and troublesome problems. There are questions about who shall benefit from and who shall pay for the use of new technologies. Shall a person be denied life simply because he does not have enough money for an organ transplant?

There will be questions about the use and abuse of power. When and under what circumstances can organs be removed for transplanting? Who should decide how long a person is to be kept alive by the use of a machine? . . .

There will be questions about our duties to future generations and about the limits on what we can and can not do to the unborn. Is it ethical for a man and wife, each carrying a gene for a serious hereditary disease, to procreate, knowing that their children have a significant chance of acquiring the disease? Should the law enjoin certain marriages or require sterilization for such eugenic consideration? What rights do unborn children have to protect them in experiments involving genetic engineering or test-tube fertilization? . . .

We shall face questions concerning the desirable limits of the voluntary manipulations of our own bodies and minds. Some have expressed concern over the possible dehumanizing consequences of increasing the laboratory control over human procreation or of the increasing use and abuse of drugs which alter states of consciousness.

We shall face questions about the impact of biomedical technology on our social institutions. What will be the effect of genetic manipulation or laboratory-based reproduction on the human family? If laboratory fertilization can produce children for sterile couples, what will be the consequences for those orphaned or abandoned children who might otherwise have been adopted by these couples? What will be the effect on the generation gap of any further increases in longevity?

We shall face serious questions of law and legal institutions. What will the predicted new-fangled modes of reproduction do to the laws of paternity and inheritance? What would happen to the concept of legal responsibility if certain

* 117 *Congressional Record* S3708-S3709 (March 24, 1971).

genetic diseases were shown to predispose to anti-social or criminal behavior? What would be done to those individuals with such traits?

We should expect that some people will try to have certain particularly frightening technologies banned by statute. Should this be done? Could such prohibition be effective?

Finally, we as legislators will face problems of public policy. We shall need to be informed of coming developments, of the promises they hold forth and the problems they present, and of public attitudes in these matters. We shall need to decide what avenues of research hold out the most promise for human progress. And we shall need to help devise the means for preventing undesirable consequences.

* * *

[W]e can ill afford to wait until the crush of events forces us to make hasty and often ill-considered decisions. We cannot again allow events to pass us by. We face an increasing number of new and far-reaching technological possibilities, touching the very nature of man. We face the need for some wise, deliberate, and sober decisions. These questions are not going to go away or answer themselves. They will become progressively more difficult as time goes on. As Dr. Watson said in his testimony:

"If we do not think about the matter now, the possibility of our having a free choice will one day suddenly be gone."

It would be foolish to expect the Commission to provide answers to all the questions we face, but we can expect that it will provide help in making some of our difficult decisions. The findings and considered judgments of excellent minds with a wide range of experience and training will be invaluable to individuals who must struggle with the awesome responsibility of coping with these new technologies.

* * *

NOTE 2.

ABRAM CHAYES AND JOSEPH GOLDSTEIN
LETTER OF INVITATION FOR THE SALK
INSTITUTE COMMISSION ON BIOLOGY, ETHICS,
AND THE LAW—SEPTEMBER 24, 1970*

We wish to invite you to become a member of the Commission on Biology, Ethics, and the Law.

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Concurrent with educating ourselves about the state of knowledge and potential developments in the life sciences, with your help, we plan to concentrate upon two major but more general problems:

First, the development of a framework for judging the occasions and the desirable extent of official intervention by local, state, national, and international decision-making bodies concerning the use and implementation of new biological knowledge and technique; and

Second, the design of procedures and agencies of decision for continuous evaluation of the significance of developments in the life sciences.

As to the first, it appears that major decisions about the dissemination and use of new knowledge and new procedures in the biological sciences, some of them having fundamental implications for the future of the human race, are, with certain important exceptions, made by private individuals—researchers, doctors, patients—without significant public intervention or regulation. It further appears that the general "set" of the decision-making apparatus is predisposed toward these laissez-faire premises. The Commission will attempt to verify these general impressions and to ask how far these premises ought to prevail. In particular, it will examine the possibility of a more aggressively "interventionist" approach. The Commission recognizes that one major form of intervention is public support of research. Because many other groups are now studying the appropriate criteria for public funding of scientific work, we will not place major emphasis on this question. Thus the Commission, working in the context of a governmental role in funding research, will attempt to set forth guides for decisions about the implementation and use of new knowledge and techniques.

The search for these criteria leads to the second and perhaps major concern of the Commission. This is the design of agencies and processes for decisions at local, state, national, and international levels in the area of technological and scientific assessment which may determine the need, if any, and methods of socially controlling the implementation of new techniques and knowledge. One of us, in a memo prepared for the Life Sciences and Social Policy Panel of the National Research Council, briefly posed that problem in this way:

What institutions and procedures exist or need to be established at local, state, national, and/or inter-

national levels for the purposes of (i) *identifying* and (ii) *assessing* on a continuing basis major developments in science and technology as well as for the purposes of (iii) *recommending* and (iv) *implementing* opportunities for action or nonaction (governmental and private) which will maximize gains for and minimize harm to preferred human values and arrangements?

In making assessments and recommendations to what extent can and should second-, third-, and more remote-order consequences for these values and arrangements be consciously considered or consciously left to chance?

How can private and public decision-making institutions and procedures, to the extent existing ones are inadequate, be established?

* * *

[ii]

*President's Commission on Heart Disease,
Cancer, and Stroke
A National Program to Conquer Heart
Disease, Cancer, and Stroke**

The conquest of heart disease, cancer, and stroke requires the continuation and expansion of our highly productive medical research effort in the years ahead.

Today's successes in detection, treatment, and cure sprang from yesterday's research. But many problems related to these three diseases remain beyond our scientific capability. Of these, a large number appear to be just outside our grasp. We stand on the threshold of further advances.

To cross this threshold as soon as possible—to take advantage of the tremendous momentum built up by our biomedical research enterprises in the recent past—certain new elements should be added to our existing scientific resources. In addition, current procedures need to be strengthened or modified to assure ever-increasing productivity of new life-saving knowledge.

The national network of regional centers, each primarily oriented toward the solution of a specific disease problem, will generate and verify a tremendous amount of new information on heart disease, cancer, and stroke.

But there is also the need for a more general research attack on the fundamental problems of human biology, to which all the sciences basic to medicine can contribute. In addition there is need for highly specialized

avenues of research related to heart disease, cancer, and stroke.

* * *

Recommendation 13. The Commission recommends the establishment of 25 non-categorical biomedical research institutes at qualified institutions throughout the country.

* * *

The Commission recognizes the importance and promise of non-categorical biomedical research. Indeed, such research is essential to basic understanding of heart disease, cancer, and stroke. Clues of great significance, coming from such endeavors, can be used effectively by research groups investigating specific disease problems.

For example, through such research, we can hope to attain the more detailed understanding of the living cell which may reveal the nature of the delicate change in the balance of cellular activities which manifests itself as cancer. Hopefully, also, there may be an unraveling of the next layer of understanding—the manner in which highly specialized cells such as those of the brain, kidney, or heart perform the specific functions which, uniquely, they contribute to the total living organism.

* * *

Recommendation 14. The Commission recommends the establishment of Specialized Research Centers for intensive study of specific aspects of heart disease, cancer and stroke to supplement the research and training efforts of the regional centers previously described.

Specifically, at least 10 such centers in heart disease, 10 in cancer, and 10 in stroke should be established in various health and medical research facilities throughout the country over a 5-year period.

In addition, it is recommended that three Bioengineering Centers and three Rehabilitation Biomedical Engineering Research Centers be established over a 5-year period in order to take advantage of the potential offered by bioengineering research in heart disease, cancer, and stroke.

* * *

Recommendation 15. The Commission endorses the existing system of review of research project grants by study sections and advisory councils at the National Institutes of Health and

* Washington, D.C.: U.S. Government Printing Office 47-52 (1964).

recommends intensified and expanded support of research in heart disease, cancer, and stroke.

Specifically it recommends:

That a total of \$40 million be appropriated to the National Heart Institute, \$40 million to the National Cancer Institute, \$15 million to the National Institute of General Medical Sciences, and \$10 million to the National Institute of Neurological Diseases and Blindness in a 3-year period over and above current appropriations to these institutes for research project grants.

* * *

That several important areas of research be given special emphasis because of the valuable contribution in the past and their high potential for the future. For example, epidemiological studies provide evidence which may lead to the identification of factors causing a specific disease or condition.

Of vital importance is the strong support of broad clinical field trials of drugs and other methods of treatment. As we have emphasized a number of times, there is a critical lag between the research discovery of new medication and the rapid evaluation of its effectiveness against a particular form of disease. We must wait too long while individual investigators report their limited findings in technical publications which print articles 12 to 18 months after their submission.

* * *

Recommendation 17. The Commission recommends that the existing General Research Support Grants Program of the National Institutes of Health be expanded as rapidly as possible to a level of 15 percent of the total NIH research and training budget and that the program be altered to increase its effectiveness.

Specifically, the Commission recommends:

That graduate schools engaged in biomedical research, supported by grants from NIH, should be permitted to receive grants under the general research support program; and

That general research support grants should be awarded in two categories: (1) unrestricted funds to be devoted to research, as at present, and awarded on a formula basis; and (2) negotiated awards, based on documented applications to defray the direct and indirect costs of the supporting organization and services provided by each institution to facilitate the conduct of research and which are not ordinarily chargeable as indirect costs.

* * *

NOTES

NOTE 1.

FRANCIS D. MOORE

THERAPEUTIC INNOVATION—ETHICAL
BOUNDARIES IN THE INITIAL CLINICAL TRIALS OF
NEW DRUGS AND SURGICAL PROCEDURES*

* * *

[W]e should mention the present crisis in laboratory finance in the biomedical sphere. While the 1968 cutback is considered by the Congress in terms of budget savings, and by the scientific public as one of the highly undesirable consequences of our military involvement in Southeast Asia, the sudden withdrawal of large amounts of federal support for biomedical research is going to have an inevitable ethical consequence: The necessary preliminary laboratory work is going to be severely curtailed in the instance of many forthcoming therapeutic innovations.

During the past ten years, the expense of conducting laboratory experimental work has doubled as a result of inflationary spirals in all the goods and services concerned. Prior to 1967, the National Institutes of Health budget increases had barely kept pace with laboratory inflation, but these had been sufficiently large so that other sources of laboratory support (such as certain philanthropic foundations and industry) had tended to withdraw from the field. With the withdrawal of laboratory financial support due to the congressional policy of pursuing military action in Southeast Asia, we are greeted with an almost unsupportable situation in biological research. An ironic example will illustrate. A certain young man of excellent medical background had just completed two years of service as a military surgeon in Vietnam. Here he had been handsomely supported in one of the largest and most wasteful of military encounters, and had worked himself without stint and without surcease to assist in the care of the wounded. Returning to civilian life, he was to become a Research Fellow in our laboratories to study the transplantation of the liver (liver transplant being a potential help to babies born with bile duct anomalies, to individuals with liver tumors, and to soldiers with severe bullet wounds of the liver). On returning to civilian life, he

* 98 *Daedalus* 502, 512-513 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

was told by the government that although his name had been accorded one of the highest places in the priority list for Senior Research Fellowships, funds were not available to support him. In the Sunday supplements that week, there was an account of new research being done to make a lunar module perform in a high vacuum simulating the surface of the moon, a research expending more money each month than has ever been spent on any aspect of tissue transplantation. It is clear, then, that ethical considerations in preliminary laboratory trial go to the roots of our society and to the question of what we regard as suitable priorities for human effort at this time.

* * *

NOTE 2.

PAUL FREUND ETHICAL PROBLEMS IN HUMAN EXPERIMENTATION*

* * *

The law on the whole subject of experimentation will be worked out in close reliance on the moral sensibilities of the community. It therefore behooves the medical profession to take the public into its confidence and to educate public opinion rather than to risk the shock and explosion of pent-up revulsion if the lid is pressed down on information and then blown up by some melodramatic case like that of the hospital for chronic diseases. The primary step is to recognize that difficult moral problems—indeed, moral dilemmas—do exist on which help and guidance may be sought from many sources.

* * *

NOTE 3.

H. S. CONRAD CLEARANCE OF QUESTIONNAIRES WITH RESPECT TO "INVASION OF PRIVACY," PUBLIC SENSITIVITIES, ETHICAL STANDARDS, ETC.†

* * *

... Who makes the rules by which acceptability is judged? Who interprets and applies the rules? What are the checks and balances, if any, in the whole process?

In the last analysis, I suppose that in a de-

mocracy it is the people who ultimately make the rules. By "people" I do not, of course, mean any abstract, homogeneous mass; but rather such forces as, first, custom and generally accepted ethics; second, the pressures of organized, interested, active groups; and third, the influence of Government officials (both legislative and administrative), from Congress on down to the local school superintendent and principal. Beyond these there are the two key persons in any study involving data-gathering instruments: namely, first, the individual researcher, whose sense of discretion and professional ethics can generally be relied on to recognize desirable restraints; and second, the individual respondent, who can always frustrate an inquiry simply by withholding or falsifying his answers.

* * *

... To leave the decision entirely to the individual researcher himself, or to a group of his colleagues, would seem to us to violate seriously what some political scientists term *the principle of shared or countervailing force*. The researcher and his colleagues represent a party at interest—the scientific party: And there is good reason to believe that any party at interest is likely, more often than not, to give himself the "benefit of the doubt." Whether he does or not, the public generally *thinks* or *suspects* that he does. And in our democracy, both theoretically and pragmatically, the views of the public must be recognized as of paramount importance.

As we see it, the role of Government ... is to serve as an honest broker between the scientist who presses for scientific freedom, and the public which, generally speaking, places considerably greater emphasis on the value of personal privacy.

* * *

... *The ultimate authority rests with the people*, and with the legislators and administrators who respond to the will of the people. In bluntest terms, the Federal appropriation of millions of dollars for research cannot be expected to continue and grow, unless scientists pay reasonable respect to the wishes of the people and their elected representatives. There doubtless are some exceptions to this rule for a field like engineering, or for certain segments of medicine; but the rule appears to hold true with special force for the behavioral sciences.

... *Social science must not become identi-*

* 273 *New England Journal of Medicine* 687, 691 (1965). Reprinted by permission.

† 22 *American Psychologist* 358-59 (1967). Reprinted by permission.

fied in the public mind with "snooping" and "prying"—i.e., with the unwarranted invasion of privacy. To this end, professional discretion in the preparation and use of questionnaires is essential; and—in the case of Government-supported research—appropriate regulations, reasonably enforced, are required. Such regulations, in practice, generally have only minimal (if any) effect on the quality and productivity of research. In any event, social scientists cannot expect to operate free from societal restraints. With reasonable adaptation to normal restraints, an increase in both budgetary and public support for the social sciences may be anticipated, and the future of the social sciences should be bright.

NOTE 4.

R. J. V. PULVERTAFT

THE INDIVIDUAL AND THE GROUP IN MODERN MEDICINE*

* * *

I recall an occasion in the late war when a very limited amount of typhus vaccine was made available by the American manufacturers for civilian distribution during a typhus epidemic. My own view was that it should be given to armament workers and other men of importance in the prosecution of the war; my American colleague insisted that it should be distributed without regard to age, sex, race, or occupation. He won. . . .

* * *

b.

Deciding about the Ambit of Experimentation?

[i]

R. A. McCance

The Practice of Experimental Medicine†

* * *

Let us start with the word experiment, which most biologists use very loosely to cover any investigation, however trifling, made to advance knowledge. The term generally implies some deliberate change of conditions without foreknowledge of the results but with subsequent observation of them. It may be used, however, even when the conditions are not being deliberately changed, when the term observation

would be more correct. Many doctors would not regard the attempt to cure an individual patient as an experiment, yet it undoubtedly may be, if the results are observed and followed up, for the essence of treatment is to do something positive to a patient, i.e., alter his condition, in the hope that the effect will be of benefit to him.

People who are sick are often apprehensive. They long for reassurance which they do not find in the word "experiment." Worse still, the word may conjure up alarming possibilities in their minds. . . .

There is one fundamental difference between the investigator and the physician. A good investigator may be as full of bedside charm and therapeutic ability as a good physician, but he must primarily be interested in his problem. The physician is interested first, last, and all the time in his patients. . . .

Patients provide the problems, and disease may produce conditions which could never have been achieved experimentally and which demand detailed investigation, but if the illness is acute and treatable it is usually unjustifiable to withhold the remedy for long enough to make all the observations desirable in a satisfactory experiment. . . .

* * *

We should, I think, for present purposes, regard anything done to a patient, which is not generally accepted as being for his direct therapeutic benefit or as contributing to the diagnosis of his disease, as constituting an experiment, and falling, therefore, within the scope of the term experimental medicine. The definition, however, should not include all those unplanned experiments which are inseparable from the admission of any child or adult to a hospital, and which are often attended with considerable physical and psychological dangers, nor should it include the administration of established prophylactic remedies, even though some of them, particularly the attenuated viruses, may involve risk. The experiment visualized may be one of omission and consist of withholding treatment from a "control," or it may be one of commission and consist of making some test on a patient for which there is no obvious and immediate need. Whatever the problem interesting the investigator, however, it is, of course, true to say that the results of such tests must always help to characterize the diseased state and when known may sometimes be of benefit to the patient on whom the tests have been made. There is a case to be

* 2 *The Lancet* 841 (1952). Reprinted by permission.

† 44 *Proceedings of the Royal Society of Medicine* 189-194 (1950). Reprinted by permission.

made out for regarding all these tests as being "investigations" conducted in the sufferer's best interests and therefore not constituting an experiment made solely for the advancement of knowledge. Wassermann reactions [blood test for syphilis] are carried out on every patient admitted to some hospitals and every patient entering the Mayo Clinic is, I believe, subjected to an elaborate series of investigations. The real distinction is a subtle one and may depend upon the mental approach of the man who makes the tests. Nevertheless, I regard collecting an extra specimen of urine or taking an extra 5 cc. of blood from a vein puncture, made purely for established diagnostic or therapeutic purposes, as falling within the range of the term "experiment"; I would certainly regard weighing a baby "unnecessarily" as an experiment. Some people may think I am taking up a ridiculous attitude over this, but if an experiment is not defined in this way, where is the line to be drawn?

All experiments involve some risk. It may be an infinitesimally small one, but it is always there—you, or the nurse, may drop the baby, for instance. If the experiment involves special vein punctures, or perhaps infusions, the risk is considerably enhanced, but it still remains immeasurably small in the hands of an experienced operator. Nevertheless, I have myself seen and experienced the most alarming effects from pyrogens and I think it quite likely that the virus which gave me a mild attack of jaundice in 1939 reached me through a syringe. In assessing the risks involved in any experiment and therefore the justification for doing it, there are many factors which require consideration. The skill and experience of the investigator are important ones, but so is the place where the experiment is to be performed. A procedure which would be perfectly safe in a well-equipped and well-staffed establishment might be quite unjustifiable somewhere else. . . .

* * *

If an experiment is the first of a series it involves much more risk than one which has been made many times before by the same people out of the same bottles. I never worry at all, however, about trying out an unknown substance on man, for with a little patience one can work up the dose on oneself or other normal people so gradually that the risk can be reduced to vanishing point, but I do not think I would ever have had the temerity to carry out the first hepatic biopsy or cardiac catheteriza-

tion. Our pioneer studies of renal function in newborn infants were made on babies which had been born with inoperable meningomyeloceles. Hundreds of these experiments have now been made on normal newborn and on premature infants in other countries—yet I am still hesitating about doing so.

The risk involved in any experiment depends very much on whether the investigator knows that he will always retain control of the situation. An experiment on salt deficiency or dehydration can be pushed till the subject is showing severe effects, because the remedy is available all the time. To inoculate someone with icterogenic serum is a risk that I personally would never take, nor would I ever have cared to take it even before the risks were so well known, for once the inoculation had been made, I would have lost control. Everyone working experimentally with normal human subjects or with patients must remember not only his responsibility to the subject or patient but also his responsibility to the discipline of experimental medicine. One irresponsible experimenter can do great harm to medical science.

* * *

NOTES

NOTE 1.

WALTER MODEL.
LET EACH NEW PATIENT BE A COMPLETE
EXPERIENCE*

* * *

. . . If meticulous observers do not execute a disciplined experiment with a drug in a limited number of carefully chosen and well-controlled subjects, there will inevitably be an undisciplined natural experiment with it on a much larger uncontrolled group of indiscriminately chosen patients—conducted by much less critical observers—which will take much longer to tell its gory or (less likely) glorious tale. One needs only to recall that, not so very long ago, when lithium chloride was used as a salt substitute, it caused several hundred disasters and deaths simply because it was introduced into medical practice without appropriate consideration of existing experimental information and without appropriate clinical trial. In this instance, it was actually the practicing physicians

* 174 *Journal of the American Medical Association* 1717 (1960). Reprinted by permission.

who unwittingly conducted the critical pharmacologic experiments on man. The potential for disaster in these natural experiments on large sections of the population is far greater than when a new drug is used in a circumscribed and well-controlled scientific experiment. Every practitioner who would not consciously deprive his patient of effective medication will, therefore, have done so unconsciously a thousand times over in haphazard, dangerous, and wasteful trials on his own patients if he does not rest his therapy on carefully thought out private investigations as well as carefully disciplined clinical evaluations. Moreover, his unwitting "subjects" will have been unwittingly tested by him for their responses to new drugs with something less than the minimal requirements for experimentation in man. . . .

NOTE 2.

JAY KATZ
THE EDUCATION OF THE
PHYSICIAN-INVESTIGATOR*

* * *

Experimentation in the practice of medicine is as old as medicine itself. Hippocrates tells us that while treating a boy whose cortex was exposed, he not only picked out the spicules of bone embedded in the brain, but also "gently scratched the surface of the cortex with his fingernail" and observed convulsions on the opposite side of the body. Physicians throughout history have seized similar opportunities to combine therapy with the quest for knowledge. But only during the last hundred years, since the age of Pasteur, has medicine become more aware of the need for deliberate and well-planned experimentation; at the same time it has realized how difficult it is to separate the practice of medicine from experimentation. The oft-made distinction that the physician is primarily concerned with the patient qua patient and the investigator with the research is not a useful one for the majority of medical situations, for most investigations occur in the context of "clinical research combined with professional care." As A. C. Ivy points out, "the therapy of disease is, and will always be, an experimental aspect of medicine." Moreover, in terms of consequences to the patient

and subject, distinctions between therapy and research contribute little. Louis Lasagna has observed, for example, that "the patient is, paradoxically, often better served by the restraint observed in therapeutic approach by the critical experimentalist." What is new in medicine is not experimentation on man, but the realization that experiment and therapy have much in common and that knowledge can only be acquired by experimentation, ultimately only by experiment on man.

Thus the recent increased concern about the ethics of medical experimentation extends to the ethics of therapeutic care. Contributing to the reluctance to examine these issues is the conscious or unconscious realization that any resolution of the problems posed by human experimentation cannot be limited to research settings, but instead has far-reaching consequences for medical practice. . . .

* * *

[ii]

Carmichael v. Reitz

17 Cal. App. 3d 958, 95 Cal. Rptr. 381 (1971)

* * *

ALSO, ASSOCIATE JUSTICE:

Plaintiff Vira Dee Mae Carmichael . . . brought this action for damages against defendants James Reitz, M.D., J. G. Dahlquist, M.D., the Harriman-Jones Medical Clinic, and G. D. Searle & Company, a corporation (hereinafter "Searle"), for pulmonary embolisms and thrombophlebitis allegedly caused by Dr. Reitz's having prescribed the drug Enovid, manufactured and marketed by Searle, in treating plaintiff for endometriosis.

* * *

The trial was completed as to Searle, and the jury returned a verdict in its favor. Plaintiff . . . appeals from the judgment entered on the verdict.

* * *

Plaintiff first sought the professional services of Dr. Reitz, a specialist in obstetrics and gynecology, on July 10, 1963. She complained that she was experiencing pain in conjugal sexual intercourse, that she had a "dropped uterus," and that she had been married for a period of two and one-half years without becoming preg-

* 98 *Daedalus* 480, 481-482 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

nant. She also informed Dr. Reitz that she was having "a great deal of pain with her menstrual periods" and "had been passing formed blood clots" during these periods. . . .

During this visit, Dr. Reitz conducted a physical examination which, in addition to the pelvic area, encompassed the chest, head, neck, abdomen, rectum, and extremities. Percussion and auscultation examinations of the chest indicated no abnormality and no chest problems as of that time. An X-ray of the chest was also taken; it proved negative for abnormalities. . . .

Dr. Reitz diagnosed a minimal case of endometriosis. He recommended that plaintiff attempt to become pregnant and prescribed Cyclex, a combination diuretic and tranquilizer, for the abdominal bloating and personality changes (premenstrual tension) of which plaintiff complained. He advised her to return in a year. . . .

Plaintiff returned to Dr. Reitz's office on May 12, 1964. The doctor noted on this occasion that there had been no progression in her symptoms; in fact, they were slightly more favorable despite her having been unable to become pregnant since her July 10, 1963, visit. Plaintiff stated that she was desirous of becoming pregnant. . . . She informed the doctor that she had been suffering from "flu" for a few weeks prior to her visit.

On this May, 12, 1964, occasion plaintiff was not given a complete physical examination. Dr. Reitz examined her chest by percussion and auscultation; the indications were that it was then clear. No X-ray was taken as less than a year had elapsed since his taking of the X-ray in July 1963. Plaintiff stated that she was being seen elsewhere for her chest problem. Dr. Reitz relied upon the physician treating her for her "flu" to take X-rays if that doctor should feel it necessary. He also believed that X-rays had been taken in that other doctor's office. Plaintiff did not complain of any present chest pain on this second examination. On the basis of the July 10, 1963, chest X-ray and his current physical examination of the chest area, Dr. Reitz at that time ruled out any pulmonary embolisms up to that time. Consequently, he did not inquire further about any chest pains.

* * *

Dr. Reitz decided to prescribe Enovid, which he considered the drug of choice, for . . . treating the endometriosis (including premenstrual tension syndrome); treating the heavy ("characterized by the passage of clotted blood")

and painful menstrual flow (dysmenorrhea); and assisting in achieving pregnancy.

Dr. Reitz testified that he advised plaintiff of the risks and hazards of breakthrough bleeding, nausea, and vomiting in taking Enovid, and instructed her that if she had problems with the medicine to contact him. Plaintiff testified that Dr. Reitz discussed endometriosis with her; that it caused blood cysts; that he informed her that in some instances Enovid might be helpful in treating endometriosis and that a purpose for prescribing Enovid was to treat the endometriosis.

Prior to his prescribing Enovid for plaintiff, Dr. Reitz knew of a statistical relationship between thromboembolic episodes and Enovid, but he did not believe that there was a causal relationship between the two. The *Physicians' Desk Reference* for the 1964 (copyrighted in 1963), which he used, indicated that no contraindications were known. . . .

The prescription was filled at a pharmacy on May 14, 1964. The directions on the label were: "One tablet daily for 14 days then one tablet 2 times a day." Plaintiff waited until May 25, 1964, before she started taking the pills. . . . By Friday, June 5, 1964, she was spitting up blood and experiencing chest pains and shortness of breath. . . .

Plaintiff was examined by Dr. Reitz on Monday, June 8, 1964, and was instructed to continue with the antibiotic as prescribed by Dr. Horvitch. Her pain continued to get worse, so she went to the clinic on Tuesday as soon as it opened. Dr. Reitz examined her again and then turned her over to Dr. Joseph G. Dahlquist (originally a codefendant, a partner of Dr. Reitz in the Harriman-Jones Medical Clinic, and a specialist in internal medicine) for further treatment. Dr. Dahlquist had plaintiff immediately hospitalized in the Long Beach Community Hospital. He took a detailed history from plaintiff at the time of her admission to the hospital on June 9, 1964. His diagnosis, as of this date, was pneumonia with possible pulmonary embolism originating from a pelvic thrombophlebitis.

On June 10, 1964, Dr. Dahlquist inquired into plaintiff's chemical exposure and learned that she had taken Enovid as prescribed by Dr. Reitz. He then made a notation of the "possibility of Enovid-induced embolism." Due to Dr. Dahlquist's absence from the city for the next four days, plaintiff was cared for during Dr. Dahlquist's absence by Dr. Martin, Dr. Dahl-

quist's associate and also a board-certified internal medicine specialist. Dr. Martin recorded on Thursday, June 11, 1964, that he had no doubt but that plaintiff had suffered a pulmonary embolism. Dr. Martin contacted Dr. Dahlquist by telephone just as soon as the latter returned . . . around 4 P.M. on Sunday, June 14, 1964, and informed Dr. Dahlquist that a venogram disclosed large clots in the inferior vena cava, and that "they" felt that immediate surgery to tie off the inferior vena cava should be performed to prevent further possibly massive and fatal pulmonary embolism. Following consent to the operation, a plication of the inferior vena cava was performed that day by Dr. Gaspar, a surgeon, who was "already scrubbing" when Dr. Dahlquist returned.

A D & T (diagnostic and therapeutic) conference was held at the Harriman-Jones Clinic following the operation. Prior to the conference, a more detailed history of the plaintiff was obtained. What plaintiff had characterized as "flu" consisted of "generalized chest pain and symptoms of coryza" (common cold). There were also revealed episodes in 1961 and 1963 wherein plaintiff had experienced a sudden onset of pain in the right chest with low-grade fever, along with coughing of blood in 1963. Dr. Dahlquist testified that these symptoms were consistent with thromboembolism; that low-grade fever would generally cause a doctor to suspect thromboembolism.

* * *

The plication of plaintiff's vena cava inferior performed on June 14, 1964, by Dr. Gaspar was successful. Postoperatively, plaintiff was placed on Coumadin, an anticoagulant drug, by Dr. Dahlquist, who further instructed plaintiff to wear elastic stockings. She remained under Dr. Dahlquist's care, notwithstanding the fact that she had named him as a defendant in this action filed on May 3, 1965. When Dr. Dahlquist saw her on March 1, 1966, plaintiff had made an excellent recovery from her 1964 problems. She was not on any anticoagulant, and was not wearing elastic stockings. He was informed by plaintiff that she was able to walk, hike, swim, and engage in similar activities, which he had encouraged her to undertake. He had interdicted only heavy lifting and the like. She had no varicose veins at that time. She was working full time.

On May 13, 1967, plaintiff suffered a

thrombophlebitis of the right calf. She had ingested Enovid just prior to her admission to the Long Beach Community Hospital on June 10, 1964. It was almost one year after plaintiff had been completely taken off of anticoagulant therapy in July 1966. Plaintiff returned to Dr. Dahlquist for treatment; he again placed her upon Coumadin and a tranquilizer to minimize the risk of another pulmonary embolism.

While still under Dr. Dahlquist's treatment, plaintiff was referred by her attorneys in this action to Dr. Arthur Samuels for the purposes of his conducting a clinical experimental study on plaintiff involving the use of Enovid. He testified that because the May 13, 1967, thrombophlebitis was "spontaneous," there was some question as to its cause. One purpose of the study was to either prove or disprove a causal relationship between Enovid and plaintiff's thrombophlebitis and pulmonary embolism. He also knew that another purpose of the experiment was to enhance plaintiff's position in this action.

July 11, 1967. Dr. Samuels saw plaintiff for the first time. He took a detailed (some ten pages) history from her, but he, like Dr. Reitz, did not pick up plaintiff's chest ailments of 1961 and 1963 other than as "flu" and accepted that to be true. A large blood specimen was taken for laboratory test purposes. On this date, Mr. Wolfe, plaintiff's associate counsel who had referred plaintiff to Dr. Samuels, advised the latter to keep this hematological consultation private and to refrain from contacting Dr. Dahlquist until further notice from Mr. Wolfe.

July 12, 1967. Dr. Samuels examined plaintiff physically. Although he found a rather prominent pulmonary sound (P-2), an indication that something might be wrong with her pulmonary circulatory system, he concluded that plaintiff was "medically asymptomatic and in a reasonable state of clinical equilibrium while taking her daily anticoagulant and tranquilizer therapy."

July 18, 1967. Actual studies were commenced. Another blood specimen was taken and laboratory tests thereon performed. Plaintiff told Dr. Samuels that she was experiencing pain in the lower right side of her chest. At this time, Dr. Samuels attributed these pains to anxiety-imagination. In retrospect, Dr. Samuels diagnosed these complaints as indicative of "thrombi and emboli possibly to lung for two weeks prior to discontinuation of Coumadin," and that plaintiff had "presence of pulmonary emboli" on July 18.

July 24, 1967. Plaintiff stopped taking Coumadin upon Dr. Samuels' direction. Mr. Wolfe instructed Dr. Samuels that he would now be permitted to contact plaintiff's personal physician.

July 25, 1967. Although good clinical practice called for tapering off when taking a patient off of an anticoagulant Dr. Samuels in this instance suddenly stopped plaintiff's ingestion of Coumadin. He was aware of the hazard that thrombophlebitis could result from the "rebound" or "overshoot" reaction from suddenly stopping the taking of Coumadin. But he had advised plaintiff of this hazard as well as the hazard of having plaintiff take Enovid. In fact, this study on plaintiff was "a very hazardous life-threatening study." He testified that he informed both plaintiff and her husband of the risks involved. And according to him, plaintiff realized that to get her answers to her problems, "she might have to further submit herself to further hazards." Dr. Samuels had plaintiff execute a so-called written informed consent form on this date (July 25, 1967), which was witnessed by Dr. Samuels' office manager. Dr. Samuels phoned the Harriman-Jones Clinic on this date, but was informed that Dr. Dahlquist was out of town and would not be back for two weeks from the time he had left.

July 27, 1967. Plaintiff was still having pain in her mid-epigastrium and her lower chest.

July 28, 1967. Dr. Samuels noted an acceleration of blood clotting time in plaintiff after the discontinuance of the anticoagulant and tranquilizer. He also wrote a letter informing Dr. Dahlquist that he had "recommended" discontinuance of the anticoagulant therapy. He did not tell Dr. Dahlquist that it had in fact been discontinued, and that it had been discontinued abruptly. (Dr. Dahlquist testified that when he first heard of the sudden termination of the anticoagulant, his reaction was, "Oh, my God!") Dr. Samuels did not inform Dr. Dahlquist that one purpose of the study was to enhance plaintiff's position in this lawsuit against him. He did not inform Dr. Dahlquist of his intention of using Enovid in the study.

August 2, 1967. Dr. Samuels first talked to Dr. Dahlquist over the telephone.

August 3, 1967. Plaintiff was given one 10-milligram tablet of Enovid out of the 1964 container. No chemical assay of the tablets was made. Plaintiff also took one tablet daily on August 4, 5, 6, 7, 8, 9, 10, and 11, 1967.

August 7, 1967. Dr. Samuels noted the

plaintiff reported to him as feeling nauseous and having abdominal pain. She was afraid. The pain did not resemble the pain of 1964, although the nausea did.

August 8, 1967. Dr. Samuels noted: patient reports symptoms of discomfort in the right calf. "Telephone conversation from Mr. Carmichael. Upset about lack of definiteness of effect of Enovid—patient not experiencing same effects—patient upset about not experiencing same effects—as two years ago and not producing results."

August 9, 1967. Dr. Samuels held a conference with Mr. Carmichael and Mr. Wolfe as to whether clinical study should be continued. Apparently, it was decided that it should be. Communication of the decision to plaintiff was left up to Mr. Carmichael.

August 10, 1967. Dr. Samuels noted: "Discomfort in right side of chest, particularly on deep breathing, particularly in back. Coughed up spot of blood in A.M. once. Tenderness in right calf." He testified that there was a Homan's sign, definitely showing thrombophlebitis and recurrent pulmonary emboli. He gave plaintiff the choice of taking or not taking the Enovid pill that day. Plaintiff chose to go ahead. She told him: "I am not getting the same reaction at all as before although I have a lot more fear."

August 11, 1967. Plaintiff took another Enovid pill. At this time Dr. Samuels had a thorough discussion with plaintiff; he warned her of the hazards of further continuing with the studies. At the same time he informed her that there were now good theoretical grounds on which "to expect that she might now demonstrate maximum sensitivity to Enovid." On this date she had thrombophlebitis in both legs. Plaintiff was re-started on her anticoagulant and tranquilizer therapy. She was given a maximum dose (4 tablets; 20 milligrams) of Coumadin and instructed to thereafter take 2 tablets (total of 10 milligrams) daily. Plaintiff turned out, however, to be "particularly resistant to anticoagulant therapy" so she was given 4 tablets for 3 days and 3 tablets per day for the balance of the week. She was given as much as 25 milligrams on one occasion. Dr. Samuels instructed her to return to Dr. Dahlquist on August 12 and then report back to him the following Monday.

In the meantime, diagnosis of endometriosis had been confirmed at the UCLA Medical Center. Dr. Samuels agreed that Enovid is a treatment for endometriosis.

August 17, 1967. Dr. Samuels received con-

firmation from Dr. Dan Simmons, a pulmonary expert, that Dr. Simmons' studies (which included a lung scan on August 17, 1967) were partially complete. The lung scan indicated "a far advanced degree of pulmonary disease particularly on the right, including lower base."

Plaintiff required a "ligation" operation as a result of her 1967 pulmonary embolisms, in which her inferior vena cava was entirely tied off. Dr. Samuels testified: "Very unexpectedly Mrs. Carmichael suffered a minimum of symptoms right after surgery, of which we were terribly delighted, and since that time has done extremely well." At the time she was examined by Dr. Joseph Boyle, an internist, on behalf of defendant Searle in 1969; plaintiff was working. He opined that plaintiff should be able to carry on life "in a completely normal fashion without any difficulty."

The question, whether Enovid caused plaintiff's thrombophlebitis and pulmonary embolism in 1964 or whether it was due to her idiosyncratic hypersensitivity resulting from her endometriosis and abnormal blood clotting time, was hotly disputed. On direct examination, Dr. Samuels stated: "I believe that Mrs. Carmichael was *uniquely sensitive* to Enovid and sustained an adverse effect on her blood-clotting mechanism as a result of that ingestion," which would make Enovid medically defective in her case. (Emphasis added.) On cross-examination he stated that he thought plaintiff's endometriosis was a substantial factor in causing her thromboembolism. The blood factor changes induced by taking Enovid would have no clinically significant effect on normal women. On redirect examination, however, he believed that Enovid rather than the endometriosis was the causative factor producing the 1964 pulmonary embolism. A biochemist, Laurence Pilgeram, Ph.D., and Dr. John D. Wilson, a board-certified general surgeon, testified in support of the theory that Enovid was the cause.

On behalf of Searle, Dr. Robert W. Kistner, board-certified in obstetrics and gynecology, testified that there was no cause-and-effect relationship between Enovid and intravascular clotting, thromboembolism, or pulmonary embolism. He did not think the studies introduced into evidence established any definitive causal relationship. The pulmonary embolism in this case was not due to the ingestion of Enovid; the two events were coincidental. Dr. Joseph Boyle, an internist specializing in heart and lung disease, testified that plaintiff's pulmonary embolism in

1964 was caused by a chronic pelvic thrombophlebitis which had existed over a period of years. He noted the possibility of endometriosis itself having caused the thrombophlebitis in this case. The sudden discontinuance of Coumadin in the course of Dr. Samuels' clinical experimental study aggravated the plaintiff's problems due to her 1967 right calf thrombophlebitis episode. Dr. Herbert S. Sise, an internist specializing in cardiology and thrombosis, had no opinion as to the cause of the 1964 thromboembolism. His own studies performed in 1964 disclosed no really significant changes in the blood of women who took Enovid. He criticized Dr. Samuels' study as inadequate for lack of proper control data. Gerard Lanchantin, Ph.D., a biochemist, testified showing wherein biochemist Pilgeram's study was inadequate.

* * *

Plaintiff complains of the giving of the instruction which stated that Searle had the burden of proving that plaintiff and Dr. Samuels were aware of any dangers in the use of Enovid by plaintiff in August 1967 and that they "nevertheless proceeded to make use of Enovid despite such knowledge." She strenuously argues that the concept of assumption of risk properly belongs to a negligence theory of recovery and has no place in strict liability, detailing the requirements for invoking "assumption of risk" in negligence cases. We have already seen that a special type of "contributory negligence" or "assumption of risk" has its place as a defense to a claim of strict liability. . . . If a user or a consumer discovers a defect in the article and is aware of the dangers of such defect, but nevertheless proceeds to unreasonably make use of the product and suffers injury by it, he may not recover.

Here, plaintiff was seeking damages not only for the pulmonary episode of June 1964, but also for episodes following the experimental studies Dr. Samuels conducted on plaintiff by having her ingest Enovid for nine days in August 1967, at a time when he knew that plaintiff had previously suffered thrombophlebitis, when he had the benefit of her previous history, when the extent of available medical literature was much more extensive than in 1964, and when the need for prescribing Enovid, by his own admission, was not overwhelming. Consequently, this contention of error lacks merit.

* * *

c.

Deciding about Harm?

[i]

*Ninety-first Congress, Second Session
Comprehensive Drug Abuse Prevention and
Control Act of 1970**

SEC. 101. The Congress makes the following findings and declarations:

(1) Many of the drugs included within this title have a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people.

(2) The illegal importation, manufacture, distribution, and possession and improper use of controlled substances have a substantial and detrimental effect on the health and general welfare of the American people.

* * *

SEC. 502. (a) The Attorney General is authorized to carry out educational and research programs directly related to enforcement of the laws under his jurisdiction concerning drugs or other substances which are or may be subject to control under this title. Such programs may include—

(1) educational and training programs on drug abuse and controlled substances law enforcement for local, State, and Federal personnel;

(2) studies or special projects designed to compare the deterrent effects of various enforcement strategies on drug use and abuse;

(3) studies or special projects designed to assess and detect accurately the presence in the human body of drugs or other substances which are or may be subject to control under this title, including the development of rapid field identification methods which would enable agents to detect microquantities of such drugs or other substances;

(4) studies or special projects designed to evaluate the nature and sources of the supply of illegal drugs throughout the country;

(5) studies or special projects to develop more effective methods to prevent diversion of controlled substances into illegal channels; and

(6) studies or special projects to develop information necessary to carry out his functions under section 201 of this title.

(b) The Attorney General may enter into contracts for such educational and research activities without performance bonds and without regard to section 3709 of the Revised Statutes (41 U.S.C. 5).

(c) The Attorney General may authorize persons engaged in research to withhold the names and other identifying characteristics of persons who are the subjects of such research. Persons who obtain this authorization may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding to identify the subjects of research for which such authorization was obtained.

(d) The Attorney General, on his own motion or at the request of the Secretary, may authorize the possession, distribution, and dispensing of controlled substances by persons engaged in research. Persons who obtain this authorization shall be exempt from State or Federal prosecution for possession, distribution, and dispensing of controlled substances to the extent authorized by the Attorney General.

* * *

SEC. 601. (a) There is established a commission to be known as the Commission on Marihuana and Drug Abuse (hereafter in this section referred to as the "Commission"). The Commission shall be composed of—

(1) two members of the Senate appointed by the President of the Senate;

(2) two members of the House of Representatives appointed by the Speaker of the House of Representatives; and

(3) nine members appointed by the President of the United States.

* * *

(d) (1) The Commission shall conduct a study of marihuana including, but not limited to, the following areas:

(A) the extent of use of marihuana in the United States to include its various sources, the number of users, number of arrests, number of convictions, amount of marihuana seized, type of user, nature of use;

(B) an evaluation of the efficacy of existing marihuana laws;

(C) a study of the pharmacology of

* Act of October 27, 1970, Pub. Law No. 91-513, 84 Stat. 1271, 1280-1281.

marihuana and its immediate and long-term effects, both physiological and psychological;

(D) the relationship of marihuana use to aggressive behavior and crime;

(E) the relationship between marihuana and the use of other drugs; and

(F) the international control of marihuana.

(2) Within one year after the date on which funds first become available to carry out this section, the Commission shall submit to the President and the Congress a comprehensive report on its study and investigation under this subsection which shall include its recommendations and such proposals for legislation and administrative action as may be necessary to carry out its recommendations.

(e) The Commission shall conduct a comprehensive study and investigation of the causes of drug abuse and their relative significance. The Commission shall submit to the President and the Congress such interim reports as it deems advisable and shall within two years after the date on which funds first become available to carry out this section submit to the President and the Congress a final report which shall contain a detailed statement of its findings and conclusions and also such recommendations for legislation and administrative actions as it deems appropriate. The Commission shall cease to exist sixty days after the final report is submitted under this subsection.

(f) Total expenditures of the Commission shall not exceed \$1,000,000.

* * *

NOTES

NOTE 1.

JONATHAN O. COLE
DANGERS IN THE DRUG-ABUSE BILL*

My review of the version of the Administration's drug-abuse bill which has come out of the Senate leads me to believe that the section dealing with penalties is a modest improvement over the bill originally filed by Senator Dirksen and a substantial improvement over existing statutes governing opiates and marijuana.

The regulatory sections which would affect scientists doing research on dangerous drugs

are, unfortunately, very vague and leave a great deal to the Attorney General and the Department of Justice in determining how research work with these drugs will be encouraged, regulated, or hindered. The very vagueness—it is not even clear how a Ph.D. scientist doing work with these drugs would be licensed or registered and how he would obtain the drugs—makes it possible to take either an optimistic or a pessimistic view of the bill's effect on research on drugs liable to abuse.

An *optimist* who assumes there will always be a benign and science-oriented Attorney General and a sensitive, flexible, research-oriented staff of the Bureau of Narcotics and Dangerous Drugs would paint the following picture:

Two excellent sections in the bill give the Attorney General the right to assure investigators full confidentiality for their research data involving human subjects and permit him to enable investigators to do research with controlled drugs even in states where law might prevent this. The provisions would enable the Attorney General to improve substantially the status of both sociologic and pharmacologic research on drugs of abuse. The staff of the Department of Justice could ensure that all investigators were registered to use appropriate drugs for research rapidly and with a minimum of red tape and could ensure that adequate quantities of drugs not currently used for medical purposes were made available for research. Given an adequate budget, the bill would even permit the Department of Justice to support a good deal of research on drugs of abuse under the contract mechanism.

A *pessimist* would paint the following picture:

The Department of Justice, which has absorbed the Bureau of Narcotics (*not* widely known for its permissiveness in the research area), could essentially stifle research in drugs of abuse by denying registration to qualified investigators on the grounds that their research was not in the public interest.

The public interest is so broadly defined as to make almost anyone's research capable of being suppressed. The Attorney General can suppress all research with drugs such as heroin, marijuana, and LSD by simply preventing their manufacture or preparation. He designates the amounts of such drugs which can be made; the amount can, obviously, be zero. Such projects as were allowed to proceed could be harassed by frequent inspections of all records. The Attorney

* 4 *Hospital Tribune* 1, 9 (February 23, 1970). Reprinted by courtesy of *Hospital Tribune*.

General would even have the right, with a court's acquiescence, to break and enter the investigator's premises to make sure that no drugs were being diverted illicitly. All in all, the bill provides power by which most research could be brought to a screeching halt.

Unenthusiastic administration of mildly restrictive regulations could in itself discourage a good many investigators from working in this area. Further, the red tape and bureaucratic harassment could extend to drugs such as the amphetamines and minor tranquilizers not currently covered in any such restrictive manner under existing laws.

In short, the bill has potentialities for both considerable good and great harm to research. This makes me very apprehensive. I would like to see it rewritten in such a way that an unbiased group of nongovernmental scientists selected in a manner outside the control of the Department of Justice had the major say in all matters dealing with research on these drugs. Such controls would be best set up under the Department of Health, Education, and Welfare, an agency likely to be more responsive to the needs of the medical and scientific community than the Department of Justice. I would also like to see the section giving the Attorney General the power to support contract research in the area of drug abuse more tightly written, so that only research directly applicable to his enforcement mission was authorized. I would also like to see built into that part of the law a provision that outside scientific review groups be used in screening such contract proposals in a manner similar to that currently employed at the National Institutes of Health.

* * *

... I view with real alarm the vesting in the Department of Justice of such major power over medical research and medical practice. I know of no evidence that either area is responsible for more than an infinitesimal fraction of the current drug-abuse problem. An enforcement mission focused on major illicit sales of really dangerous drugs seems to me to be the legitimate mission of a Department of Justice. Medical and research issues belong in the Department of Health, Education, and Welfare. The major need for much more research on drug abuse makes it necessary that research with drugs of abuse not be discouraged by bureaucratic systems.

NOTE 2.

DANIEL X. FREEDMAN
THE COST OF SILENCE NOW*

In December, 1968, the American Psychiatric Association publicly warned of dangers lurking in the early drafts of the Administration's drug-abuse control bill. That statement urged increased support to provide skills and programs to combat epidemics of drug abuse and stated that the separation of needed enforcement measures from health-related research and education was imperative.

The statement also noted that research and education conducted under the direction of the Bureau of Narcotics and Dangerous Drugs would not be likely to compel confidence or belief. Education and *not* propaganda, facts and *not* distortions, are the powerful and credible means of assessing the dangers of drugs and dealing with the anguish and confusion of parents and youth.

What provoked the 1968 statement? It was not the commendable effort of the Narcotics Bureau to coordinate drug law enforcement. It was, I think, the bureaucratic impulse to extend the stranglehold of former Commissioner Anslinger on "narcotics" to many other drugs—an approach of wielding vague threat and legal authority—which for 40 years stifled and distorted research, information, and innovative medical treatment.

What began in the summer of 1968 as an attempt of Justice Department agents to merely codify complex drug regulations has—after a year and a half—revealed a history of bureaucratic intransigence if not slyness. In the process the BNDD has documented its contempt for relevant advice and expertise while endowing itself with sweeping powers.

These new powers are not simply the authority to prosecute drug abusers and traffickers. Rather, there is *new* power to initially and finally decide—to judge—with respect to a wide range of commonly used and therapeutically valuable drugs: (1) acceptable medical practice; (2) acceptable medical research; (3) who is competent to conduct this. The essential new power is to adjudicate the abuse potential and medical usefulness not only of old but of newly discovered substances and the conditions under which they may be used—not only in everyday medical

* 4 *Hospital Tribune* 7 (March 9, 1970). Reprinted by courtesy of *Hospital Tribune*.

practice, but for any conceivable kind of scientific investigation.

* * *

The unwritten tale of the consequences of the Administration bill should be heard. If passed, it *will* be! The fact that 35 per cent or more of legal prescriptions are for the drugs covered in this bill indicates the extent to which legitimate medical practice is covered. With the vague wording and legal twists and turns in the bill, potential dangers do indeed exist. The fact that a patient's confidential records can be available for inspection, even though his pill may be a mild tranquilizer or sedative, should alert all patients and physicians. The bathroom cabinet as well as the street are in the scenario in which we can see future action!

* * *

What is tragic, then, is that apparently a large segment of the practice of medicine and the advancement of badly needed knowledge is being politicized. In fact, we should strive to keep matters of public health in sane focus, to use the best instruments with which Western civilization has endowed us to arrive at informal decisions.

Health professionals, pharmaceutical specialists, and experts in drug-abuse education should have been brought together with experts in governmental administration, regulatory practices, and law enforcement to review the entire complex issue of the manufacture and distribution of medicinals and the appropriate measures to combat illicit diversion and criminal use. It is clear that this will eventually have to be done—perhaps by the National Academy of Sciences.

* * *

[ii]

United Nations

*Draft Covenant on Civil and Political Rights**

* * *

3. Article 7 of the draft Covenant on Civil and Political Rights, as submitted by the Commission on Human Rights reads as follows:

No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one

shall be subjected without his free consent to medical or scientific experimentation involving risk, where such is not required by his state of physical or mental health.

* * *

Amendments Submitted

* * *

6. The amendment of the Netherlands called for the deletion of the words: "involving risk, where such is not required by his state of physical or mental health" from the second sentence.

7. The amendment of Pakistan consisted in replacing the full stop after the words "treatment or punishment" by a comma and in replacing the words "In particular, no one shall be" by the words "or even." At the 854th meeting, the representative of Pakistan withdrew the amendment.

8. The Philippine amendment called for the insertion of the word "unusual" between the words "inhuman" and "or degrading" in the first sentence. The representative of the Philippines withdrew this amendment at the 853rd meeting.

9. The Ecuadorian amendment consisted in the deletion of the words "involving risk" from the second sentence. The representative of Ecuador withdrew this amendment at the 853rd meeting, on the understanding that a separate vote would be taken on the words "involving risk" in the Netherlands amendment.

10. The amendments of Guatemala called for:

(1) The amendment of article 7 to read as follows:

No person shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment.

(2) The insertion of an additional article reading as follows:

Article 8. No person shall be subjected without his free and spontaneous consent to medical or scientific experimentation. Medical experimentation shall not be permitted in the case of a person who is incapable of giving his free and spontaneous consent, unless the main and essential purpose of the experimentation is the restoration of the physical and mental health of the said person and in that case the consent shall be obtained from those persons who in accordance with the law of the coun-

* Report of the Third Committee, Doc. A/4045.
13 *United Nations General Assembly Official Records, Annexes, Agenda Item No. 32 (1958).*

try concerned are the legal representatives of the person who is incapacitated from giving his consent.

The subsequent articles were to be renumbered accordingly.

At the 853rd meeting, the representative of Guatemala withdrew these amendments.

11. The Australian amendment called for the replacement of the full stop after the word "punishment" by a comma and the replacement of the text thereafter by the following words: "and in particular no one shall be subjected to such treatment in the form of medical or scientific experimentation."

12. The revised amendment of Greece and Italy called for the replacement of the second sentence by the following: "No one shall, *inter alia*, be subjected without his free consent to medical or scientific experimentation."

13. Canada submitted a sub-amendment to the revised amendment of Greece and Italy replacing the words "No one shall, *inter alia*, be subjected" by the following: "*Inter alia*, no one shall be made to undergo any form of torture or cruel treatment by being subjected." The representative of Canada accepted a suggestion by the representative of Ireland to the effect that the words "inhuman or degrading" should be inserted between the words "cruel" and "treatment."

14. The representative of Mexico re-introduced the original amendment of Greece and Italy submitting it as a sub-amendment to the revised text. The original Greek-Italian amendment consisted in the replacement of the second sentence of the article by the following text:

No one shall be made to undergo any other form of torture or cruel treatment by being subjected without his free consent to medical or scientific experimentation when such experimentation is not required by his state of physical or mental health.

At the 855th meeting, the Mexican representative withdrew this sub-amendment.

15. The word "unusual" proposed in the Philippine amendment gave rise to some discussion. It was argued that while cruel, degrading and inhuman treatment or punishment might be "unusual," the converse was not necessarily true. The amendment was supported by some representatives who felt that it might be applicable to certain actual practices which, although not intentionally cruel, inhuman or degrading, nevertheless affected the physical or moral integrity of the human person. On the other hand, it was

objected that the term "unusual" was vague. What was "unusual" in one country might not be so in other countries.

16. Most of the discussion centered on the second sentence. Some felt that the sentence was unnecessary, since what it sought to prohibit was already covered by the first sentence. Moreover, it weakened the article in that it directed attention to only one of the many forms of cruel, inhuman or degrading treatment, thereby lessening the importance of the general prohibition laid down in the first sentence. On the other hand, most representatives attached special importance to the second sentence which, they pointed out, was intended to prevent the recurrence of atrocities such as those which had been committed in Nazi concentration camps during the Second World War. In their view the second sentence, far from being superfluous, seemed to complement the provisions of the first.

17. Several suggestions were made with a view to meeting the objection that the second part of the article was emphasized at the expense of the first. One was to replace the words "in particular" in the second sentence by the words "*inter alia*," as proposed by Greece and Italy. Others thought that the substance of the second sentence might be embodied in a separate paragraph or, as proposed by Guatemala, in a separate article. However, these proposals were opposed by those who regarded the first and second sentences as closely linked and wished, therefore, to preserve the unity of the article. The amendment of Pakistan sought to resolve the difficulty by combining the two clauses of the article in a single sentence, thereby making the act covered in the second clause an addition to that covered in the first. The main objection to this amendment was that it weakened the second clause. As the debate developed, it became apparent that there was wide agreement that the second sentence should be retained. Some representatives, however, felt that, as drafted, it lacked precision and clarity. The main problem was how to find a formulation which, while outlawing criminal experimentation, would not hinder legitimate scientific or medical practices. There was general agreement that the Covenant should not attempt to lay down rules concerning medical treatment, as that was a matter which should be left to national legislation and the medical profession.

18. One approach to the problem, exemplified by the Australian amendment was to limit explicitly the scope of the provision to scientific and medical experimentation which constituted

torture or cruel, inhuman or degrading treatment. However, the Australian proposal was opposed on the grounds that, by not referring to "free consent," it failed to provide a satisfactory criterion for determining whether a given experiment was of the prohibited type or not. It was also pointed out that the proposed text sought to cover only experiments of a cruel, inhuman or degrading nature, while permitting other experiments conducted without the consent, or even the knowledge, of the subject.

19. Another approach, proposed by the Netherlands, was simply to eliminate from the text any references to legitimate medical practices. It was pointed out that the term "experimentation" did not cover medical treatment required in the interest of the patient's health. Hence, the clause "where such is not required by his state of physical or mental health" should be deleted, as it only served to confuse the meaning and intent of the provision by implying that medical or scientific practices having the welfare of the patient in view came within its scope. A similar approach was proposed by Greece and Italy in their revised amendment, except that the words "in particular" were to be replaced by "*inter alia*." However, several representatives preferred the term "in particular," since it linked the second sentence to the first more closely, making it clear that what was referred to was medical or scientific experimentation which amounted to torture or cruel, inhuman or degrading treatment.

20. Some doubts were raised as to the desirability of retaining the words "without his free consent" if the intention of the provision was solely to prohibit criminal experimentation. It was argued that the words were not only redundant, but might open the door to abuses in that it would be possible to justify experimentation of a criminal nature on the pretext that the subject had given his "consent." Such practices should be forbidden even if undertaken with the free consent of the subject. In reply, it was argued that consent given under pressure could never be regarded as "free" consent. It was unthinkable that anyone would freely submit himself to torture or cruel, inhuman or degrading practices. The introduction of the notion of "free consent" provided not only a safeguard, but also a criterion for determining whether an experiment was legitimate or not. Certain kinds of treatment became cruel, inhuman or degrading only because they were administered without the subject's free consent.

* * *

Text as Adopted

22. Article 7, as adopted by the Committee, reads as follows:

No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.

NOTE

WALTER MODELL HAZARDS OF NEW DRUGS*

No drug, no matter how thoroughly tested by time or trial, is absolutely safe. The size of the problem is indicated by a report in the *Journal of the American Medical Association* that one of every 20 patients admitted to a large hospital in New York City was there because of adverse reaction to treatment. Serious reactions occur with all therapies—the safe as well as the hazardous, the useful as well as the useless, the old as well as the new, the folk remedy as well as the modern miracle drug. What seems an innocent therapeutic procedure may have serious unanticipated effects. . . . Nothing must be accepted at face value in modern medicine; modern proof by modern standards is essential. The thoroughgoing scientific experiment and the scientific attitude are the only safeguards against the specter of drug disaster.

The aim with all new therapies is to establish a more favorable ratio between probable adverse effect of treatment and probable adverse effect of untreated disease. Testing new drugs involves developing and pursuing the most effective methods for determining therapeutic effectiveness and reaction hazard. Only with tested drugs is there an index of danger of adverse reaction and of potential for therapeutic usefulness. If the information is substantial, one can elect to use the drug on the basis of a calculable risk; without such information one has no way of knowing whether the clinical use of the new drug is defensible.

* * *

Obviously, testing should be conducted with minimum risk to the subject, but since there is no drug without hazard, there can be no testing of new drugs without risk. The justification for

* 139 *Science* 1180 (1963). Copyright 1963 by the American Association for the Advancement of Science. Reprinted by permission.

taking this risk is that without it there can be no reasonable basis for introducing and using new drugs, and that the danger involved in using them clinically without such testing would be greater than the danger involved in preclinical testing. Therefore, society must recognize that in its demand for new drugs there is clearly implicit a license for qualified individuals to take calculable risks in using them clinically. Medical science is obligated to keep these risks within reasonable limits. But both the medical profession and society in general must be fully aware of the potentiality of drugs to produce disaster.

(iii)

*Ninety-first Congress, Second Session
An Act to Promote Public Health and
Welfare by Expanding, Improving, and
Better Coordinating the Family Planning Services
and Population Research Activities of the
Federal Government, and for Other Purposes**

* * *

SEC. 2. It is the purpose of this Act—

(1) to assist in making comprehensive voluntary family planning services readily available to all persons desiring such services;

(2) To coordinate domestic population and family planning research with the present and future needs of family planning programs. . . .

* * *

(8) to establish an Office of Population Affairs in the Department of Health, Education, and Welfare as a primary focus within the Federal Government on matters pertaining to population research and family planning, through which the Secretary of Health, Education, and Welfare (hereafter in this Act referred to as the "Secretary") shall carry out the purposes of this Act.

* * *

SEC. 6. . . .

(c) The Public Health Service Act is . . . amended by adding after title IX the following new title:

**TITLE X—POPULATION RESEARCH
AND VOLUNTARY FAMILY PLANNING
PROGRAMS**

*Project Grants and Contracts for Family
Planning Services*

* Act of December 24, 1970, Pub. Law No. 91-572, 84 Stat. 1504; see 42 U.S.C. § 201 (1971).

SEC. 1001. (a) The Secretary is authorized to make grants to and enter into contracts with public or nonprofit private entities to assist in the establishment and operation of voluntary family planning projects.

(b) In making grants and contracts under this section the Secretary shall take into account the number of patients to be served, the extent to which family planning services are needed locally, the relative need of the applicant, and its capacity to make rapid and effective use of such assistance.

(c) For the purpose of making grants and contracts under this section, there are authorized to be appropriated \$30,000,000 for the fiscal year ending June 30, 1971; \$60,000,000 for the fiscal year ending June 30, 1972; and \$90,000,000 for the fiscal year ending June 30, 1973.

* * *

SEC. 1004. (a) In order to promote research in the biomedical, contraceptive development, behavioral, and program implementation fields related to family planning and population, the Secretary is authorized to make grants to public or nonprofit private entities and to enter into contracts with public or private entities and individuals for projects for research and research training in such fields.

(b) For the purpose of making payments pursuant to grants and contracts under this section, there are authorized to be appropriated \$30,000,000 for the fiscal year ending June 30, 1971; \$50,000,000 for the fiscal year ending June 30, 1972; and \$65,000,000 for the fiscal year ending June 30, 1973.

* * *

SEC. 1007. The acceptance by any individual of family planning services or family planning or population growth information (including educational materials) provided through financial assistance under this title (whether by grant or contract) shall be voluntary and shall not be a prerequisite to eligibility for or receipt of any other service or assistance from, or to participation in, any other program of the entity or individual that provided such service or information.

SEC. 1008. None of the funds appropriated under this title shall be used in programs where abortion is a method of family planning.

NOTES

NOTE 1.

MARTI MUELLER
ORAL CONTRACEPTIVES—
GOVERNMENT-SUPPORTED PROGRAMS
ARE QUESTIONED*

Last year a VISTA volunteer in Alaska watched in dismay as an Eskimo woman being treated in a federally financed birth-control center was handed a sack of oral contraceptives, given no counseling on how to take them, and told to come back in a year.

At a time when questions are being raised about the safety of the pill, the federal government has become one of the major distributors of the oral contraceptive in family-planning programs for the poor. Some doubts have been expressed about how safely these programs are administered. Officials within the Food and Drug Administration (FDA) have suggested in the past, for example, that its parent, the Department of Health, Education, and Welfare (HEW) has been lenient in monitoring side effects and adverse reactions to the pill and in supervising general medical health standards in its own programs. One reason for such shortcomings, if they exist, may be that, while HEW programs are federally financed, many are administered on the local level by states, cities, and private organizations, and, as former HEW Assistant Secretary Philip Lee has said, "in many cases we are buying into the existing program."

Lee also commented to *Science* that the quality of care for the poor in the United States is well below what it should be. "We thought we were doing much better than we are doing," Lee said. "The poor were not getting adequate care, either therapeutic or diagnostic." Lee . . . estimates there are 5 million women of childbearing age at or below the poverty level in the United States. He told *Science* that giving medically supervised family-planning guidance to the entire 5 million would cost about \$30 per woman, or about \$150 million in all. (This year Congress appropriated about \$50 million for birth control programs for the poor, which now serve about a million women.) . . .

* * *

HEW officials deny that a physician has any direct responsibility to HEW to submit a report

* 163 *Science* 553-554 (1969). Copyright 1969 by the American Association for the Advancement of Science. Reprinted by permission.

on adverse drug reactions. Lee sees the problem as a jurisdictional one. He feels, in effect, responsibility for monitoring medical practices belongs to the American Medical Association; Lee, a physician, says HEW must rely on the built-in systems of peer review to ensure that physicians practice medicine responsibly. Others feel this is an uncertain means of ensuring safety, particularly in government-supported family planning. . . .

* * *

NOTE 2.

USSR PICKS IUD OVER THE PILL*

Spurred by a spiraling abortion rate and by citizens' demands for modern contraceptives, the Soviet Union has launched a major birth control program. Soviet health leaders have given their official blessing to intrauterine devices as the basis of the new effort. Other methods will also be made available, though free choice of contraceptives is not being encouraged.

More than 300,000 IUDs have already been produced in the Soviet Union, reports Dr. Boris Petrovsky, Minister of Public Health. He estimates that the total output this year will reach one million. Among the Soviet Union's population of 230 million are about 55 million women of childbearing age.

* * *

Until now, abortions, legal since 1955 and costing the equivalent of \$5.50, have been the most common method of preventing unwanted births. But assembly-line abortions have been widely criticized for medical and psychological reasons.

Up to now, Soviet couples have also been able to obtain three types of contraceptives from Soviet pharmacies: a condom, a spermicidal jelly, and a suppository—all of limited effectiveness.

Dr. Petrovsky said his government's decision to mass-produce IUDs was based on experience gained from other countries—and on their own three-year comparative studies of the IUD and the pill. These were conducted by the Soviet Academy of Medicine's Scientific Research Institute of Obstetrics and Gynecology and the Public Health Ministry's All-Union Scientific Research Institute of Obstetrics and Gynecology.

* *Medical World News* 16-18 (January 10, 1969). Copyright 1969, McGraw-Hill, Inc. Reprinted by permission.

Dr. Leonid Persiyaninov, director of the Academy of Medicine's ob-gyn institute, called the IUD the "lesser of two evils." Soviet research showed that both methods were more than 90 percent effective, Dr. Persiyaninov said, so that the decision to mass-produce IUDs over pills was based primarily on differences in side effects.

* * *

Despite judgment against the pill, research on it and limited clinical trials will be carried out in the Soviet Union. The Russians plan to continue importing from Hungary a hormonal preparation called *Infecundin*. And they are reportedly tooling up for production of a progestogen-estrogen preparation similar to a U.S. brand.

[T]he recent Soviet decision to mass-produce IUDs fits in with their generally conservative approach to medicine. "They favor a mechanical device over a chemical one because its effects are limited to the uterus. But they do not want to miss out on something that might prove to be better, so they are proceeding cautiously in many directions. Meanwhile, the Western world is their guinea pig for the pill."

* * *

Dr. George Langmuir, medical director of Planned Parenthood, sees another factor behind the Soviet choice of the IUD over the pill. Abortion is legal in the Soviet Union, he emphasizes, so a contraceptive need not be 100 percent effective. The Russian approach to contraception may parallel what has occurred in Sweden, he suggests. Both countries practice conservative medicine and sanction abortions, though far fewer are performed in Sweden. Swedes use mechanical means of contraception most often, and only a small number of prescriptions are filled for the pill.

* * *

[iv]

*United States Congress
A Bill to Provide for Humane Treatment of
Animals Used in Experiment and Research by
Recipients of Grants from the United
States, and by Agencies and Instrumentalities
of the United States, and for Other Purposes**

[I]t is declared to be the policy of the United States that animals used in experiments, tests, the teaching of scientific methods and techniques, and

the production of medical and pharmaceutical materials shall be spared avoidable pain, stress, discomfort, and fear, that they shall be used only when no other feasible and satisfactory method can be used to obtain necessary scientific information for the cure of disease, alleviation of suffering, prolongation of life, or for military requirements, that the number of animals used for these purposes shall be reduced as far as possible, and that all animals so used shall be comfortably housed, well fed, and humanely treated.

SEC. 2. As used in this Act—

(1) The term "animal" means any living creature of any vertebrate species;

(2) The term "stress" means the effect of any condition of housing, diet, climate, confinement, care or use unsuitable to the species or to the particular animal, or differing from its ordinary and normal mode of life, to a degree which produces physical deterioration in any respect or markedly a typical conduct or reaction, or which, if prolonged, would have a tendency to produce either of the above aberrations from normal condition or reaction;

(3) The term "pain" means any sensation which, if felt by a human being, a competent and conscientious physician would ordinarily take steps to relieve, by anesthesia, sedation, nursing care, or otherwise;

(4) The term "substitution" means the use in any research project, test, demonstration, or production procedure of a less highly developed species of animal for species more highly developed, the development to be evaluated on the basis of the brain and nervous system of the species, in terms of its elaboration and sensitivity to pain;

(5) The term "reduction" means the use of a reduced number of animals, by means of the application of statistical techniques, use of insentient material or models, or any other method;

* * *

SEC. 3. There is hereby established in the Department of Justice of the United States an Agency for Laboratory Animal Control (hereinafter in this Act referred to as the "Agency"). The Agency shall be headed by a Commissioner of Laboratory Animal Control, who shall be appointed by the President of the United States, by and with the advice and consent of the Senate. To be eligible for appointment as Commissioner, a person must be an attorney eligible for admission to practice before the Supreme Court of the United States.

* H.R. 3036; 111 *Congressional Record* 831 (1965).

SEC. 4. After the one hundred and eightieth day following the date of enactment of this Act, no agency or instrumentality of the United States shall use any animal for research, experiments, tests, training in scientific or technical procedures, or production of materials unless the agency or instrumentality has been granted a certificate of compliance with this Act, issued by the Commissioner for Laboratory Animal Control.

* * *

SEC. 8. No certificate of compliance shall be issued by the Commissioner unless the laboratory applying for such certificate shall have agreed, in writing, that authorized representatives of the Commissioner and law enforcement officers of the State in which the laboratory operates shall be given access at any time to the animals, premises, and records of the laboratory, for the purpose of obtaining information relevant to the administration and enforcement of this Act: except that no laboratory shall be required to permit access to any person not duly cleared for such access with respect to any materials or area which is restricted pursuant to any law of the United States relating to the national security.

SEC. 9. No use of animals shall be undertaken by any holder of a certificate of compliance with this Act until a project plan has been filed with the Agency in such form as the Commissioner shall prescribe, describing the nature and purposes of the proposed use of animals, and the project plan has been approved by the Commissioner. The Commissioner shall refuse to approve a project plan that would not comply with this Act and the policies enunciated herein.

SEC. 10. The Commissioner shall upon application issue a letter of qualification to use animals in research to persons having all of the following qualifications:

(1) the applicant has been awarded a doctoral degree in medicine, veterinary medicine, physiology, psychology, or zoological science by an accredited university or college;

(2) the applicant has never been convicted of cruelty to animals or been found by the Commissioner to have participated knowingly in a violation of this Act;

* * *

SEC. 12. Every laboratory holding a certificate of compliance, and every agency or in-

strumentality of the United States that uses animals in research, experiments, tests, training in scientific procedures, or technique, or the production of materials, shall comply with the following requirements:

(1) all projects shall be designed and executed so as to obtain maximum reduction and substitution;

(2) animals used in any way that would cause pain shall be anesthetized so as to prevent the animals from feeling pain during the experiment or procedure, except that the Commissioner may waive this requirement for a specified project if the Commissioner, with the concurrence of the Surgeon General, finds that anesthesia would frustrate the purpose of the project;

(3) no unanesthetized animal shall be burned, scalded, or subjected to major surgery or to any similarly acutely painful procedure;

(4) regardless of the nature or purpose of any experiment or procedure, animals that would suffer prolonged pain or stress as a result of an experiment or procedure shall be painlessly killed immediately after the procedure causing pain or stress is completed, whether or not the objective of the experiment or procedure has been attained;

(5) animals used in surgery or other procedures causing pain or stress shall be given pain-relieving care and convalescence conditions substantially equal to those customarily or usually given to human patients before, during, and after similar procedures;

* * *

(9) all premises where animals are kept shall provide a comfortable resting place, adequate space and facilities for exercise normal to the species, sanitary and comfortable cleanliness, and lighting, temperature, humidity, and ventilation appropriate to the species;

(10) animals shall receive food and water adequate to maintain health and comfort and shall not be permitted to suffer pain or stress through neglect or mishandling;

(11) an accurate record shall be maintained of all experiments and procedures performed and the records shall be in such form as to make possible the identification of animals subjected to specified experiments and tests, and a record shall be kept of the disposition of all animals;

(12) all cages or enclosures containing animals shall at all times be identified by cards stating the nature of the experiment or test in progress and identifying the project approved by the Commissioner;

(13) an annual report and such additional reports or information as the Commissioner may require by regulation or individual request shall be submitted to the Commissioner. The annual report shall specify, for each project plan previously filed and approved, the number and species of animals used, the procedure employed, the sources from which all animals were acquired, and such matters as the Commissioner may prescribe, and shall include a copy of any published work prepared or sponsored by the reporting person or laboratory, involving the use of animals;

* * *

SEC. 14. The Commissioner shall suspend or revoke any certificate of compliance or any letter of compliance issued pursuant to this Act upon a determination on the record after opportunity for an agency hearing of failure to comply with any provision of this Act or the policy stated herein or for refusal to permit inspection or to produce records pursuant to the agreement required in section 8. . . .

d.

Deciding about Choice of Subjects?

[8]

*United States Congress
A Bill for the Regulation of Scientific
Experiments upon Human Beings in the
District of Columbia**

SEC. 1. [No] physician, surgeon, pathologist, student of medicine or of science, or any other person shall make or perform upon the body of any human being, in any hospital, asylum, retreat, or infirmary established for the treatment of the sick, or in any other place in the District of Columbia, any scientific experiment involving pain, distress, or risk to life and health, whether by administration of poisonous drugs for the purpose of ascertaining their toxicity, by inoculating the germs of disease, by grafting cancerous tumors into healthy tissues, or by performance of any surgical operation for any other object than

the amelioration of the patient, except subject to the restrictions and regulations hereinafter prescribed. Any person performing, advising, or assisting in the performance of any such experiment upon any newborn babe, pregnant woman, lunatic, idiot, or patient, in any public or private hospital, in any infants' home, hospital asylum, or private house, or upon any other person whatsoever, shall be deemed guilty of the crime of human vivisection, and upon conviction shall be liable to a fine of not less than one thousand dollars or imprisonment for not less than one year, or both. If any such experiment shall be followed within forty-eight hours by the death of the person thus operated upon, or if it shall appear that death was accelerated in any way by such experiment, the performance of any such experiment shall be deemed manslaughter or murder, as the circumstances of the case shall determine; and all persons taking part therein shall be liable to the penalties prescribed for such crime.

SEC. 2. That any physician or surgeon duly qualified to practice medicine in the District of Columbia, or any medical student, who shall perform any such scientific experiment, or who by his advice or presence shall in any way assist, aid, or abet the performance of any such experiment, shall, upon conviction, be forever disqualified from the practice of medicine in the District of Columbia. Any person engaged in any capacity in the service of the United States Government or in any of its departments who shall perform, or by his presence, suggestion, or advice, aid or abet the performance of any such experiment upon a human being, shall, upon conviction, in addition to other penalties herein provided, be forthwith dismissed from Government service and be forever disqualified therefor.

SEC. 3. That any description or account of any such experiment upon a human being, printed or published in any scientific or medical periodical or book, or in any reputable newspaper, shall be deemed evidence demanding immediate inquiry into all the circumstances of the alleged crime, and, if corroborated by further evidence, shall be accepted as testimony in regard to the offense.

SEC. 4. That an experiment performed upon a human being with a view to the advancement by new discovery of physiological or pathological knowledge shall, if it involves pain or distress, be permitted only under the following restrictions:

(a) The experiment must be performed only by a duly qualified physician or surgeon

* S. 3424; 33 *Congressional Record* 2460 (1900).

holding such special license from the Commissioners of the District of Columbia as in this Act mentioned; and

(b) The subject of such experiment must be not less than twenty years of age and in full and complete possession of all his or her reasoning faculties. No scientific experiment of any kind liable to cause pain or distress shall be permissible upon any newborn babe, infant, child, or youth; nor upon any woman during pregnancy nor within a year after her confinement, nor upon any aged, infirm, epileptic, insane, or feeble-minded person under any circumstances whatever.

(c) The physician or surgeon proposing to make any such experiment or series of experiments shall, at least one week in advance, apply to the Commissioners of the District of Columbia for license permitting such experiment or experiments to be performed. Such application shall fully state the objects and methods of the proposed experiments, and shall be accompanied with the written permission of the subject of the proposed experimentation, agreeing thereto, signed in presence of two witnesses and duly acknowledged before a public notary under seal.

(d) Upon receipt of such application, the Commissioners of the District of Columbia shall cause investigation to be made; and if it shall appear that the experiments involve no risk to human life; that the person offering himself or herself for experimentation is of requisite age, in full possession of all his or her reasoning faculties, and fully aware of the nature of the proposed experiment, and desires that it be made, then the Commissioners may issue a license authorizing such scientific experiment or series of experiments as desired; but

(e) No such experiment shall at any time be continued against the expressed will of the person experimented upon.

(f) The Commissioners of the District of Columbia shall require a report to be made to them of the methods employed and the results attained of each experiment or series of experiments thus made. Such report need not be made public until after six months from the beginning of the experimentation, in order to permit the investigator to present the results of his work in his own way. But in the event of any untoward circumstance attending any such experimentation, the full details shall immediately be reported and printed.

SEC. 5. That nothing in this Act contained shall be construed to prohibit or interfere with

any properly conducted method of medical treatment or surgical operation, whether experimental or otherwise, having for its demonstrable end and object the amelioration of suffering or recovery of the patient thus treated or operated upon.

SEC. 6. That nothing in this Act contained shall be construed to prohibit or interfere with any experiments whatsoever made by medical students, physicians, surgeons, physiologists, or pathologists upon one another.

[ii]

Sir John Eccles

*Animal Experimentation versus
Human Experimentation**

... It has been traditional that quite a lot of the experimentation related to medicine is done with human subjects. As we become more and more expert in applying experimental procedures to animals, in finding the right animals, and in carrying out these procedures under the appropriate scientific conditions, there will be progressively less necessity for human experimentation. We must try to diminish human experimentation as far as possible by substituting animal experimentation.

I think that no serious and hazardous experimental procedure should be done on humans unless it is quite impossible to carry them out on animals. Such a statement severely limits human experimentation. Furthermore, experimenting on humans in any way that involves risk, should be preceded by experiments on animals by which the technical procedures can be developed.

* * *

[W]e must plan to minimize human experimentation and maximize animal experimentation, and we must define quite rigorously the conditions under which human experimentation can be carried out. This is something that the societies concerned with animals, animal care, and animal experimentation should understand. They should recognize, moreover, how important animals are and how significant they are in minimizing human experimentation. The more effective

* *Defining the Laboratory Animal*. Washington, D.C.: National Academy of Sciences 285-292 (1971). Publication ISBN 0-309-01862-5, International Committee on Laboratory Animals and The Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council, Washington, D.C. Reprinted by permission.

tive animal research centers can become and the more facilities they can provide, the more they will be able to eliminate the really dangerous and damaging forms of human experimentation.

Let us also consider allowable forms of human experimentation. Many such experiments are quite without risk. For example, during the final three terms of physiology, which I taught from 1944 to 1951 at the medical school of the University of Otago, New Zealand, the students performed 85 percent of the total experiments on themselves. I had three three-hour courses on the systematic study of pain—muscle pain, skin pain, all kinds of inflammatory pains, and periosteal pain. Of course, a great many procedures like this can be performed on human subjects without any danger and with little discomfort. I designed these courses originally because we were so short of animals, and I discovered that it was far better to use the students as subjects. They investigated their own muscle contractions, stimulated their nerves and tested their reflexes. This experimentation can be effectively and appropriately done by medical students on themselves in order to give them some feeling for their eventual work in neurology. Similarly, excellent experiments on respiration and urinary secretion can be carried out on human subjects.

* * *

There are also advanced levels of experimentation that require human subjects. . . . a friend of mine subjected some volunteer medical students to an aseptic operation in which small cutaneous nerves in the forearm were dissected down until there was only a single fiber left. He was then able to test their sensory perceptions aroused by stimulating these single fibers in cutaneous nerves. I think this is about the limit to which one can ask students to participate!

* * *

In California today, Libet is doing most ethical and careful work on the sensations evoked in human subjects by varying the parameters of gentle electrical stimulation of the somesthetic area of the cerebral cortex. This work relates to some most interesting philosophical problems about how man actually derives conscious sensations from the complex patterned impulse transmission in the neural machinery of his brain. It is much more complicated than anybody had imagined. This type of investigation has to be done on human subjects who can report what they feel. But this is done only on vol-

unteers whose brains are exposed for the purpose of a therapeutic operation, for example in a patient suffering from Parkinsonism. It is explained to the patient that the experiment has nothing whatsoever to do with the therapeutic procedures. Nevertheless, almost all volunteer under those conditions to give half an hour of their time on the operating table unanesthetized.

* * *

There are, however, several problems relative to unethical human experimentation. For the most part such experiments are carried out by people who are loathe to use primates or by people who do not have the cost structure for primate investigations and are unwilling to ask for it. One such experiment involves chronically implanted electrodes in the human brain. In animals this is a marvelous technique. It is being employed at the National Institutes of Health with monkeys in which electrodes have been implanted in the various parts of the cerebral cortex and the cerebellum. With microelectrode recording the investigators study the responses of single nerve cells in the cerebrum and cerebellum while the animals carry out trained procedures of various kinds. It is beautiful work and can lead to new levels of understanding of the mode of action of the brain.

It does, however, require an immense cooperative effort, because the people involved must ensure that highly trained animals will be kept under the best conditions and be well nurtured. Under ideal conditions the animals can go on for many weeks or months learning and being experimented on. Animals can learn only when they are comfortable and happy, so such investigations demand highly skilled experimenters and technicians.

The value of this kind of work in understanding the nervous system is becoming more and more apparent. The more perfect animal experimentation can become, the more obvious it will be that no one should subject human beings to chronically implanted electrodes. Surprisingly, it is cheaper to do the experiment on human subjects. Patients come along with some kind of psychosis or neurosis, and the doctors say "Yes, now we have to study your brain more. We will have to drill some holes and put some things in." A cap is placed over the assemblage of implanted electrodes, and these people go about their work at home and so on, and come in every now and then for recordings from these electrodes.

I regard this work as quite unethical. Be-

cause of these buried implanted electrodes, the brain will never be the same and many people will suffer from epileptic seizures. Because this procedure is destructive, and not at all therapeutic, it is unethical. I do not countenance any destruction or damage to the brain under conditions that are not related to the therapeutic treatment of the patient. This kind of human experimentation should be stopped completely, and to remove the need for it, we must establish primate centers. The centers we have in this country are very good ones, but we need more facilities in primate centers, so no one will be tempted to do these unethical human experiments.

* * *

[T]he task facing the laboratory animal researcher is a tremendous one. It is one that will become greater in the future. It will become necessary to provide a much wider variety of animals for specific purposes. Certain problems in living organisms are best investigated with invertebrates, like the nerve impulse and synapse in squid or the ganglia of aplysia. So a wide variety of animals, an almost zoological collection, must be made available for research. This will provide a tremendous service not only in advancing biological and medical science, but also in saving humans from suffering the risks and the travail that come when unethical experiments are done upon them.

* * *

NOTE

DWIGHT E. HARKEN
HEART TRANSPLANTATION—
A BOSTON PERSPECTIVE*

* * *

Why . . . are human heart transplants *not* being performed at the Peter Bent Brigham? . . .

. . . In spite of extensive experience with the relatively reproducible surgical technics contributed by Shumway and Hanlon and others to make orthotopic transplants realistic, the vast majority of our animals die within 24 hours, often of unexplained causes, including atelectasis. Furthermore, although laboratories throughout the world have conducted *thousands of animal heart transplants*, there have been, to our knowl-

edge, but a trivial number of long-term survivors. Indeed, the most successful among these is Kantrowitz's puppy recipient of a littermate donor heart. This animal matured and bore puppies. Probably fewer than a dozen recipients of non-littermate canine transplants have survived for one year.

It becomes urgent that we have a clearer knowledge of the *incidence of survival* in cases of canine (and other) unselected orthotopic homotransplants; it is not enough simply to know that there can be long-term survival in animals of undetermined genetic constitution.

Experience with heart-lung machines taught us that *canine survival is not necessarily a prerequisite to human experiment*. However, much useful information could be obtained if we could achieve a significant number of long-term survivors, which is not consistently possible now. This fact becomes even more significant if we accept the likelihood that the rejection mechanisms are similar in dogs, rats and man.

* * *

[iii]

American Medical Association
*Ethical Guidelines for Clinical Investigation**

* * *

The following guidelines are intended to aid physicians in fulfilling their ethical responsibilities when they engage in the clinical investigation of new drugs and procedures.

- (1) A physician may participate in clinical investigation only to the extent that his activities are a part of a systematic program competently designed, under accepted standards of scientific research, to produce data which are scientifically valid and significant.
- (2) In conducting clinical investigation, the investigator should demonstrate the same concern and caution for the welfare, safety, and comfort of the person involved as is required of a physician who is furnishing medical care to a patient independent of any clinical investigation.
- (3) In clinical investigation *primarily for treatment*—
 - A. The physician must recognize that the physician-patient relationship exists and that he is expected to exercise his pro-

* 22 *American Journal of Cardiology* 449-450 (1968). Copyright 1968 by the Reuben H. Donnelly Corp. Reprinted by permission.

* *Opinions and Reports of the Judicial Council*. Chicago: American Medical Association 9-11 (1969). Reprinted by permission.

professional judgment and skill in the best interest of the patient.

- B. Voluntary consent must be obtained from the patient, or from his legally authorized representative if the patient lacks the capacity to consent, following: (a) disclosure that the physician intends to use an investigational drug or experimental procedure, (b) a reasonable explanation of the nature of the drug or procedure to be used, risks to be expected, and possible therapeutic benefits, (c) an offer to answer any inquiries concerning the drug or procedure, and (d) a disclosure of alternative drugs or procedures that may be available.

i. In exceptional circumstances and to the extent that disclosure of information concerning the nature of the drug or experimental procedure or risks would be expected to materially affect the health of the patient and would be detrimental to his best interests, such information may be withheld from the patient. In such circumstances such information shall be disclosed to a responsible relative or friend of the patient where possible.

ii. Ordinarily, consent should be in writing, except where the physician deems it necessary to rely upon consent in other than written form because of the physical or emotional state of the patient.

iii. Where emergency treatment is necessary and the patient is incapable of giving consent and no one is available who has authority to act on his behalf, consent is assumed.

- (4) In clinical investigation *primarily for the accumulation of scientific knowledge*—

A. Adequate safeguards must be provided for the welfare, safety, and comfort of the subject.

B. Consent, in writing, should be obtained from the subject, or from his legally authorized representative if the subject lacks the capacity to consent, following: (a) a disclosure of the fact that an investigational drug or procedure is to be used, (b) a reasonable explanation of the nature of the procedure to be used and risks to be expected, and (c) an offer to answer any inquiries concerning the drug or procedure.

C. Minors or mentally incompetent persons may be used as subjects only if:

i. The nature of the investigation is such that mentally competent adults would not be suitable subjects.

ii. Consent, in writing, is given by a legally authorized representative of the subject under circumstances in which an informed and prudent adult would reasonably be expected to volunteer himself or his child as a subject.

D. No person may be used as a subject against his will.

* * *

NOTES

NOTE 1.

DANIEL C. MARTIN, JOHN D. ARNOLD,
T. F. ZIMMERMAN, AND ROBERT H. RICHART
HUMAN SUBJECTS IN CLINICAL RESEARCH*

* * *

[This] study dealt with general opinions about volunteerism. Who should assume the risk as the experimental subject? This may well be the most pressing of all questions related to clinical research. Subjects from a wide range of socio-economic positions (154 in number) were asked their feelings about the human subject in medical research. These people were allowed to phrase their own answers without help from the interviewer. Their responses were subsequently arranged into classes and tabulated. The results are shown in Table 4.

The most pervasive tendency to be noted is the apparent reluctance of people from many socio-economic classes to suggest the use of the sick or dying as subjects in clinical research. Since this particular question was not pursued further, we do not know whether this set of answers might be altered if specific qualifications were appended to the original question. For instance, would the use of the sick or dying in chemotherapeutic research on cancer be more acceptable to respondents than our generalized proposal for "medical research"?

Although the scale of risks used in the previous . . . studies encompasses the majority of those to be encountered in human experimentation, it omits one of the extremes. We believe this extreme is presently represented by the problem of the single-organ transplant. . . .

* 279 *New England Journal of Medicine* 1426, 1429-1430 (1968). Reprinted by permission.

TABLE 4
Preferred Source of Volunteers

<i>Source</i>	<i>Frequency of Selection</i>	<i>Rank of Acceptability</i>
Anybody who is willing to volunteer	60	1
Prisoners	44	2
Don't know	17	3
People involved doing research	15	4
Institutions—mental, custodial, juvenile etc.	6	5
Sick or dying	6	5
Paid unemployed (welfare)	6	5
Total respondents	154	

The heart transplant requires the participation of two human experimental subjects. One subject must give up his heart. The other accepts the donated heart and its potential benefits. The once abstract, philosophical and academic considerations of "life" and "death" have become real.

The person who becomes the donor of a heart faces not a risk but a certainty—death, if this has not already occurred. How should this extreme "risk" be distributed in society? The other experimental partner receives potential benefit from the transplant procedure. How should this benefit be distributed in society? The investigators took these two questions to the community, using standard survey procedures.

* * *

It is obviously the donor who takes the extreme risk in the heart-transplant procedure. The results of this study indicate that the community continues to support the principle of voluntary participation. Seventy per cent of the respondents rank volunteers as the most preferred source of experimental donors. The sample population expressed once again the expectation that prisoners might become a prime source for experimental subjects. Prisoners about to be executed were specifically mentioned by a number of respondents who were given this as one of a number of possible choices. There appeared little enthusiasm in our in-depth interviews for use of the sick and dying as donors, although this may be the only large practical source of single organs for transplant. The sample population tended to consider factors outside the medical sphere in selecting both donors and recipients.

* * *

NOTE 2.

BRITISH MEDICAL RESEARCH COUNCIL MEMORANDUM ON CLINICAL INVESTIGATIONS*

* * *

To obtain the consent of the patient to a proposed investigation is not in itself enough. Owing to the special relationship of trust which exists between a patient and his doctor, most patients will consent to any proposal that is made. Further, the considerations involved are nearly always so technical as to prevent their being adequately understood by one who is not himself an expert. It must, therefore, be frankly recognized that, for practical purposes, an inescapable responsibility for determining what investigations are, or are not, undertaken on a particular patient will rest with the doctor concerned. Nearly always his judgment will be accepted by the patient as decisive.

Even in the routine case, where no question of special investigation arises, judgment may not be easy. At the frontiers of medical knowledge,

* Memorandum M.R.C. 53/649 (October 16, 1953). Reprinted by permission. In issuing their memorandum, members of the M.R.C. stated that "having recently undertaken wide responsibilities for the development of clinical research in this country . . . it would be opportune if they gave an indication of their attitude towards the considerations involved in carrying out investigations on patients. They are, therefore, circulating this memorandum to medical members of their staff and research workers in receipt of grants from the Council. Further, as this matter must be of concern to all responsible for the promotion of clinical research, the memorandum is also being sent, for information, to the Deans of Medical Faculties and Medical Schools, to the Secretaries of the Medical Scientific Societies, and to the Editors of the relevant scientific journals."

where many procedures are novel and their value to the individual patient may often be problematical, judgment is always difficult and decisions can be open to question. It is in these circumstances that doubt may be felt and views differ and that, inevitably, responsibility bears heavily on the clinical investigator.

* * *

NOTE 3.

KING HEALTH CENTER YOUR RIGHTS AS A PATIENT*

The patient has a right to consent to, or refuse, any treatment.

The patient has a right to have things explained clearly. (For example, any possible side effects of medicines.)

* * *

You have a right to refuse to participate in or be interviewed for research purposes. You have the right to full explanation of purposes and uses of the information if you do participate.

* * *

You have a right to know what's going on. Always ask questions about anything that you do not understand or that is worrying you.

* * *

e.

Deciding about Qualifications of Investigators?

Henry K. Beecher

*Tentative Statement Outlining the Philosophy and
Ethical Principles Governing the Conduct
of Research on Human Beings at the
Harvard Medical School†*

* * *

All of the so-called codes as guides to human experimentation emphasize the necessity that the experimenter be well trained and adequate as a scientist to undertake the study proposed. Medical research, when it involves treatment of any physical procedures beyond the simplest, requires that the investigator or his close associate be a qualified physician. No other pro-

fession gives such prerogatives and no other profession, probably, presents such a generally high level of unselfishness and compassion in directly caring for the sick or in planning procedures for the future. Of the qualities of the investigators, unselfishness is the most important for subject and project alike. Imagination, objectivity and the power to generalize soundly are all essential. In the forefront of the qualities which lead to protection of subject and patient in investigation is a deep sense of responsibility on the part of the investigator, coupled with unselfishness and a keen and well-trained intelligence. . . .

* * *

After some years of careful study of the available codes of the past which have been established to guide the medical investigator and after earnest attempts to write down a comprehensive code, the writer has had to conclude that it is not possible to lay down very many "rules" in terms of a code which can govern experimentation in man. In most cases these are more likely to do harm than good. Rules will not curb the unscrupulous.

* * *

It is the writer's point of view that the best approach concerns the character, wisdom, experience, honesty, imaginativeness and sense of responsibility of the investigator who, in all cases of doubt or where serious consequences might remotely occur, will call in his peers and get the benefit of their counsel. Rigid rules will jeopardize the research establishments of this country where experimentation in man is essential.

NOTES

NOTE 1.

NEW YORK EDUCATION LAWS (1970)

* * *

§ 6501. *Definitions.* . . . 4. The practice of medicine is defined as follows: A person practices medicine within the meaning of this article, except as hereinafter stated, who holds himself out as being able to diagnose, treat, operate or prescribe for any human disease, pain, injury, deformity or physical condition, and who shall either offer or undertake, by any means or method, to diagnose, treat, operate or prescribe for any human disease, pain, injury, deformity or physical condition.

* * *

* Bronx, N.Y.: Dr. Martin Luther King, Jr. Health Center 3-7 (1970). Reprinted by permission of Mr. Liery Wynn, Community Health Advocacy Office, Montefiore Hospital.

† Unpublished manuscript (undated). Printed by permission of the author who retains all rights.

§ 6502. *Qualification for practice.* No person shall practice medicine . . . unless licensed by the department and registered as required by this article. No person shall practice osteopathy or physiotherapy, unless licensed by the department and registered as required by this article. No person shall be licensed to practice under this article who has ever been convicted of a felony by any court, or whose authority to practice is suspended or revoked by the department. The conviction of felony shall be the conviction of any offense which if committed within the state of New York would constitute a felony under the laws thereof. If a person convicted of a felony is subsequently pardoned by the governor of the state where such conviction was had, or by the president of the United States, or if such a person shall receive a certificate of good conduct granted by the board of parole pursuant to the provisions of the executive law to remove the disability under this section because of such conviction, the regents may, in their discretion, on application of such person, and on the submission to them of satisfactory evidence, restore to such person the right to practice medicine, osteopathy or physiotherapy in this state.

* * *

§ 6506. *Admission to examination.* The department shall admit to examination any candidate who pays a fee of thirty dollars and submits evidence, verified by oath, and satisfactory to the department, that he: 1. Is more than Twenty-one years of age and a citizen of the United States or has declared his intention of becoming such citizen.

2. Is of good moral character.

3. Had prior to beginning the first year of medical study the preliminary general education required by the rules of the department, except where the application is for a license to practice osteopathy, in which case he must have had the general education required by the rules of the department preliminary to receiving the degree of doctor of osteopathy.

4. Has completed not less than four satisfactory courses of at least eight months each in a medical school in this country or Canada registered as maintaining at the time a standard satisfactory to the department, or in a medical school in a foreign country maintaining a standard not lower than that prescribed for medical schools in this state.

5. Has received the degree of bachelor or doctor of medicine from a medical school in this

country or Canada, registered as maintaining at the time a standard satisfactory to the department. . . .

* * *

NOTE 2.

CALIFORNIA HEALTH AND
SAFETY CODE (1970)

§ 1700. *Legislative findings.* The effective diagnosis, care, treatment, or cure of persons suffering from cancer is of paramount public importance. Vital statistics indicate that approximately 16 percent of the total deaths in the United States annually result from one or another of the forms of cancer. It is established that accurate and early diagnosis of many forms of cancer, followed by prompt application of methods of treatment which are scientifically proven, either materially reduces the likelihood of death from cancer or may materially prolong the useful life of individuals suffering therefrom.

Despite intensive campaigns of public education, there is a lack of adequate and accurate information among the public with respect to presently proven methods for the diagnosis, treatment, and cure of cancer. Various persons in this State have represented and continue to represent themselves as possessing medicines, methods, techniques, skills, or devices for the effective diagnosis, treatment, or cure of cancer, which representations are misleading to the public, with the result that large numbers of the public, relying on such representations, needlessly die of cancer, and substantial amounts of the savings of individuals and families relying on such representations are needlessly wasted.

It is, therefore, in the public interest that the public be afforded full and accurate knowledge as to the facilities and methods for the diagnosis, treatment, and cure of cancer available in this State and that to that end there be provided means for testing and investigating the value or lack thereof of alleged cancer remedies, devices, drugs, or compounds, and informing the public of the facts found, and protecting the public from misrepresentation in such matters.

The importance of continuing scientific research to determine the cause or cure of cancer is recognized, and the department shall administer this chapter with due regard for the importance of bona fide scientific research and the clinical testing in hospitals, clinics, or similar institutions of new drugs or compounds.

* * *

§ 1704. *Powers and duties of department of public health.* The department shall:

(a) Prescribe reasonable rules and regulations with respect to the administration of this chapter.

(b) Investigate violations of the provisions of this chapter, and report such violations to the appropriate enforcement authority.

(c) Secure the investigation and testing of the content, method of preparation, efficacy, or use of drugs, medicines, compounds, or devices proposed to be used, or used, by any individual, person, firm, association, or other entity in the state for the diagnosis, treatment, or cure of cancer, prescribe reasonable regulations with respect to such investigation and testing, and make findings of fact and recommendations upon completion of any such investigation and testing.

(d) Adopt a regulation prohibiting the prescription, administration, sale, or other distribution of any drug, substance, or device found to be harmful or of no value in the diagnosis, prevention, or treatment of cancer.

* * *

§ 1706. *Necessity of license for treatment of cancer by use of drugs, surgery, or radiation.* No person may undertake to treat or alleviate cancer by use of drugs, surgery, or radiation unless such person holds a license issued under a law of this State expressly authorizing the diagnosis and treatment of disease by use of drugs, surgery, or radiation.

* * *

§ 1708. *Exemptions from chapter.* This chapter shall not apply to the use of any drug, medicine, compound, or device intended solely for legitimate and bona fide investigational purposes by experts qualified by scientific training and experience to investigate the safety and therapeutic value thereof unless the department shall find that such drug, medicine, compound, or device is being used in diagnosis or treatment for compensation and profit. In order to qualify for an exemption under this section there shall be on file with the Federal Department of Health, Education, and Welfare a current and unrevoked investigational new drug application issued pursuant to Section 5051 of the Federal Food, Drug, and Cosmetics Act, or the following conditions shall be complied with:

(a) The label of the drug, medicine, compound, or device shall bear the statement "Caution: New drug (or medicine or compound or

device). Use in the diagnosis, treatment, alleviation, or cure of cancer limited by law to investigational use."

(b) The drug, medicine, compound, or device has had adequate testing on appropriate experimental animals to demonstrate a lack of toxicity and hazard sufficient to permit its use in or on human beings and to establish with clarity the margins of safety ordinarily recognized by experts qualified by scientific training and experience to investigate the safety and effectiveness of such drugs, substances or devices.

(c) The drug, medicine, compound, or device is to be used solely for investigational use by, or under the direction of, an expert qualified by scientific training and experience to investigate the safety and effectiveness of such drug, medicine, compound, or device.

(d) A written statement signed by the expert has been filed with the board. The statement shall show what facilities the expert will use for the investigation to be conducted by him, and that the drug, medicine, compound, or device will be used solely by him or under his direction for the investigation. The statement shall contain information identifying any assistant or agent of the expert who uses the drug, medicine, compound, or device under the direction of the expert.

(e) Complete records of the investigation shall be kept by the expert and all records shall be made available by the expert for inspection upon the request of any agent of the board at any reasonable hour as long as the expert desires exemption.

(f) The expert shall inform any persons who participate in the investigation as patients, that such drug, medicine, compound, or device is being used for investigational purposes and shall obtain the consent of such persons or their representatives.

NOTE 3.

RENÉE C. FOX
EXPERIMENT PERILOUS*

* * *

The facts that the hormones with which the Metabolic Group was experimenting had unanticipated negative side effects on patients and that they were proving to be ameliorative rather

* Glencoe, Ill.: The Free Press 19-20 (1959). Copyright 1959 by The Free Press. Reprinted by permission of the Macmillan Company.

than curative, along with their difficulties in keeping alive and managing the clinical course of patients who had undergone radical experimental surgery, account for many of the stressful problems which these research physicians faced at the time this study was made.

"Viewed from a few years later, we seem rather sophomoric," a member of the Metabolic Group commented when he read this book in manuscript. "In fact, we *were* young," he went on to say, "relatively inexperienced and enthusiastic, with less good judgment and more immediate goals than are probably ideal for clinical investigation". . . .

[T]he members of the Group were young. The oldest among them was thirty-four years of age, the youngest twenty-eight, and the majority (seven) between the ages of thirty and thirty-one.

The members of the Group were not only young chronologically. They were also in a relatively early phase of their professional careers. All had completed their internships and served as residents. Two members of the Group had Ph.D. degrees (one in Pharmacology, the other in Biochemistry). All had done some teaching, some research (for the most part, basic rather than clinical research), and (with the exception of one physician) each had published several articles before joining the Group. (Eight members of the Group had published two articles; one had published four; and the physician with a Ph.D. in Pharmacology had published twelve articles.) Only one member of the Group had spent any time in practice (one and a half years).

These physicians were all seriously interested in having a career in academic medicine which would combine "work with patients, teaching, and clinical research." However, although committed to an academic career in this general sense, they were less decisive about some of its more specific aspects. They did not know exactly what kind of balance between caring for patients, teaching, and research they wished to strike permanently; and they were not yet sure about the kinds of metabolic-endocrine problems they would most like to investigate. In fact, without exception, these young physicians looked upon their affiliation with the Group as an opportunity to "get excellent fundamental training, in a very stimulating environment, in the field of metabolic-endocrine disease . . . to learn how to do clinical research in this area . . . to see how [they] would like this sort of research . . . [and] on that basis to definitely decide how much of

[their] professional career [they] would devote to it."

One final distinguishing characteristic of the Group as a whole was that they were exceptionally competent, select young physicians who had been carefully chosen by the Professor of Medicine who was their Chief on the basis of their demonstrated and potential abilities as clinicians and investigators.

* * *

f.

Deciding about Delegation of Authority to Control, Review, and Reformulate the Process?

[i]

New York Assembly

*A Bill to Amend the Education Law, in Relation to Scientific Research on Human Subjects, to Provide for the Advancement of Such Research through the Protection of its Subjects, and to Establish a State Board on Human Research**

* * *

Section 7801. *Legislative findings and declaration of purpose.* 1. It is hereby found that research and experimentation that employs human subjects, properly planned and conducted, is essential to the progress of medicine, psychology, and other sciences related to human health and contentment. Accompanying the progress of such sciences has been an unprecedented increase in the number of researches and experimentation that employ human subjects. The protection of the subject of such research and experimentation is found to be wholly consistent with the progress of scientific investigation, and a system of regulation that advances both is found to be in the public interest.

2. It is the purpose of this article to provide for the establishment and continuing development of regulations to govern the conduct of research and experimentation employing human subjects, in accordance with legislative guidelines, and to protect the human subject by regular review committees established by the several research institutions in the state, and by the establishment of a state board on human research to exercise general supervisory control over and to regulate research and experimentation using

* A. 1837, introduced January 13, 1971, by Assemblyman Leonard P. Stavisky.

human subjects, to such an extent as may be necessary.

* * *

§ 7803. *Definitions.* 1. Board means the state board on human research established by this article.

2. Institutional committee means the institution research review committee established by this article.

3. Research institution means any corporation, association, or other organization, including but not limited to a hospital, university, laboratory, and institute, that conducts or is responsible for conducting, or on whose premises there is conducted any human experimentation or research.

4. Human experimentation or research means the physical, medical, or psychological manipulation of human subjects for the purpose of observation and collection of data, unrelated to the furnishing of medical or psychological services, including diagnosis or therapy, to such subjects.

5. Investigator means the person directing or supervising human experimentation or research.

6. Subject or human subject means a human individual who is subjected to manipulation in human experimentation or research.

§ 7804. *Scope.* This act shall regulate all human experimentation or research conducted in this State. No investigator or research institution shall conduct any human experimentation or research without compliance with the provisions of this act.

§ 7805. *State board on human research.* 1. There is established within the department of education a state board on human research, to consist of nine members appointed by the governor with the advice of the board of regents. The membership of the board shall include five members who are licensed physicians and psychologists or other professional persons with experience in human experimentation or research, and four members who include persons from non-scientific professional fields, such as social workers, teachers, and lawyers.* Members of the

board shall serve overlapping terms of three years; of the members first appointed, however, one-third shall serve for terms of one, two, and three years respectively. The governor shall designate the chairman.

2. The board shall meet at least once every three months and as often as necessary. A majority of the members shall constitute a quorum for the conduct of the board's business. The board shall keep a record of its proceedings. It shall make rules of procedure for its own conduct and for the calling of regular and special meetings upon notice.

3. Members of the board shall receive a per diem compensation of one hundred dollars and shall be reimbursed for actual and necessary expenses incurred in the performance of their duties.

4. The Board shall employ a staff director and, subject to applicable provision of the civil service law, a staff to assist it in the performance of its duties.

§ 7806. *State board on human research; regulations; guidelines for human experimentation or research.* The board shall make rules and regulations, and at its discretion amend or repeal the same, for the conduct of human experimentation and research, and for the operation of institutional research review committees. In making rules and regulations, the board may make reasonable classifications and may differentiate in the applicability of its rules and regulations between different kinds of human experimentation or research, and may make separate rules and regulations for different kinds of psychological, medical or other scientific investigation as it may deem appropriate. All of the rules and regulations made by the board shall, however, be guided by and be consistent with the following standards:

a) The informed consent of the human subject or his guardian or representative as specified hereinafter is essential. This means that the person providing consent must have the legal capacity or authority to give consent; must be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and must have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an

* The original draft of this bill, which was prepared by Prof. Frank Grad of Columbia University, included "representatives of the general public" as board members. See 169 *Annals of the New York Academy of Sciences* 542 (1970).

affirmative decision by the subject or other person having authority to consent there shall be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly result from the participation in the experiment.

b) The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

c) The experiment should be so designed and based whenever feasible or appropriate on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

d) The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

e) No experiment should be conducted where there is a prior reason to believe that death or disabling injury may occur.

f) The degree of risk taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

g) Proper preparations should be made and adequate facilities provided to protect the subject against even the most remote possibilities of injury, disability, or death.

h) The experiment should be conducted only by scientifically qualified persons.

i) Procedures should be established to allow the subject to terminate the experiment at any time if he feels that he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

j) The experimenter should be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of good faith, superior skill, and careful judgment that a continuation of the experiment is likely to result in injury, disability, or death to the subject.

§ 7807 *State board on human research; powers.* The board shall have jurisdiction over all human experimentation and research within the state. In pursuance of its jurisdiction, it shall have the following powers:

a) To review institutional rules for the con-

duct of human experimentation and research submitted to it by institutional committees, and to require changes or modifications in such rules;

b) To look into the conduct of any human experimentation and research, and to require the change or modification of the research design, or the suspension or termination of the human experimentation or research whenever the same fails to comply with the rules of the institutional committee, the rules and regulations of the board, or with the provisions of state or federal law or regulation, or when such research otherwise endangers the health and safety of the subjects.

c) To hold public hearings, conduct investigations, issue subpoenas and compel the attendance of witnesses; inspect research institutions; require the maintenance of adequate records by all investigators and research institutions, and to inspect and copy such records at all reasonable times in accordance with applicable legal provision governing such inspections.

d) To issue cease and desist orders for the protection of subjects and to take other measures to enforce the requirements of law and regulations, in accordance with the provisions of section 7809.

e) To issue advisory opinions with respect to proposed projects of human experimentation and research, or with respect to rules proposed by an institutional committee whenever requested to do so.

§ 7808 *Institutional research review committees; membership; powers and duties.* a) The chief administrative officer of a research institution shall establish an institutional research review committee to consist of no fewer than five and no more than fifteen members, to serve for fixed terms of not less than one year. The membership shall include at least two persons who are not scientists who engage in human experimentation or research, and such other persons as the board may require by rule or regulation. The committee shall take no action without the affirmative vote of a majority of its members. Each committee shall adopt its own rules of procedure.

b) Each institutional committee shall make rules for the conduct of human experimentation and research at the research institution. Such rules shall comply with the rules and regulations of the board and the requirements of law. The committee shall submit its rules to the board for review, but the research institute may operate

pursuant to such rules until the board has ordered that they be modified or changed.

c) Each institutional committee shall review all proposals for human experimentation and research at the research institution for compliance with its own rules, with the rules and regulations of the board, and with the requirements of law, and no human experimentation or research shall be undertaken at any research institute unless it has been approved by its institutional committee. The institutional committee should not review a proposal unless it has been submitted in writing, in such form as may be required. The committee may require a modification of the research design and may require an opportunity to review the actual conduct of human experimentation and research as a condition of its approval. The committee may also request an advisory opinion from the board before giving its approval.

d) The committee shall maintain full records of its proceedings and deliberations, and of all proposals, reports, and other papers submitted to it, which shall be open to inspection by the board at all reasonable times.

e) No member of an institutional committee shall review a proposal in which he is the investigator.

§ 7809 *Enforcement; review.* a) When a research institution, institutional committee, or an investigator violates any provision of this article or of any rule or regulation made pursuant thereto, the board may serve a written notice of complaint specifying the nature of the violation upon the violator, and setting a reasonable time for compliance. If the respondent fails to comply, the board shall require him upon proper notice to answer the complaint at a hearing before the board, or before any designated committee or hearing officer of the board. The respondent may file an answer, appear with counsel, and submit testimony, and may request the board to exercise its power of subpoena to compel the attendance of witnesses with the production of papers on his behalf. The board may also apply to the supreme court for its assistance in the appearance of witnesses and the production of evidence. Testimony taken at hearings before the board shall be under oath and shall be recorded. After hearing and considering all of the evidence offered, or upon default of the appearance of the respondent, the board shall make such a final determination or order as it may deem appropriate to assure the respondent's future compliance with law and regulations.

b) Any final determination or order of the board shall be subject to review pursuant to article seventy-eight of the civil practice law and rules.

c) The board may bring an action for an injunction to compel compliance with its orders. In any such action for injunction, any determination of the board shall be *prima facie* evidence of the facts found therein.

d) In an emergency situation, the board may issue cease and desist and other appropriate orders in advance of employing the procedures provided in this section.

e) Nothing contained in this section shall prevent the board from seeking to obtain compliance by such informal and non-coercive means as it may deem appropriate.

§ 7810 *Subject's consent; strict liability.*

a) No person's consent to become a subject shall be valid when there is a reasonable possibility that the particular human experimentation or research will result in death, serious injury, permanent or temporary physical impairment, or psychological injury.

b) Valid consent for an incompetent to become a subject may be given by his legal guardian if the human experimentation or research bears directly upon such incompetent's condition or disability.

c) Valid consent for a person under the age of eighteen years may be given by his parent or legal guardian only if there is no reason to believe that the human experimentation or research will result in physical or psychological injury or harm.

d) A written, witnessed statement is required for each subject as evidence of his consent. The statement shall include a written statement of the purposes of the experiment, the techniques to be employed, and the possible risks to the subject. Such statements are not conclusive evidence of consent and may be rebutted by other evidence or testimony of witnesses.*

* * *

* The draft bill further provided that: "e) Notwithstanding the valid and informed consent of a subject, the investigator and the research institution shall be absolutely liable, severally and jointly, for any damages resulting from any physical or psychological injury suffered by the subject in consequence of his participation in human experimentation or research." See 169 *Annals of the New York Academy of Sciences* 545 (1970).

[ii]

*United States Public Health Service
Clinical Research and Investigation
Involving Human Beings**

Expanding Public Health Service support of clinical research and investigation involving human beings emphasizes the need for more formal attention to the critical issues raised by such research.

In December 1965 the National Advisory Health Council, after study of these critical issues, made certain recommendations to me which I have now formulated as the following Public Health Service grant policy:

No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. A description of the committee of the associates who will provide the review shall be included in the application.

Effective immediately, this policy will be included in all future statements of Public Health Service research and research training grant policy. The wisdom and sound professional judgment of you and your staff will determine what constitutes the rights and welfare of human subjects in research, what constitutes informed consent, and what constitutes the risks and potential medical benefits of a particular investigation.

I wish to define more explicitly, however, what is meant by a committee of his institutional associates to assure an independent determination because the policy requires that the application include a description of the associates who will provide the review. The committee would need to be made up of staff of, or consultants to, your institution who are at the same time acquainted with the investigator under review, free to assess his judgment without placing in jeopardy their own goals, and sufficiently mature

and competent to make the necessary assessment. It is important that some of the members be drawn from different disciplines or interests that do not overlap those of the investigator under review.

The policy does not ask for the names of the members of the committee. It does ask for a description of its composition; e.g., the number of members and the professional or public interests they reflect.

I have directed all my staff who administer the initial review of applications for grants for clinical research and investigation involving human beings—regardless of whether these applications are for new, supplemental, renewal, or continuation support—to ascertain that each application includes the information required by this policy and to obtain this information, whenever necessary, in a document signed by both the principal investigator or program director and the official for the institution.

I know that you are as deeply concerned with this issue as are any of us in the Public Health Service. I urgently request that you give my staff your cooperation in making this policy an effective instrument for the good of the public and science.

NOTE

GUIDO CALABRESI
REFLECTIONS ON MEDICAL
EXPERIMENTATION IN HUMANS*

* * *

... No one has purposefully chosen the market method of controlling accidents, and no one, in our society, has the clear responsibility for making radical changes in the method. These facts happily leave us with the feeling that no one is directly responsible for any specific life taken and that neither as individuals nor as a society do we choose against lives in order to save money. Yet it remains true that we are unlikely to want to scrap the system of control that luckily has come into being. And to say this is precisely to say that a method which gives *satisfactory* control of the choice between lives and cost is operating without anyone bearing the onus of having purposefully chosen the method, let alone the onus of seeming to destroy individual lives

* Memorandum of Surgeon General William H. Stewart to the Heads of Institutions Conducting Research with Public Health Grants (February 8, 1966).

* 98 *Daedalus* 387, 393-394 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

for the sake of money. Since no adequate control system over medical experiments has arisen by itself, we cannot avoid the onus of working purposefully toward establishing a control system. This indicates that we will not end with so psychologically satisfactory a result as we have in the field of accidents. But, if anything, this fact heightens the need for establishing a system in which the actual choice over the taking of lives is as diffuse as possible.

Thus, the question remains as to whether or not we can find a control system in the medical experiment field that affords an adequate balancing of present against future lives and is still sufficiently indirect and self-enforcing as to avoid clear and purposive choices to kill individuals for the collective good. It is not my purpose in this article to suggest any complete control system for medical experiments. That task—even if feasible—would require an intimate knowledge of medicine. A few of the problems involved in establishing a control system and a few suggestions leading toward such a system can, however, be mentioned.

In the first place, a direct collective societal control—like approval of research plans by a qualified government agency—is not the answer. Not only is such a device likely to be too cumbersome but, perhaps more importantly, it seems to place the whole society in the position of openly approving the taking of individual lives. Analogy to accident law suggests that this situation is to be avoided if possible, and that the best role for the government is that of watchdog to step in and demand higher standards in specific situations where a general control system, independent of the government, has failed to work adequately.

Leaving the choice to the individual doctor might be all right were there some way to insure that such a choice would tend to coincide with the choice between present and future lives that society wants. No exact correspondence is needed (any more than we require the market to bring about a perfect correspondence between accidents and costs of avoiding them). But there must be the assurance that, on the whole, the individual choice will approach what society would choose. Unfortunately, there is no such assurance today. Some doctors will be too concerned with the individual patient and thereby sacrifice too many future lives by cutting off an experiment too soon. Others will be too concerned with the unavailability of their result and, therefore, continue an experiment beyond the point at

which society's interest in future lives is met. We cannot, moreover, rely on individual consciences to reduce these errors, because individual doctors do not and cannot know the degree to which our society wants present risks to be taken for future benefits. And the best a conscience can do is make individuals adhere to society's wants as these are made known by society. In contrast, the beauty of the accident system, with all its faults, is that through the market it conveys to individual deciders what society more or less wants without requiring an identifiable societal statement. (Furthermore it relies on self-interest rather than conscience to effectuate even this decision.)

* * *

2.

In Administering Research

a.

Who Should Participate, within What Structure, in State Regulation?

[i]

*Eighty-seventh Congress, Second Session
An Act to Protect the Public Health by
Amending the Federal Food, Drug, and
Cosmetic Act to Assure the Safety,
Effectiveness, and Reliability of Drugs . . .
and for Other Purposes**

§ 355. New drugs—Necessity of effective approval of application.

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug.

Filing application; contents

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the arti-

* Act of October 10, 1962, Pub. Law No. 87-781, §§ 102(b)-(d), 103(a)-(b), 104(a)-(d2), 76 Stat. 781-785; see 21 U.S.C. § 355 (1964).

cles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

Grounds for refusing application; approval of application; "substantial evidence" defined

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for

use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated to-

gether with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j) of this section, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this sub-

section shall state the findings upon which it is based.

Revocation of order refusing, withdrawing, or suspending approval of application

(f) Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

* * *

Appeal from order

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. . . .

Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(i) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, or preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(2) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to

him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section.

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

Records and reports; required information; regulations and orders; access to records

(j) (1) In the case of any drug for which an approval of an application filed pursuant to this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section: *Provided, however,* That regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and

shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records. . . .

* * *

NOTES

NOTE 1.

ALFRED GILMAN
RESPONSIBILITIES OF THE ACADEMIC
MEDICAL SCIENCES AND THE PROFESSION IN
THE EVALUATION OF DRUGS*

* * *

[In 1962] there were no statutes in the United States that required the proof of efficacy of drugs. All that was demanded was the proof of safety and these demands were not very stringent. At this time, the Kefauver Committee of the United States Senate was investigating the drug industry—not in terms of the efficacy and safety of drugs but rather in terms of the economics of the industrial profits. By a rare coincidence, the time of these hearings coincided with the dramatic and explosive disclosure of the convincing evidence of the teratogenicity of thalidomide. Profit motives became a secondary issue and safety and efficacy of drugs primary. The result of this unique juxtaposition of events was the passage of the Kefauver-Harris amendment to the U.S. Pure Food and Drug Laws, the first such amendment since 1938. . . . A major feature of the amendment required proof of efficacy as well as safety of a drug. Extensive toxicity data in animals and the submission of an Investigation of a New Drug application were required before a drug could be tested in man. Detailed protocols for the testing of the efficacy of a drug in man were outlined. Toxicity tests in animals were made much more stringent before a New Drug Application could be approved. Mechanisms for reporting the untoward effects

* *Evaluation of Drugs: Whose Responsibility?* Liège: Council for International Organizations of Medical Sciences 15-18 (1970). Reprinted by permission.

of new drugs as well as those already on the market also were made more stringent.

No one could take serious exception to these logical demands, and though it meant greatly increased research and development costs to the drug industry, insofar as I know it did not in any way diminish research activities. However, a federal agency was given the full responsibility of assessing the adequacy of the data submitted by the pharmaceutical industry with respect to the safety as well as the efficacy of a drug. Needless to say, the lines of battle were quickly drawn. New drug applications were returned by the score with comments from the Commissioner of the Food and Drug Administration that pharmaceutical research by industry was poorly conducted, inadequately controlled and directed toward selfish interests. The response from the industry was predictable. The research efforts of their eminent scientists and outstanding clinical investigators were being judged by a group of individuals whose background and training were inadequate for their responsibilities.

[A] second provision of the Kefauver-Harris amendments of 1962 . . . stated that all drugs marketed under a New Drug Application between years 1938 and 1962 be reevaluated by the Food and Drug Administration for the newly required proof of efficacy as well as the former requirement relating only to safety. If efficacy was questionable, the drug was to be withdrawn from the market. . . . A physician who is deprived of a new drug by a federal dictate, a drug that he has never had occasion to use—or one of whose potential or existence he may be unaware—will have little or no reaction if a governmental agency denies a New Drug Application. On the other hand, if he is deprived of a drug that he has used in his own practice for a period up to thirty years, what will be his reaction when this decision for revocation has been made by a government agency?

It is little wonder that the Food and Drug Administration, overwhelmed by their new responsibilities as a result of the Kefauver-Harris amendments, chose to procrastinate on implementing its retroactive features. But Congress was not to be denied. Therefore in 1966, Commissioner Goddard of the Food and Drug Administration addressed a memorandum to President Seitz of the National Academy of Sciences, requesting the Academy to act as an advisory body to the Food and Drug Administration to ascertain the efficacy of all drugs introduced into therapy between the years 1938 and 1962. I need

not emphasize . . . the enormity of this task. These were golden years of pharmacotherapy, spanning the time from the early sulfonamide days to the very recent past. Close to 4,000 drugs were involved, single entities and combinations, requiring more than 10,000 decisions of efficacy because many drugs made several therapeutic claims.

* * *

To make a long story short, the request of Dr. Goddard was approved by the subcommittee and later by the Governing Board of the National Academy of Sciences, since the Academy is advisory to government agencies and this was a request for a single, albeit an enormous advisory, task but not one of a continuing nature.

The implementation of the Efficacy Review can be summarized briefly. Thirty panels, the members of which were experts in all representative areas of drug therapy, were designated. Each panel consisted of a chairman and five members. Nominations for chairmen and membership of the panels were received from their peers, usually from professional societies, and the selection was made by an Advisory Board to the Drug Efficacy Study. Almost invariably the panel members were academicians. . . . The organizational arrangements were achieved within a period of three months and at the present time, just two years later, practically all efficacy decisions have been made and most are already in the hands of the Food and Drug Administration.

* * *

Why did Commissioner Goddard and other administrative officials of the Food and Drug Administration request the advisory help from the National Academy of Sciences? They could have set up advisory panels under their own supervision.

Did they feel that outstanding academicians would perform their arduous task at the request of the National Academy of Sciences and refuse to serve in a similar capacity for the Food and Drug Administration, a federal bureau?

Did they feel that the strict conflict of interest regulations of governmental agencies precluded the possibility of enlisting the best minds in academic medicine—many of whom consult for pharmaceutical industries?

Did they anticipate unfavorable decisions with respect to the efficacy of drugs in current use that would largely absolve the Food and

Drug Administration from further conflict with organized medicine and pharmaceutical industry?

Did they feel that standards of academic medicine would be equally or more demanding than those of the Food and Drug Administration although based upon somewhat different criteria?

Were they truly concerned with raising the level of drug therapy, and therefore sought the knowledge and prestige of the National Academy?

Was this purely a device to placate the Congress and allow the Food and Drug Administration to catch up with a large backlog of unfinished business, since all future decisions as to efficacy would be in their hands?

Do they have any intention to involve academic medicine in future decisions of drug efficacy?

* * *

[T]he review in my mind has been an unqualified success. The panels have worked diligently, and interest of the participants in general has been high. In many instances panels, in addition to their evaluation of individual drugs, have written comprehensive reports outlining the criteria for good therapeutic practices in their particular field. Some contemplate similar reviews to be published in the open literature. In brief, in my opinion, the study has been a great academic success. However, not all panel chairmen were equally enthusiastic about their responsibilities. In fact, one wrote to me that it was a particularly arduous and unrewarding task.

It must be borne in mind that this was a single, non-continuing review. Evaluations of efficacy were based on the published literature and the panel's background of experience. No one was evaluating drugs outside of the area of his own particular interests. What would be the reaction of the panel members if asked to continue these reviews indefinitely and base their evaluations on the volumes of data submitted by the pharmaceutical industry relating both to animal and clinical experimentation, the latter largely in the form of individual case reports? I doubt that many of these busy academicians would accept an invitation for continuous consultant activity to the Food and Drug Administration, and I doubt if the responses would be much more enthusiastic if the National Academy of Sciences were still involved.

* * *

NOTE 2.

FREEMAN H. QUIMBY
MEDICAL EXPERIMENTATION ON
HUMAN BEINGS*

* * *

The chart below shows a marked reduction in the production of new pharmaceutical specialties since 1959. This includes all forms of new products as well as new single chemical drugs.

	<i>New Single Chemicals</i>	<i>Total Number of New Products Marketed</i>
1955	31	403
1956	42	401
1957	51	400
1958	44	370
1959	63	315
1960	45	311
1961	41	265
1962	28	255
1963	18	213
1964	17	162
1965	23	119
1966	13	82

These data may reflect the now slower process of obtaining approved New Drug Applications from FDA since the enactment of the 1962 amendments, or they may not. Since the downturn predates the amendments, it is difficult to point to the amendments as the cause of any effect except possibly the continuation of the trend since 1962. The low number of new single chemicals marketed in 1966 (13) and the total number of new products (82) is a bit on the alarming side in view of the nation's overall competence in organic and pharmaceutical chemistry and in view of the large amounts of funds invested by government and industry for developing new drugs. Research and Development spending by both government and drug firms has been especially high in recent years in the areas of cancer chemotherapy, psychopharmaceuticals, vaccines, and antibiotics. It is unlikely that the 1966 data in the above chart reflect the July 1, 1966, policies from Bethesda or the August 24, 1966, "patient consent in writing" policy of FDA.

* Washington, D.C.: Library of Congress Reference Service 80-81 (1967). Reprinted by permission.

The low number of new drugs in some categories probably indicates industrial efforts to concentrate research on more original and effective drugs and perhaps on newer methods of comparative physiology and chemical testing. The purpose of these new methods is to "signal" the promise, or lack of it, of a new chemical without the risk and expense of human trials. Fewer products and the extensive technical information required by FDA, of course, increase the cost per product. The Pharmaceutical Manufacturers Association now estimates the average cost of a single fundamental new drug entity at \$5 million. DuPont's "Symmetril" cost \$8 million dollars. . . .

* * *

NOTE 3.

CODE OF FEDERAL REGULATIONS TITLE 21—FOOD AND DRUGS (1971)

§ 130.3. *New drugs for investigational use in human beings; exemptions from section 505(a).**

(a) A shipment or other delivery of a new drug shall be exempt from section 505(a) of the act if all the following conditions are met:

(1) The label of such drug bears the statement "Caution: New drug—Limited by Federal (or United States) law to investigational use."

(2) The person claiming the exemption has filed with the Food and Drug Administration a completed and signed "Notice of Claimed Investigational Exemption for a New Drug" in triplicate—with the information shown below in form FD 1571; and not less than 30 days have elapsed following the date of receipt of the notice by the Food and Drug Administration; and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects. The 30-day delay requirement may be waived by the Food and Drug Administration upon a showing of good reason for such waiver.

[Form FD-1571 appears on the pages which follow.]

Provided, however, That where a new drug limited to investigational use is proposed for shipment to a foreign country and the circumstances are such that the submission of the "Notice of

Claimed Investigational Exemption for a New Drug" (Form FD 1571) is not feasible, the Commissioner may authorize the shipment of the drug if he receives, through the U.S. Department of State, a formal request to allow such shipment from the government of the country to which the drug is proposed to be shipped. This request should specify that said government has adequate information about the drug and its proposed use and is satisfied that the drug may legally be used by the intended consignee in that country.

(3) Each shipment or delivery is made in accordance with the commitments in the "Notice of claimed investigational exemption for a new drug."

(4) The sponsor maintains adequate records showing the investigator to whom shipped, date, quantity, and batch or code mark of each such shipment and delivery, until 2 years after a new-drug application is approved for the drug; or, if an application is not approved, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the Food and Drug Administration has been so notified. Upon the request of a scientifically trained and properly authorized employee of the Department at reasonable times, the sponsor makes the records referred to in this subparagraph and in subparagraph (2) of this paragraph available for inspection, and upon written request submits such records or copies of them to the Food and Drug Administration.

(5) The sponsor monitors the progress of the investigations and currently evaluates the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigators. Accurate progress reports of the investigations and significant findings, together with any significant changes in the informational material supplied to investigators, shall be submitted to the Food and Drug Administration at reasonable intervals, not exceeding 1 year. All reports of the investigation shall be retained until 2 years after a new-drug application is approved for the drug; or, if an application is not approved, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the Food and Drug Administration so notified. Upon request of a scientifically trained and properly authorized employee of the Department, at reasonable times, these reports shall be made available for inspection, and on written request copies of these reports shall be submitted to the Food and Drug Administration.

* Section 505 refers to the numbering of 21 U.S.C. § 355 as it appeared in the Federal Food, Drug, and Cosmetic Act of June 25, 1938, 52 Stat. 1040, as amended.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0030

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Name of Sponsor _____

Address _____

Date _____

Name of Investigational Drug _____

Commissioner
Food and Drug Administration
Bureau of Drugs (BD-26)
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir:

The sponsor, _____, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto, in triplicate, are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the

preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pre-existing information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of three copies of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD 1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

c. Institutional review committee. If the phases of clinical study as described under 10a and b above are conducted on institutionalized subjects or are conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. Assurance must be presented that neither the sponsor nor the investigator has participated in selection of committee members; that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee); that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards; that reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations; that the review committee is provided all the information on the research project necessary for its complete review of the project; and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in obtaining informed consent, committee discussion on substantive issues and their

resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of institutional review committees are contained in guidelines issued pursuant to Chapter 1-40 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD 1571 will be regarded as providing the above necessary assurances. If the institution, however, has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance," and the same committee is to review the proposed study using the same procedures, this is acceptable in lieu of the above assurances and a statement to this effect should be provided with the signed FD 1571. (In addition to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investiga-

tions in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)

11. It is understood that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. It is understood that the sponsor will notify each investigator if a new drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, an additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

Very truly yours,

SPONSOR	PER
	INDICATE AUTHORITY

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPPLICATE.

(6) The sponsor shall promptly investigate and report to the Food and Drug Administration and to all investigators any findings associated with use of the drug that may suggest significant hazards, contraindications, side effects, and precautions pertinent to the safety of the drug. If the finding is alarming, it shall be reported immediately and the clinical investigation discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed.

(7) If the investigations adduce facts showing that there is substantial doubt that they may be continued safely in relation to the drug's potential therapeutic effects, the sponsor shall promptly discontinue the investigation, notify all investigators and the Food and Drug Administration, recall all stocks of the drug outstanding, and furnish the Food and Drug Administration with a full report of the reason for discontinuing the investigation. The Food and Drug Administration will be prepared to confer with the sponsor on the need to discontinue the investigation.

(8) The sponsor shall discontinue shipments or deliveries of the new drug to any investigator who has repeatedly or deliberately failed to maintain or make available his records or reports of his investigations.

(9) The sponsor shall not unduly prolong distribution of the drug for investigational use but shall submit an application for the drug pursuant to section 505(b) of the act (or give reasons for not submitting such application, or a statement that the investigation has been discontinued and the reasons therefor):

(i) With reasonable promptness after finding that the results of such investigation appear to establish the safety and effectiveness of the drug; or

(ii) Within 60 days after receipt of a written request for such an application from the Commissioner.

(10) Neither the sponsor nor any person acting for or on behalf of the sponsor shall disseminate any promotional material representing that the drug being distributed interstate for investigational use is safe or useful for the purposes for which it is under investigation. This regulation is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay communications media; its sole intent is to restrict promotional claims of safety or effectiveness by the sponsor while the drug is under investigation to establish its safety or effectiveness.

(11) The sponsor shall not commercially distribute nor test-market the drug until a new-drug application is approved pursuant to section 505(b) of the act.

(12) The sponsor shall obtain from each investigator involved in clinical pharmacology a signed statement in the following form:

[Form FD-1572 appears on the pages which follow.]

(13) The sponsor shall obtain from each investigator involved in clinical trials a signed statement in the following form:

[Form FD-1573 appears on the pages which follow.]

* * *

(c) (1) Whenever the Food and Drug Administration has information indicating that an investigator has repeatedly or deliberately failed to comply with the conditions of these exempting regulations outlined in Form FD-1572 or FD-1573 . . . or has submitted to the sponsor of the investigation false information in his Form FD-1572 or FD-1573 or in any required report, the Director of the Bureau of Medicine will furnish the investigator written notice of the matter complained of in general terms and offer him an opportunity to explain the matter in an informal conference and/or in writing. If an explanation is offered but not accepted by the Bureau of Medicine, the Commissioner will provide the investigator an opportunity for an informal hearing on the question of whether the investigator is entitled to receive investigational-use drugs, if the hearing is requested within 10 days after receipt of notification that the explanation is not acceptable.

(2) After evaluating all available information, including any explanation and assurance presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations in this section or has repeatedly or deliberately submitted false information to the sponsor of an investigation and has failed to furnish adequate assurance that the conditions of the exemption will be met, the Commissioner will notify the investigator and the sponsor of any investigation in which he has been named as a participant that the investigator is not entitled to receive investigational-use drugs with a statement of the basis for such determination.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION 5600 FISHERS LANE ROCKVILLE, MARYLAND 20852		STATEMENT OF INVESTIGATOR (Clinical Pharmacology)		Form Approved OMB No. 57-R0031
TO: SUPPLIER OF THE DRUG (Name and address, include Zip Code)		NAME OF INVESTIGATOR (Print or Type)		
		DATE		
		NAME OF DRUG		
Dear Sir: The undersigned, _____, submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical pharmacology with a new drug limited by Federal (or United States) law to investigational use.				
1. STATE THE EDUCATION AND TRAINING YOU HAVE HAD THAT QUALIFIES YOU FOR CLINICAL PHARMACOLOGY				
2. GIVE NAME AND ADDRESS OF THE MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL PHARMACOLOGY WILL BE CONDUCTED				
<p>3. If the experimental project is to be conducted on institutionalized subjects or is conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. Assurance must be presented that the investigator has not participated in the selection of committee members; that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee); that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards; that reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations; that the review committee is provided all the information on the research project; and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in obtaining informed consent, committee discussion on substantive issues and their resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of institutional review committees are contained in guidelines issued pursuant to Chapter 1-40 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD 1572 will be regarded as providing the above necessary assurance; however, if the institution has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance," and the same committee is to review the proposed study using the same procedures, this is acceptable in lieu of the above assurances and a statement to this effect should be provided with the signed FD 1572. (In addition to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investigations in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)</p>				

4. ESTIMATE DURATION OF THE PROJECT AND INDICATE THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED

5. GENERAL OUTLINE OF THE PROJECT TO BE UNDERTAKEN (Modification is permitted on the basis of experience gained without advance submission of amendments to the general outline, but with the approval of the review committee and upon notification of the sponsor.)

6. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE GOVERN HIS RECEIPT AND USE OF THIS INVESTIGATIONAL DRUG

- a. The sponsor is required to supply the investigator with full information concerning the preclinical investigation that justifies clinical pharmacology.
- b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantity, and use by subjects, and if the clinical pharmacology is suspended or terminated to return to the sponsor any unused supply of the drug.
- c. The investigator is required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology.
- d. The investigator is required to furnish his reports to the sponsor who is responsible for collecting and evaluating the results, and presenting progress reports to the Food and Drug Administration at appropriate intervals, not exceeding 1 year. Any adverse effect which may reasonably be regarded as caused by, or is probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming it shall be reported immediately. An adequate report of the clinical pharmacology should be furnished to the sponsor shortly after completion.
- e. The investigator shall maintain the records of disposition of the drug and the case reports described above for a period of 2 years following the date the new-drug application is approved for the drug; or if no application is to be filed or is approved until 2 years after the investigation is discontinued and the Food and Drug Administration so notified. Upon the request of a scientifically trained and specifically authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The

names of the subjects need not be divulged unless the records of the particular subjects require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual studies or do not represent actual results obtained.

- f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him.

and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

- g. The investigator certifies that he will inform any patients or any persons used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.
- h. The investigator is required to assure the sponsor that for investigations involving institutionalized subjects the studies will not be initiated until the institutional review committee has reviewed and approved the study. (The organization and procedure requirements for such a committee should be explained to the investigator by the sponsor as set forth in Form FD-1571, division 10, unit c.)

Very truly yours,

 (Name of Investigator)

 (Address)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION 5600 FISHERS LANE ROCKVILLE, MARYLAND 20852		STATEMENT OF INVESTIGATOR		Form Approved OMB No. 57-R0029
TO: SUPPLIER OF DRUG (Name and address, include Zip Code)		NAME OF INVESTIGATOR (Print or Type)		
		DATE		
		NAME OF DRUG		
Dear Sir: The undersigned, _____, submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical investigations with a new drug limited by Federal (or United States) law to investigational use.				
1. STATEMENT OF EDUCATION AND EXPERIENCE				
a. COLLEGES, UNIVERSITIES, AND MEDICAL OR OTHER PROFESSIONAL SCHOOLS ATTENDED, WITH DATES OF ATTENDANCE, DEGREES, AND DATES DEGREES WERE AWARDED				
b. POSTGRADUATE MEDICAL OR OTHER PROFESSIONAL TRAINING (Indicate dates, names of institutions, and nature of training)				
c. TEACHING OR RESEARCH EXPERIENCE (Indicate dates, institutions, and brief description of experience)				
d. EXPERIENCE IN MEDICAL PRACTICE OR OTHER PROFESSIONAL EXPERIENCE (Indicate dates, institutional affiliations, nature of practice, or other professional experience)				
e. REPRESENTATIVE LIST OF PERTINENT MEDICAL OR OTHER SCIENTIFIC PUBLICATIONS (Indicate titles of articles, names of publications and volume, page number, and date)				

2a. If the investigation is to be conducted on institutionalized subjects or is conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice and community acceptance. Assurance must be presented that the investigator has not participated in the selection of committee members; that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee) that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards; that reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations; that the review committee is provided all the information on the research project necessary for its complete review of the project; and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in ob-

taining informed consent, committee discussion on substantive issues and their resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of institutional review committees are contained in guidelines issued pursuant to Chapter 140 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD 1573 will be regarded as providing the above necessary assurances; however, if the institution has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance," and the same committee is to review the proposed study using the same procedures, this is acceptable in lieu of the above assurances and a statement to this effect should be provided with the signed FD 1573. (In addition to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investigations in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)

b. A description of any clinical laboratory facilities that will be used. (If this information has been submitted to the sponsor and reported by him on Form FD 1571, reference to the previous submission will be adequate).

3. OUTLINE THE PLAN OF INVESTIGATION (include approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; clinical uses to be investigated; characteristics of subjects by age, sex and condition; the kind of clinical observations and laboratory tests to be undertaken prior to, during, and after administration of the drug; the estimated duration of the investigation; and a description of copies of report forms to be used to maintain an adequate record of the observations and tests results obtained. This plan may include reasonable alternates and variations and should be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.)

4. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS, GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE, GOVERN HIS RECEIPT AND USE OF THIS INVESTIGATIONAL DRUG

- a. The sponsor is required to supply the investigator with full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.
- b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantities, and use by subjects, and if the investigation is terminated to return to the sponsor any unused supply of the drug.
- c. The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.
- d. The investigator is required to furnish his reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained by various investigators. The sponsor is required to present progress reports to the Food and Drug Administration at appropriate intervals not exceeding 1 year. Any adverse effect that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming, it shall be reported immediately. An adequate report of the investigation should be furnished to the sponsor shortly after completion of the investigation.
- e. The investigator shall maintain the records of disposition of the drug and the case histories described above for a period of 2 years following the date a new-drug application is approved for the drug; or if the application is not approved, until 2 years after the investigation

is discontinued. Upon the request of a scientifically trained and properly authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The subjects' names need not be divulged unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied, or do not represent actual results obtained.

- f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him,

and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

- g. The investigator certifies that he will inform any subjects, including subjects used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.
- h. The investigator is required to assure the sponsor that for investigations involving institutionalized subjects, the studies will not be initiated until the institutional review committee has reviewed and approved the study. (The organization and procedure requirements for such a committee should be explained to the investigator by the sponsor as set forth in form FD 1571, division 10, unit c.)

Very truly yours,

(Name of Investigator)

(Address)

(This form should be supplemented or amended from time to time if new subjects are added or if significant changes are made in the plan of investigation.)

(3) Each "Notice of Claimed Investigational Exemption for a New Drug" [Form FD 1571] and each approved new-drug application containing data reported by an investigator who has been determined to be ineligible to receive investigational-use drugs will be examined to determine whether he has submitted unreliable data that are essential to the approval of any new-drug application.

(4) If the Commissioner determines after the unreliable data submitted by the investigator are eliminated from consideration that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, he will notify the sponsor and provide him with an opportunity for a conference and an informal hearing in accordance with paragraph (d) of this section. If an imminent hazard to the public health exists, however, he shall terminate the exemption forthwith and notify the sponsor of the termination. In such event the Commissioner, on request, will afford the sponsor an opportunity for an informal hearing on the question of whether the exemption should be reinstated.

(5) If the Commissioner determines after the unreliable data submitted by the investigator are eliminated from consideration that the data remaining are such that a new-drug application would not have been approved, he will proceed to withdraw approval of the application in accordance with section 505(e) of the act.

(6) An investigator who has been determined to be ineligible may be reinstated as eligible to receive investigational-use drugs when the Commissioner determines that he has presented adequate assurance that he will employ such drugs solely in compliance with the exempting regulations in this section for investigational-use drugs.

(d) If the Commissioner of Food and Drugs finds that:

(1) The submitted "Notice of claimed investigational exemption for a new drug" contains an untrue statement of a material fact or omits material information required by said notice; or

(2) The results of prior investigations made with the drug are inadequate to support a conclusion that it is reasonably safe to initiate or continue the intended clinical investigations with the drug; or

(3) There is substantial evidence to show that the drug is unsafe for the purposes and in the manner for which it is offered for investigational use; or

(4) There is convincing evidence that the drug is ineffective for the purposes for which it is offered for investigational use; or

(5) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug; or

(6) The plan for clinical investigations of the drugs described under section 10 of the "Notice of claimed investigational exemption for a new drug" is not a reasonable plan in whole or in part, solely for a bona fide scientific investigation to determine whether or not the drug is safe and effective for use; or

(7) The clinical investigations are not being conducted in accordance with the plan submitted in the "Notice of claimed investigational exemption for a new drug"; or

(8) The drug is not intended solely for investigational use, since it is being or is to be sold or otherwise distributed for commercial purposes not justified by the requirements of the investigation; or

(9) The labeling or other informational material submitted for the drug as required by section 7 of the "Notice of claimed investigational exemption for a new drug" or any other labeling of the drug disseminated within the United States by or on behalf of the sponsor fails to contain an accurate description of prior investigations or experience and their results pertinent to the safety and possible usefulness of the drug, including all relevant hazards, contraindications, side effects, and precautions; or any promotional material disseminated within the United States by or on behalf of the sponsor contains any representation or suggestion that the drug is safe or that its usefulness has been established for the purposes for which it is offered for investigations; or

(10) The sponsor fails to submit accurate reports of the progress of the investigations with significant findings at intervals not exceeding 1 year; or

(11) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of newly found serious or potentially serious hazards, contraindications, side effects, and precautions pertinent to the safety of the new drug;

he shall notify the sponsor and invite his imme-

diate correction or explanation. A conference will be arranged with the Bureau of Medicine if requested. If the Bureau of Medicine does not accept the explanation and/or the correction submitted by the sponsor, the Commissioner will provide the sponsor an opportunity for an informal hearing on the question of whether his exemption should be terminated, if the hearing is requested within 10 days after receipt of notification that the explanation or correction is not acceptable. After evaluating all the available information including any explanation and/or correction submitted by the sponsor, if the Commissioner determines that the exemption should be terminated he shall notify the sponsor of the termination of the exemption and the sponsor shall recall unused supplies of the drug. If at any time the Commissioner concludes that continuation of the investigation presents an imminent hazard to the public health, he shall terminate the exemption forthwith and notify the sponsor of the termination. The Commissioner will inform the sponsor that the exemption is subject to reinstatement on the basis of additional submissions that eliminate such hazard(s) and will afford the sponsor an opportunity for an informal hearing, on request, on the question of whether the exemption should be reinstated. The sponsor shall recall the unused supplies of the drug upon notification of the termination.

* * *

§ 130.3a. *New drugs for investigational use in animals; exemptions from section 505(a).*

(a) *New drugs for tests in vitro and in laboratory research animals.* (1) A shipment or other delivery of a new drug intended solely for tests in vitro or in animals used only for laboratory research purposes shall be exempt from section 505(a) of the act if it is labeled as follows:

Caution—Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.

* * *

§ 130.4 *Applications.*

(a) Applications to be filed under the provisions of section 505(b) of the act shall be submitted in the form described in paragraph (c) of this section. . . .

(b) Pertinent information may be incorporated in, and will be considered as part of, an application on the basis of specific reference to such information, including information submitted under the provisions of § 130.3, in the

files of the Food and Drug Administration; however, any reference to information furnished by a person other than the applicant may not be considered unless use of such information is authorized in a written statement signed by the person who submitted it.

(c) Applications for drugs for human use shall be assembled and submitted in the manner prescribed by paragraph (e) of this section. Applications for human and veterinary drugs shall be submitted in one of the following appropriate forms. . . .

[Form FD-356H appears on the pages which follow.]

* * *

§ 130.6 *Comment on applications.*

(a) After the application has been studied, the applicant will be furnished comment on any apparent deficiencies in the data submitted or on the need for any additional data or changes in the application to facilitate its consideration.

(b) When the description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug appears adequate on its face, but it is not feasible to reach a conclusion as to the safety and effectiveness of the drug solely from consideration of this description, the applicant may be notified that an inspection is required to verify their adequacy.

(c) Withdrawal of an application may be suggested when it is found that additional evidence is required to support a finding that the drug is safe or effective or that the methods, facilities, and controls used in manufacturing, processing, and packing the drug are adequate.

(d) On the basis of preliminary consideration of an application or supplemental application containing typewritten or other draft labeling in lieu of final printed labeling, an applicant may be informed that such application is approvable when satisfactory final printed labeling identical in content to such draft copy is submitted.

§ 130.7 *Amended applications.*

The applicant may submit an amendment to an application that is pending, but in the case of a substantive amendment, the unamended application may be considered as withdrawn and the amended application may be considered resubmitted on the date on which the amendment is received by the Food and Drug Administration. The applicant will be notified of such date.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION (DRUGS FOR HUMAN USE)
(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant _____

Address _____

Date _____

Name of new drug _____

- ☐ Original application (regulation § 130.4). ☐ Amendment to abbreviated, unapproved application (regulation § 130.7).
- ☐ Amendment to original, unapproved application (regulation § 130.7). ☐ Supplement to an approved application (regulation § 130.9).
- ☐ Abbreviated application (regulation § 130.4(f)). ☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with § 1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of § 130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in § 130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in § 130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

- a. Chemistry.
 - i. Chemical structural formula or description for any new-drug substance.
 - ii. Relationship to other chemically or pharmacologically related drugs.
 - iii. Description of dosage form and quantitative composition.

- b. Scientific rationale and purpose the drug is to serve.
- c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

- d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

- i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

- ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

- e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

- i. Special studies not described elsewhere.
- ii. Dose-range studies.
- iii. Controlled clinical studies.
- iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).
- v. Clinical laboratory studies related to effectiveness.
- vi. Clinical laboratory studies related to safety.
- vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

- b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed

components of the finished drug: *Provided, however*, That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW, Food and Drug Administration, Bureau of Drugs (BD-200) Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

(Applicant)

Per _____
(Responsible official or agent)

(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

§ 130.8 Withdrawal of applications without prejudice.

The applicant may at any time withdraw his pending application from consideration as a new-drug application upon written notification to the Food and Drug Administration. Such withdrawal may be made without prejudice to a future filing. Upon resubmission, the time limitation will begin to run from the date the resubmission is received by the Food and Drug Administration. The application itself will be retained by the Food and Drug Administration although it is considered withdrawn, but the applicant shall be furnished a copy at cost, on request.

* * *

§ 130.10 Notification of applicant of approval of application.

If the Commissioner determines that none of the grounds for denying approval specified in section 505(d) of the act applies, the applicant shall be notified in writing that the application is approved and the application shall be approved on the date of the notification.

* * *

§ 130.12 Refusal to approve the application.

(a) If the Commissioner determines upon the basis of the application, or upon the basis of other information before him with respect to the new drug, that:

(1) The investigations, reports of which are required to be submitted pursuant to section 505(b) of the act, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; or

(2) The results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; or

(3) The methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or

(4) Upon the basis of the information submitted to the Food and Drug Administration as part of the application, or upon the basis of any other information before it with respect to such drug, it has insufficient information to determine whether such drug is safe for use under such conditions; or

(5) (i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(a) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(1) A clear statement of the objectives of the study.

(2) A method of selection of the subjects that—

(i) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(ii) Assigns the subjects to test groups in such a way as to minimize bias.

(iii) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and

the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(i) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(ii) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(iii) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(iv) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(5) A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods.

Provided, however, That any of the above criteria may be waived in whole or in part, either prior to the investigation or in the evaluation of a completed study, by the Director of the Bureau of Drugs with respect to a specific clinical investigation; a petition for such a waiver may be filed by any person who would be adversely affected by the application of the criteria to a particular clinical investigation; the petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be, or have been followed, the results of which will or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if

any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(b) For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(c) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(6) Based on a fair evaluation of all material facts, such labeling is false or misleading in any particular;

the Commissioner shall within 180 days after the filing of the application inform the applicant in writing of his intention to issue a notice of hearing on a proposal to refuse to approve the application.

(b) Unless by the 30th day following the date of issuance of the letter informing the applicant of the intention to issue a notice of hearing, the applicant:

(1) Withdraws the application; or

(2) Waives the opportunity for a hearing; or

(3) Agrees with the Commissioner on an additional period to precede issuance of such notice of hearing,

the Commissioner shall expeditiously notify the applicant of an opportunity for a hearing on the question of whether such application is approvable as provided in §130.14.

§ 130.13 Records and reports concerning experience on drugs for which an approval is in effect.

(a) On receiving notification that an appli-

cation for a new drug is approved, the applicant shall establish and maintain records and make reports that are necessary to facilitate a determination whether there may be grounds for invoking section 505(c) of the act to suspend or withdraw approval of the application, including adequately organized and indexed files containing full reports of any of the following kinds of information, pertinent to the safety or effectiveness of the drug or the adequacy of the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug to assure and preserve its identity, strength, quality, and purity, that has not previously been submitted as part of his application for the drug and which is received or otherwise obtained by him from any source:

(1) Unpublished reports of clinical experience, studies, investigations, and tests conducted by the applicant or reported to him by any person involving the drug that is the subject of the application and related drugs, and reports in the scientific literature involving the drug that is the subject of application. An adequate summary and bibliography of reports in the scientific literature will ordinarily suffice. (The applicant must identify at the time of each report submission each drug he considers related to the subject drug.)

(2) Unpublished reports of animal experience, studies, investigations, and tests conducted by the applicant or reported to him by any person involving the drug that is the subject of the application and related drugs, and reports in the scientific literature involving the drug that is the subject of the application. An adequate summary and bibliography of reports in the scientific literature will ordinarily suffice. (The applicant must identify at the time of each report submission each drug he considers related to the subject drug.)

(3) Experience, investigations, studies, or tests involving the chemical or physical properties or any other properties of the drug; such as, its behavior or properties in relation to micro-organisms, including both the effects of the drug on micro-organisms and the effects of micro-organisms on the drug.

(4) The information required by this section shall include, when known, adequate identification of its source, including the name and post office address of the person who furnished such information.

(5) Copies of all mailing pieces and other

labeling, and if it is a prescription drug all advertising, other than that contained in the application, used in promoting the drug; and copies of the currently used package labeling that gives full information for use of the drug, whether or not such labeling is contained in the application.

(6) Information concerning the quantity of the drug distributed, in a manner and form that facilitates estimates of the incidence of any adverse effects reported to be associated with the use of the drug. This does not require disclosure of financial or pricing data.

(7) Information concerning any previously unreported changes from the conditions described in an application. . . .

(b) The applicant shall submit to the Food and Drug Administration copies of the records and reports described in paragraph (a) of this section (except routine assay and control records) appropriately identified with the new-drug application(s) to which they relate as follows. . . .

(1) Immediately upon receipt by the applicant, complete records or reports covering information of the following kinds:

(i) Information concerning any mixup in the drug or its labeling with another article.

(ii) Information concerning any bacteriological, or any significant chemical, physical, or other change or deterioration in the drug, or any failure of one or more distributed batches of the drug to meet the specifications established for it in the new-drug application.

(2) As soon as possible, and in any event within 15 working days of its receipt by the applicant, complete records or reports concerning any information of the following kinds:

(i) Information concerning any unexpected side effect, injury, toxicity, or sensitivity reaction, or any unexpected incidence or severity thereof associated with clinical uses, studies, investigations, or tests, whether or not determined to be attributable to the drug, except that this requirement shall not apply to the submission of information described in a written communication to the applicant from the Food and Drug Administration as types of information that may be submitted at other designated intervals. "Unexpected" as used in this subdivision refers to conditions or developments not previously submitted as part of the new-drug application or not encountered during clinical trials of the drugs, or conditions or developments occurring at a rate

higher than shown by information previously submitted as part of the new-drug application, or than encountered during such clinical trials.

(ii) Information concerning any unusual failure of the drug to exhibit its expected pharmacological activity.

* * *

(c) The reports submitted under the provisions of this section are not required to furnish the names and addresses of individual patients unless the applicant is notified in writing by the Food and Drug Administration that individual patient identification is required with respect to designated reports in order to permit further investigation or because there is reason to believe that such reports do not represent actual results obtained.

(d) The applicant shall upon request of any properly authorized officer or employee of the Department, at reasonable times, permit such officers to have access to and copy and verify any records and reports established and maintained under the provisions of this section.

(e) If the Food and Drug Administration finds that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with the provisions of this section, or that the applicant has refused to permit access to, or copying, or verification of such records or reports, the Commissioner shall give the applicant due notice and opportunity for a hearing on the question of whether to withdraw the approval of the application. . . .

* * *

§ 130.14 *Contents of notice of hearing.*

(a) The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner to refuse to approve an application or to withdraw the approval of an application will specify the grounds upon which he proposes to issue his order. On request of the applicant, the Commissioner will explain the reasons for his action. The notice of hearing will be published in the *Federal Register* and will specify that the applicant has 30 days after issuance of the notice within which he is required to file a written appearance electing whether:

(1) To avail himself of the opportunity for a hearing at the place specified in the notice of hearing; or

(2) Not to avail himself of the opportunity for a hearing.

(b) If the applicant elects to avail himself of the opportunity for a hearing, he is required to file a written appearance requesting the hearing within 30 days after the publication of the notice and giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity for a hearing. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on these data, making findings and conclusions on such data. If a hearing is requested and is justified by the applicant's response to the notice of hearing, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(c) The hearing will be open to the public: *Provided, however,* That if the Commissioner finds that portions of the application which serve as a basis for the hearing contain information concerning a method or process which as a trade secret is entitled to protection, the part of the hearing that involves such portions will not be public unless the respondent so specifies in his appearance.

* * *

§ 130.17 *Hearing examiner.*

The hearing will be conducted by a hearing examiner appointed as provided in the Administrative Procedure Act and designated for conducting the hearing. Any such designation may be made or revoked by the Commissioner at any

time. Hearings will be conducted in an informal but orderly manner in accordance with these regulations and the requirements of the Administrative Procedure Act. The hearing examiner will have the power to administer oaths and affirmations, to rule upon offers of proof and the admissibility of evidence, to receive relevant evidence, to examine witnesses, to regulate the course of the hearing, to hold conferences for the simplification of the issues, and to dispose of procedural requests, but will not have the power to decide any motion that involves final determination of the merits of the proceeding.

* * *

§ 130.24 *Tentative order.*

The hearing examiner, within a reasonable time, shall prepare tentative findings of fact and a tentative order, which shall be served upon the applicant and the Food and Drug Administration or sent to them by certified mail. If no exceptions are taken to the tentative order within 20 days or such other time specified in such order, that order shall become final.

* * *

§ 130.26 *Issuance of final order.*

Within a reasonable time after the filing of exceptions, or after oral argument (if such argument is requested), the Commissioner shall issue the final order in the proceeding. The order will include the findings of fact upon which it is based.

§ 130.27 *Withdrawal of approval of an application.*

The Commissioner shall, in writing, notify the person holding an approved new-drug application and afford an opportunity for a hearing on a proposal to withdraw approval of the application as provided in section 505(c) of the act and in accordance with the procedure in §§130.14 to 130.26, inclusive, if:

(a) The Secretary has suspended the approval of such application on a finding that there is an imminent hazard to the public health; or

(b) The Commissioner finds:

(1) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application was approved; or

(2) That new evidence of clinical experience, not contained in the application or not available to the Food and Drug Administration until after the application was approved, or tests

by new methods, or tests by methods not deemed reasonably applicable when the application was approved, evaluated together with the evidence available when the application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or

(3) Upon the basis of new information before the Food and Drug Administration with respect to the drug, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof (the provisions of §130.12(a) (5) apply to the meaning of "substantial evidence" as used in this subparagraph); or

(4) That the application contains any untrue statement of a material fact; or

(c) The Commissioner finds:

(1) That the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under section 505(j) of the act and of § 130.13, or that the applicant has refused to permit access to, or copying or verification of, such records as required; or

(2) That on the basis of new information before the Food and Drug Administration, evaluated together with the evidence available when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity; or

(3) That on the basis of new information before the Food and Drug Administration, evaluated together with the evidence available when the application was approved, the labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular; and that the matter complained of was not corrected by the applicant within a reasonable time after his receipt of written notice from the Commissioner specifying the matter complained of.

(d) Any hearing following summary suspension on a finding of imminent hazard to health shall be afforded promptly and shall proceed on an expedited basis.

* * *

[ii]

United States Code

Title 42—Public Health and Welfare (1971)

§ 218. *National Advisory Councils; composition, qualifications; appointment and tenure; duties.* (a) The National Advisory Health Council . . . shall . . . consist of the Surgeon General, who shall be chairman, the chief medical officer of the Veterans' Administration or his representative, and a medical officer designated by the Secretary of Defense, who shall be ex officio members; and twelve members appointed without regard to the civil-service laws by the Surgeon General with the approval of the Secretary of Health, Education, and Welfare. The twelve appointed members of . . . such council shall be leaders in the fields of fundamental sciences, medical sciences, or public affairs, and six of such twelve shall be selected from among leading medical or scientific authorities who . . . are skilled in the sciences related to health. . . . Each appointed member of each such council shall hold office for a term of four years. . . .

(b) The National Advisory Health Council shall advise, consult with, and make recommendations to, the Surgeon General on matters relating to health activities and functions of the Service. . . .

* * *

§ 241. *Research and investigations generally.* The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, and scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man, including water purification, sewage treatment, and pollution of lakes and streams. In carrying out the foregoing the Surgeon General is authorized to—

* * *

(d) Make grants-in-aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for such research or research training projects as are recommended by the National Advisory Health Council . . . and make, upon recommendation of the National Advisory Health Council, grants-in-aid to public or nonprofit universities, hospitals, laboratories, and other institutions for the general

support of their research and research training programs. . . .

* * *

(i) Adopt, upon recommendation of the National Advisory Health Council . . . such additional means as he deems necessary or appropriate to carry out the purposes of this section.

* * *

NOTE

HYPOTHETICAL CASES REVIEWED BY THE NATIONAL ADVISORY HEALTH COUNCIL (1971)

[All functions of the Public Health Service, including those of the Surgeon General and the Advisory Councils, were transferred to the Secretary of Health, Education, and Welfare by the President's 1966 Reorganization Plan No. 3, 31 Federal Register 8855 (1966). Suppose, however, that the National Advisory Health Council (NAHC) were again reviewing protocols submitted to the Federal government for funding. The following hypothetical cases suggest the way in which the NAHC might respond to the actions of local review committees. In studying these cases, consider the appropriateness of review and of the decisions made as well as the nature and extent of the functions such a national body should assume.]

I. Patients with a diagnosis of primary myocardial disease (PMD) were to be subjected to bilateral percutaneous cardiac biopsy using a modified Vim-Silverman needle. Samples were to be divided to permit routine histological studies, some histochemical analyses, and standard bacteriological tests. The principal investigator noted that it had not yet been established that PMD is a pathologic entity. In addition, there is no rational etiology for the condition, other than that derived from its frequent association with chronic alcoholism.

The reviewers of the National Advisory Health Council (NAHC) asked the investigator's institutional committee to provide its estimate of the possible risk to the subject through the use of closed chest cardiac biopsy. The committee replied that no such assessment had been made since the individuals involved were patients, not subjects, and the study was intended for diagnostic benefit of the patients. Under these circumstances, they did not feel that the review required by the NAHC was necessary, nor was a special form of consent

required. The NAHC then asked if closed chest biopsy was an accepted diagnostic procedure in the institution. The reply, which arrived too late to influence initial review, was negative.

NAHC noted that the mere fact that persons are admitted as "patients" does not place them in a separate category from "subjects;" that the procedure to be used here was not standard or accepted and constituted a research procedure; and that the proposed procedure was associated with a high mortality rate in experimental animals. In addition, accidental cardiac biopsies, sometimes resulting from improperly performed sternal marrow punctures, were extremely hazardous. They recommended that the project be disapproved.

II. An entomologist at Meridian Hill College proposed a series of studies on microclimate adaptive mechanisms in *Anopheles* mosquitoes. In the course of a visit to the laboratory, NAHC consultants were critical of the arrangements for containing and controlling the mosquito population. When a revised protocol showed no proposed improvement in these arrangements, the advisory group concerned asked if the project had been reviewed and accepted by the institution's committee. The institution's administration replied that no human subjects were involved, only mosquitoes. In reply NAHC staff pointed out that this genus is a potential vector for malaria and that the institution was located in an area heavily populated by recent immigrants from Puerto Rico, Cuba, and other Latin American countries, and that a substantial pool of active and latent malaria undoubtedly existed in these groups. Failure to control the mosquito population could, at least during the summer months, permit spread of malaria within the local population.

III. The investigators proposed a study using both conventional histologic techniques and electron microscopy, on human ova to be obtained from normal women at relatively short intervals after ovulation. Women presenting themselves for post-partum sterilization, would be asked to forego tubal ligation, to become pregnant, and then to undergo bilateral salpingectomy. The excised uterine tubes would be flushed to recover the ovum. Married women would become pregnant in the usual manner. Unmarried women would be asked to accept A.I.D. The NAHC reviewers rejected this proposal on several counts.

Though the proposed written consent doc-

ument was complete in its description of the potential benefits of the procedure, its efficacy, possible complications, and associated morbidity, the NAHC committee stated that the investigator could not ask for consent since salpingectomy, while standard and accepted, carried with it a higher rate of risk than the procedure of choice, tubal ligation, but no additional benefits. In the committee's opinion, in the absence of the needs of the research project, there would be no indication for salpingectomy in these cases.

The committee also expressed serious doubts that the investigator would be justified in arguing that the risks of the project could be justified "in the interests of humanity" since the scientific return from straightforward cytological and histological studies would be small.

Finally, the committee noted a minority opinion from three members pointing out that the proposal to subject women to A.I.D. solely for the purposes of the project was morally repugnant and unacceptable.

IV. An application received from a physiologist at Mideastern University involved studies of absorption from doubly perfused 20 cm. lengths of human intestine. Inquiries by the NAHC as to the review status of this project brought a reply that no human subjects were involved, only materials obtained at surgery from the Marimar Hospital. In reply the NAHC noted that use of such materials did require review of the circumstances under which the materials were obtained but that this review could be carried out in cooperation with the hospital. Copies of the correspondence were forwarded to the Marimar.

The next letter arrived from the chairman of the committee at Marimar. Their policy required that all requests for surgical materials be cleared through the Chairman of the Department of Pathology, and that patient consent be obtained for other than diagnostic use of these materials. Neither of these steps had been followed. The entire project had now been reviewed in a joint meeting of the university and hospital committees.

Review had disclosed that the investigator had approached the Chief of the Gastrointestinal Service directly to obtain 40 cm. lengths of normal intestine. The surgeon had already provided several sections for pilot studies, mostly obtained from resections performed in treating regional ileitis. While some of these had been removed together with two adjacent diseased

areas, most had been obtained by extending the area resected into normal areas. The surgeon argued that the difficulty in defining the area justified some extension of the region to be excised and that, in his judgment, this did not involve any additional risk to the patient.

The committees granted the project contingent approval. Specific written prior permission was to be obtained from each candidate patient for the use of surgically removed intestine. The consent statement proposed by the committee indicated that the material was to be used for research purposes and that removal would "cut down the length of the intestine through which food could be taken into your body. Also, since the operation will be longer and the tissues which support the intestines in your body will be more disturbed than is usually the case, there is some small but additional chance of complications." In addition, the decision as to the extent of ileotomy in each case was to be made by the attendant surgeon in agreement with one of three associates named by the committee. The attendant surgeon rejected the contingency on the grounds that this constitutes an unwarranted intrusion by the hospital into the doctor-patient relationship. The hospital committee pointed out that this relationship did not, in its opinion, include the conduct of research. No agreement being reached, permission to carry out the project was not granted.

V. The applicant proposed a study of fetal body composition to be based on therapeutic abortion material. Fetuses obtained by dilatation and curettage during the first trimester would be subjected to total body analysis. Fetuses obtained during the second and third trimesters would be delivered by cesarean section, dissected, and subjected to organ by organ analysis plus total analysis of the undissected tissues. Fetal material was to be obtained from a collaborating hospital licensed by the state to perform therapeutic abortions. Since the great majority of abortions performed in the institution were done in the first trimester, the collaborating physicians would "encourage" some participants to delay abortion until the second trimester.

The sponsoring institution objected to establishing initial and continuing review procedures since: 1) under the laws of the state no "human subjects" were involved, only fetuses which are "legal non-persons," 2) procurement of the fetal material was under the control of

another institution, and 3) the procedures proposed were customary medical practice in this state.

The reactions of the reviewers for the NAHC were: 1) despite the fact that the fetus had no legal status in this jurisdiction, the mothers did, 2) responsibility for initial and continuing review always stays with the sponsoring institution, and 3) the protocol clearly showed that choice of a procedure or timing of a procedure were to be altered to meet the requirements of the project.

The institution instituted its own review and subsequently withdrew the application without explanation.

VI. In a study involving premature infants born with respiratory distress syndrome (RDS), patients were to be exposed to either 80 percent or 90 percent oxygen therapy on a random basis. Since high tension oxygen therapy is considered "standard," the investigator suggested that no specific parental consent to an infant's participation in the project was necessary. He also pointed out that problems involved in locating the parents and explaining the project's purposes might delay treatment.

The institution's committee concurred, noting that application of "standard" procedures did not constitute research.

The NAHC questioned this decision, holding that a comparison of two accepted procedures constituted research, particularly when assignment of patients to treatment modalities was based on statistical rather than medical criteria. The NAHC cited a legal opinion that: "an informed written consent should be obtained from both, or at least one parent, prior to participation of the infant in the study even though both procedures involved are currently 'standard' and that generally, medical judgment dictates neither the one or the other."

VII. Response contingent reinforcement of infant vocal behavior was to be attempted using a variety of visual stimuli in a controlled environment. Stimuli were to be drawn from the infant's immediate world but were to center around the mother. Initially, reinforcement would be attempted using videotape of the mother moving about the room and approaching the child. The videotape would be started in the absence of vocal activity. If normal vocal activity were interrupted by crying or other "non-responsive" behavior, the tape would be shut off for varying periods. Healthy subjects

were to be introduced into the program at the age of 3 months and continued at intervals over a period of 3 years.

The consent statement to be presented to the parents or legal guardians stressed the benefits of early vocal competence and mentioned the possible hazards of temporary isolation (1-hour periods) and adjustment to companions with lesser vocal abilities.

The NAHC raised questions with regard to possible deleterious effects of such a program on the maternal-child relationship, pointing out that crying usually reflected need on the part of the child. Systematic withdrawal of the "mother image" seemed ill-advised. The investigator emphasized that volunteers had already been obtained. The committee pointed out that not all possible hazards had been explained and that the consents could not be considered informed. After some negotiation and pretesting of alternate consent statements, the project was withdrawn by mutual agreement of the investigator and the committee.

VIII. The investigator had proposed a study of the lymphatic drainage of the thoracic cavity and its relation to the route of metastases in mammary carcinoma. The initial several months of the study had coincided with an exceptionally high incidence of appropriate cases coming to autopsy, and the initial aims of the project were rapidly accomplished. The investigator proceeded to a logical second step, the cannulation of the thoracic duct and study of circulating tumor cells in the lymph of mammary cancer patients as well as studies on tumor cells in the blood.

Review by the NAHC of a renewal application led to questions as to the morbidity associated with the procedure and as to the circumstances under which consent was being obtained from cancer patients and "normal" patients. The investigator quite frankly admitted that the morbidity rate approached 25 percent, some of it serious, and that both groups of patients were being told that the procedure was necessary for diagnostic purposes. Since the cancer patients had already been diagnosed, and the criterion for selection of the "normal" group was an absence of lymphatic involvement, the patients were clearly being misinformed. The reviewers asked the institution for an explanation of its apparent approval of deliberate misinformation of patients. The institution replied, "Surely, you do not expect us to question a decision by the Chief of Surgery." The project was disapproved.

b.

Who Should Participate, within What Structure, in Professional Regulation?

[1]

*United States Public Health Service
Protection of the Individual as a Research
Subject**

Safeguarding the rights and welfare of human subjects involved in research supported by the Public Health Service is the responsibility of the institution to which support is awarded. It is the policy of the Public Health Service that no grant, award, or contract for the support of research involving human subjects shall be made unless the research is given initial and continuing review and approval by an appropriate committee of the applicant institution. This review shall assure that (a) the rights and welfare of the individuals involved are adequately protected, (b) the methods used to obtain informed consent are adequate and appropriate, and (c) the risks to the individual are outweighed by the potential benefit to him or by the importance of the knowledge to be gained.

The institution must provide written assurance to the Public Health Service that it will abide by this policy for all research involving human subjects supported by the Public Health Service. This assurance shall consist of a written statement of compliance with the requirements regarding initial and continuing review of research involving human subjects and a description of the institution's review committee structure, its review procedures, and the facilities and personnel available to protect the health and safety of human subjects. In addition to providing the assurance, the institution must also certify to the Public Health Service for each proposal involving human subjects that its committee has reviewed and approved the proposed research before an award may be made.

Since the welfare of the subject is a matter of concern to the Public Health Service as well as to the institution, PHS advisory groups, consultants, and staff will independently review all research involving human subjects, recommending unfavorable action on grants, contracts, or awards if the research presents unacceptable hazards.

Similarly, the institution should be prepared at all times to question the conduct of research,

* Washington, D.C.: U.S. Department of Health, Education, and Welfare (1969).

even though previously approved by both the institution and the Public Health Service. The safety and welfare of the subject are paramount.

If any conflict exists between institutional policy, PHS policy, or State or local laws, the more restrictive requirements will be followed.

Research subjects.

A subject is considered to be any human being exposed to any research procedure as the result of the availability of Public Health Service funds, whether provided through research, training, or other types of grants, awards, or contracts. Subjects may include, therefore, persons involved in behavioral science studies; normal volunteers; donors of services; inpatients and outpatients; living donors of body fluids, organs, and tissues; and members of the general population who may be involved in environmental or epidemiological studies or similar activities.

An individual should generally be accepted as a research subject only after he, or his legally authorized guardian or next of kin, has consented to his participation in the research. Such consent is valid, however, only if the individual is first given a fair explanation of the procedures to be followed, their possible benefits and attendant hazards and discomforts, and the reasons for pursuing the research and its general objectives.

The subject does not abdicate his rights by consenting to participate in a research project. He may withdraw his consent at any time. Further, he has the right to be secure in his person, to receive proper professional care, to enjoy privacy and confidentiality in the use of information about himself, and to be free from undue embarrassment, discomfort, and harassment.

Applicability.

This policy applies to all projects which go beyond the diagnostic and therapeutic needs of the subject, as determined by his attending professional and the institutional committee. Such projects may involve the procurement of human materials or services and may be supported by a variety of mechanisms, e.g., research training, or demonstration grants; general research support grants; and fellowship, traineeship, or contract awards.

The applicability of this policy is most obvious in medical and behavioral science research

involving procedures that may induce a potentially harmful altered state or condition. Surgical procedures; the removal of organs or tissues for biopsy, transplantation, or banking; the administration of drugs or radiation; the use of indwelling catheters or electrodes; the requirement of strenuous physical exertion; subjection to deceit, public embarrassment, and humiliation are all examples of procedures which require thorough scrutiny by institutional committees.

There is a wide range of medical, social, and behavioral research in which no immediate physical risk to the subject is involved. However, some of these may impose varying degrees of discomfort, irritation, and harassment. In addition, there may be substantial potential injury to the subject's rights if attention is not given to maintenance of the confidentiality of information obtained from the subject and the protection of the subject from misuse of findings.

There is also research concerned solely with discarded human materials obtained at surgery or in the course of diagnosis or treatment. The use of these materials involves no possible element of risk to the subject. In such instances application of the policy requires only review of the circumstances under which the materials are to be procured.

* * *

Minimum requirements for an acceptable assurance.

An acceptable assurance consists of two parts:

Formal statement.

A formal statement of compliance with Public Health Service policy must be signed by an appropriate institution official. . . .

Implementing guidelines.

The institution's description of its own procedures should embody the three headings listed below. The explanatory paragraphs following each heading indicate the type of information which should be supplied.

Statement of principles concerning the treatment of human subjects.

It is necessary that the guidelines make reference to the principles the institution will

apply in its review of research involving human subjects. The institution may adopt an already existing statement of principles (e.g., the Nuremberg Code, the Declaration of Helsinki, the Statement of Ethical Standards in Research of the American Psychological Association) or it may develop its own statement.

Description of the review committee

The committee must be composed of sufficient members with varying backgrounds to assure complete and adequate review of the research. The committee may be an existing one, or one especially appointed for the purpose. Institutions may utilize subcommittees to represent major administrative components in those instances where establishment of a single committee is impractical or inadvisable. The institution may utilize staff, consultants, or both. The membership should possess not only broad specific competence to comprehend the nature of the research, but also other competencies necessary in the judgment as to acceptability of the research in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. The committee's maturity and experience should be such as to justify respect for its advice and counsel.

No individual involved in the conduct of the research activity shall participate in its review, except to provide information to the committee.

Committee members should be identified in the assurance to the Public Health Service in terms of position, earned degrees, board certifications, licensures, memberships, and other indications of experience and competence. Names need not be given.

Description of the initial and continuing review procedures to be followed by the committee.

Timing of review.

Research described in applications and contract proposals should, whenever possible, be given institutional review and approval prior to submission to the Public Health Service. Where review prior to Public Health Service submission is not possible, the review must be made prior to issuance of the award by the Public Health Service. Review of initial applications by institutions which have not previously filed acceptable assurances must be performed after acceptance of the assurance by the Public Health Service.

There may be occasions when a second review by the committee will be required before the research

is initiated. For example, a long interval has elapsed between committee review and initiation, or the investigator proposes changes in protocol after the application has been reviewed by the committee but before the research is initiated. Perhaps the investigator has proposed research in a rapidly moving scientific area. The second review, in this case, would determine if changing standards of practice indicate a hazardous procedure unrecognized as such during the initial review (e.g., reduction of acceptable radiation levels).

Adequacy of the protection of the rights and welfare of the subjects involved.

Institutional committees should carefully examine the research plan to arrive at an independent determination of possible hazards. The committee must be alert to the possibility that investigators, program directors, or contractors may, quite unintentionally, introduce unnecessary or unacceptable hazards, or fail to provide adequate safeguards. This is particularly true of research that crosses disciplinary lines. The committees should consider the research plan as a whole in order to determine that normally minor and acceptable risks are not aggravated by the way it is designed. The severity of the risk from a procedure may vary with the circumstances under which it is carried out. Age, development, size, maturity, intercurrent disease, and other factors with respect to the subject may adversely affect the acceptability of a procedure. Simultaneous or consecutive performance of several minor tests or procedures may add up to a substantial risk. The committees must assure themselves that proper precautions will be taken to deal with emergencies that may develop even in the course of routine procedures.

Relevant to the decision of the committees are those rights of the subject that are defined by law, particularly those concerned with the rights of children and unborn infants; the termination of pregnancy; the use of prisoners, institutionalized, and military personnel; and the donation of tissues and organs.

Methods used to obtain adequate, appropriate, informed consent.

* * *

Consent should be obtained, whenever possible, from the subjects themselves. When the subjects are not legally or physically capable of giving informed consent, because of age, mental incapacity, or inability to communicate, or when the attending professional believes that the giving of full information would be contrary to the best interests of the subject, the review committee may consider the validity of consent by next of kin, legal guardians, or by other responsible third parties who are representative of the subject's interests. In the latter instances, careful consideration should be given by the committee not only to the third parties' depth of interest and concern with the subjects' rights and welfare, but

also to whether the third parties are authorized to expose the subjects to the risks involved. A parent, for example, may have no authority to expose his child to risk, except for the child's own benefit.

The review committee should determine if the consent, whether secured as a written document or given orally, or whether the consent is implicit in voluntary participation in a well-advertised activity, is adequate in the light of the risks to the subject and the circumstances of the research. The review committee should also determine if the information to be given to the subject or to qualified third parties, orally or in writing, is a fair explanation of the procedure, its possible benefits, and its attendant hazards. Where debriefing procedures are considered as a necessary part of the research plan, the committee should ascertain that these will be complete and prompt.

When the sponsoring institution routinely obtains a generalized form of consent for treatment or care, the committee shall determine whether these routine procedures provide an adequate basis for the subject's informed consent to the research procedures involved.

Relative weights of risks versus benefits.

Even though informed consent has been obtained or can be anticipated, the committee shall carefully consider the relative weights of the risks and benefits of the procedures to the subjects. If a procedure may confer a substantial benefit to the subjects, the committee may be justified in permitting them to accept an equally substantial or lesser risk. Where the potential benefits to the subjects are negligible, or nonexistent, as in some cases of normal volunteers, the committee may be justified in permitting subjects to accept a risk in the interests of humanity. In all instances, careful consideration must be given by the committee to the subjects' motivation in accepting them.

* * *

Continuing review of research.

The committee shall require the project or program director to report to the committee for review any emergent problems or proposed procedural changes which may affect the status of the research with regard to the institution's review criteria. No such changes, except those necessary to eliminate apparent immediate hazards, should be made without prior approval by the committee.

In addition, the committee shall carry out interim review of the conduct of all research in such a manner and at appropriate intervals in the light of apparent risks, existing administrative and supervisory organization, and other factors as to assure itself that its advice is being followed.

The facilities available to protect the health and safety of human subjects.

The assurance should describe in general terms the

facilities and personnel available to protect the health and safety of human subjects, particularly those requiring emergency care.

* * *

Records and reports.

The institution is required to keep informative records of group reviews and decisions on the use of human subjects, and to obtain and keep documentary evidence of informed consent relating to research carried out with the assistance of Public Health Service financial support. At a minimum these records should include a summary of the factors leading to the group decision. Documentary evidence of informed consent may consist of a record of the decision of the committee as to the type of consent which it considers acceptable. Copies of the information statement, if any, to be given to the subject, where signed consent statements are required, should be retained in institution files. Where oral or implied consents are obtained, notations should be made on official records.

* * *

NOTES

NOTE 1.

LOUIS G. WELT
REFLECTIONS ON THE PROBLEMS OF HUMAN
EXPERIMENTATION*

* * *

A letter was written to every university department of medicine in the country seeking answers to the following questions:

1. Does your department or school have a procedural document dealing with problems of human experimentation?

2. What are your personal views concerning the principles which may serve to guide the clinical investigation?

3. What criteria should be satisfied in the creation of the experimental design to assure appropriate attention to the moral and ethical problems involved?

4. Do you think a committee of disinterested faculty should review the experimental design to insure maximum protection for the subject?

Responses were received from 66 departments. Of these only eight have a procedural document and only 24 have or favor a commit-

* 25 *Connecticut Medicine* 75 (1961). Reprinted by permission of *Connecticut Medicine*.

tee to review problems in human experimentation. The discussions of the second and third questions have been interesting and helpful. Since there was no true consensus an attempt will be made to express some of the more prevalent views.

1. Many felt that a procedural document might be a poor idea. This stemmed, for the most part, because it was anticipated that no one can prepare a document which can hope to be more useful than hindering. It was felt by some that a document of rules would place obstacles in the path of legitimate research by responsible investigators, and would provide little or no protection from the irresponsible. Many would agree, perhaps, that if a document is deemed necessary it would be more reasonable to prepare a statement of general principles that would serve to guide rather than rule.

2. There is division on the question of the value of a committee to review experimental protocols. Some favor it and others see this as either useless or harmful. The latter argue that a committee cannot take responsibility, that this must always be in the hands of the individual investigators and should be shared by his department chairman who is, in fact, ultimately responsible for all that goes on within his department. The departmental chairman will seek consultation and advice when he feels this is necessary. In this fashion the valuable consultative features of the committee are available, but there is emphasis on the fact that the legal and moral responsibilities return to their rightful place in the minds and hearts of the investigators.

The other view emphasizes the more certain assurances of safety and the improvements in design that may accrue from a careful and responsible review by a committee of peers.

* * *

NOTE 2.

BERNARD BARBER, JOHN LALLY,
JULIA MAKARUSHKA, AND DANIEL SULLIVAN
THE STRUCTURE AND PROCESSES OF
PEER GROUP REVIEW*

* * *

Many people had predicted widespread opposition to the "imposition" of P.H.S. guide-

lines when they were put into effect in 1966. In fact, as our data show, the guidelines and their mandated committees have been fairly well received. In 52.5 percent of the institutions in our sample, our respondents reported that the work of the committee was "very well received." In another 36.8 percent, the committee was "fairly well received, no opposition." In only 10.7 percent of the institutions did our respondents report any opposition to the work of the committee. Assuming that our respondents have accurately estimated the response of their colleagues to the P.H.S.-initiated control over their research, what can account for this perhaps unexpectedly favorable reception to a restrictive social innovation? . . .

First . . . there was less opposition to the P.H.S.-mandated peer review committees in those institutions which already had a review procedure of their own. Though the differences . . . are small, they are significant. Further . . . if the P.H.S. guidelines required changes in the existing review procedure, the new procedures were less likely to be "very well received."

Neither of the above two findings is unexpected. Somewhat unexpected, however, is our next finding, namely, that in institutions which required that all research be reviewed, the committee was more likely to have been "very well received". . . This seems to indicate that though researchers prefer less rather than more restrictions on their work, they react favorably when local institutional policy, restrictive or not, is applied universalistically. The finding seems to imply that researchers think it more fair if no researcher is exempt just because his research is funded by some other agency than the P.H.S.

* * *

By far the largest determinant of the acceptance of peer review, however, was whether the committees actually did anything which infringed on the independence of the researchers. Where review committees rejected one or more proposals, required some revisions, or where one or more researchers withdrew proposals before the committee made a formal decision, then the P.H.S.-mandated committees were much more likely to run into some opposition. . . .

Thus, it seems fairly clear that the amount of opposition to this social innovation was as small as it was because slightly more than one-third of the review committees that were set up have never done anything but approve the research proposals that were submitted.

* A preliminary version (1970) of *Experimenting With Humans: Problems and Processes of Social Control in the Bio-Medical Research Community*. New York: Russell Sage Foundation (forthcoming). Printed by permission of the authors who retain all rights.

[ii]

*Yale Medical School Clinical Investigation
Committee*

*Instructions Regarding Medical Research
Involving Human Subjects (1968)**

The Clinical Investigation Committee is charged with the responsibility of reviewing protocols for *all research involving human subjects* by the faculty of the Yale University School of Medicine. The Committee is not only concerned with the safety of the experimental subjects but also the suitability of the study and the legal protection of each investigator. There are few hard and fast rules, but certain minimum requirements are essential.

Most research protocols submitted to the Committee are well designed and do not involve unreasonable risk, but final approval for many has been delayed because of lack of certain critical information. In order to expedite the mechanism for obtaining Committee approval and the coordination of activities in the clinical research centers new forms and new procedures have been developed. A *single form* now is used as the protocol for both the Clinical Investigation Committee and either of the clinical research centers. The following instructions and comments may be helpful:

1. *The Research Protocol*—for each study 5 copies of the Research Protocol are prepared by the investigator, signed by his departmental chairman and returned to . . . (Dr. Finch). (Protocols for multi-departmental projects should be signed by the chairman of each department.) One copy of each protocol is sent to each member of the Clinical Investigation Committee for study. Committee meetings usually are held the last Friday of each month. At that time protocols previously circularized to Committee members are reviewed. The *deadline* for protocol consideration by the Clinical Investigation Committee is one week before the monthly meeting. If the Chairman of the Clinical Investigation Committee anticipates problems concerning a particular project he may request that the senior investigator be present at the meeting. If approved, either 4 or 5 copies of the protocol are signed by the Chairman; one copy is returned to the principal investigator, one copy is retained in the files of the Clinical Investigation Committee, and two copies are for-

warded to the Dean's Office for appropriate university distribution. If the investigator requested use of a clinical research center the fifth copy of the protocol is sent to the director of the appropriate clinical research center for his records.

If clearance for *single patient* study in a *clinical research center* is needed the investigator should submit completed protocols in triplicate to the director of the clinical research center. He will promptly review the project protocol for the Clinical Research Committee. One copy of the approved protocol is retained by the director of the clinical research center, one copy is inserted in the patient's clinical record, and one copy is forwarded to the Chairman of the Clinical Investigation Committee. All single-patient protocols will be brought to the attention of the members of the CIC at their monthly meetings.

The *Research Protocol* should provide a concise, yet explicit description of the research procedure along with information concerning known or potential side effects, risks, or hazards. Background material, research objectives, and design are much less important than is information concerning the actual experimental procedure and its potential dangers. Information concerning the uses of *new drugs and new uses for old drugs* frequently is insufficient. The human administration of new drugs or foods, even in tracer amounts, requires FDA approval. If there is any question about the human use of a compound (or food) as described in the protocol, prior FDA (Bureau of Medicine, Office of New Drugs) opinion or clearance is essential.

2. *Guidelines concerning patient consent*—The Clinical Investigation Committee endorses the position taken concerning informed consent in the "AMA Ethical Guidelines for Clinical Investigation" (*Annals of Internal Medicine*, 67: Supplement 7, pp. 76-77, September, 1967). In general, the Committee will require that consent be obtained from the subject or his legal guardian in writing on a standard form (supplied by the Committee) unless, in the opinion of the investigator, written consent is inappropriate. Reasons for not requiring written consent must be clearly stated. It would be helpful in these instances if a specific exclusion from the AMA Ethical Guidelines could be cited in the research protocol.

The Committee wishes to remind investigators that in some studies, involving either new foods or drugs or new applications of established drugs, some of the options stated in the AMA

* S. C. Finch, M.D., chairman. Reprinted by permission.

Ethical Guidelines do not apply. It is the responsibility of the investigator to find out whether or not his study is covered by FDA regulations; if in doubt, he can check with the FDA; Bureau of Medicine, Office of New Drugs. In studies of new drugs, ordinarily there will be institutional sponsorship (e.g., a drug company); it is the responsibility of the sponsor to file Statement of Investigator forms with the FDA; these forms specify requirements for informed consent for each type of study. Filing an Investigational New Drug Application with the FDA is so formidable a procedure that the Committee doubts that any individual investigator would wish to proceed without institutional sponsorship. The FDA has summarized its policy regarding *drug testing* in a publication entitled *FDA Papers* dated March 1967 in an article entitled "Clinical Testing: Synopsis of the New Drug Regulations."

3. *Consent Form*—If written consent is to be obtained 5 copies of a completed form must accompany each research protocol. They are processed along with the research protocols in the same fashion. The upper portion of the consent form should contain a clear description of the program in words that are understandable to the patient. (Describe purpose, type of research and major potential hazards or side effects.) It should be emphasized to all investigators that a signed consent form provides little actual legal protection, but without such a form signed by the experimental subject, his parent, or legal guardian, the investigator's position is much less secure. The most important aspect of informed consent is to certify that the experimental subject is willing to participate in a study with full knowledge of the objectives and all major risks. . . .

* * *

NOTE

YALE MEDICAL SCHOOL CLINICAL
INVESTIGATION COMMITTEE
GUIDELINES FOR PREPARATION OF PROTOCOLS
(1971)*

* * *

The most common reason for delay of approval of a protocol is an improperly prepared consent form. The consent form should be a

* Draft Memorandum prepared by Drs. Robert J. Levine, Chairman, Clinical Investigation Committee, and George Lister. Reprinted by permission.

statement addressed to the patient and should read as such. Ordinarily, it is best to word it in the second person. It should not repeat what is stated in Section 6 on the protocol but rather should describe in language that the average layman can be expected to understand the general nature, intent, and design of the experiment with particular attention to those aspects of it in which the subject must participate. The following points must be covered:

1. The subject should understand why he has been selected for participation in the study. Ordinarily this is because of a specific disease or condition that he or one of his relatives might have.

2. Ordinarily, the study is being done not for the benefit of the subject but rather for purposes of deriving information which may in the future be of benefit to others; this should be made clear on the consent form.

3. It must be clearly stated that agreement to participate in the study bears some risk of either hazards or—at least—inconveniences.

4. When appropriate it should be stated that the subject is free to refuse to participate and that such refusal will not adversely prejudice his future treatment. Further, it should indicate that the subject is free to withdraw from the study unless the investigation, once commenced, precludes this.

5. In cases where consent will be obtained by persons other than the investigating physician this should be indicated in the lower left corner of the consent form by either replacing or adding to the word "physician."

* * *

Subjects should be invited to raise questions about anything in the consent form that they feel requires clarification. It is further recommended that subjects be given a copy of the signed consent form.

In some studies it may be appropriate to secure consent orally rather than in writing. Ordinarily such studies involve minor manipulations such as a single drawing of a small volume of blood. If the investigator feels that oral consent is appropriate for his study he should put on the consent form the information he plans to present to the subject for purposes of securing oral consent. Also on the consent form there should be a request that the CIC waive the requirement of securing consent in writing.

[iii]

*The Massachusetts General Hospital
Human Studies—Guiding Principles and
Procedures**

* * *

**Procedure in Cases of Research Involving
Human Subjects—General Hospital Division**

Whenever an investigative project is planned which will involve one or more human subjects, the investigator concerned shall first consult with the Chief of Service or Department as to the character of the project. The investigative plan shall then be referred to the Committee on Research and its Subcommittee on Human Studies for review and advice. In all instances, not only will such a review be conducted prior to and at the same time as close as possible to the initiation of the studies involved, but also all research projects will be so reviewed to assure the Committee on Research and the Board of Trustees that other projects do not in fact include studies of human subjects. . . .

In its review, after establishing that a given proposal involves human subjects, the Subcommittee on Human Studies shall carefully examine the research plan for its conformance to the "Guiding Principles" and render its advice and recommendations to the Executive Committee of the Research Committee. The Executive Committee shall forward its advice and recommendations to the Committee on Research which in turn will report its recommendations to the Chief of Service and the General Director. In the event that the Subcommittee decides that the research plan does not ensure adequately the rights and welfare of the human subject (as outlined in the "Guiding Principles"), the Committee on Research shall report its advice to the Chief of Service or Department and the General Director. Any corrective action recommended by the Committee on Research and its Subcommittee on Human Studies shall be carried out by the Chief of Service or Department.

It is the responsibility of the Chief of Service to decide whether to accept the advice of the Committee on Research or to refer the matter to the General Director and the Trustees for a definitive decision. The Trustees may seek the advice of its Advisory Committee on Research

and the Individual* in the unlikely event of disagreement among those concerned.

In addition, it shall be the Chief's responsibility to know when any significant change is contemplated or has been made in a project on his Service that involves human subjects which would then require further review.

A record will be made in the Research Office as to the actions taken with regard to any project.

The chart shows diagrammatically the decision-making process [see following page].

NOTES

NOTE 1.

**OFFICE OF SCIENCE AND TECHNOLOGY
PRIVACY AND BEHAVIORAL RESEARCH†**

* * *

Responsibility for monitoring the propriety of behavioral research must be shared by the entire community of colleagues of the investigator in his home institution. The investigator may be too deeply involved in his hoped-for outcomes, as may colleagues in his own discipline; responsibility for reviewing matters of propriety

* Trustees' Advisory Committee on Research and the Individual, 1970: The Right Reverend Henry Knox Sherrill, *Chairman*; Henry K. Beecher, M.D., *Henry Isaiah Dorr Professor of Research and Teaching in Anaesthetics and Anesthesia, Emeritus, Harvard University*; Mary I. Bunting, Ph.D., *President, Radcliffe College*; William J. Curran, LL.M., S. M. Hyg., *Frances Glessner Lee Professor of Legal Medicine, Harvard University*; Daniel D. Federman, M.D., *Associate Professor of Medicine, Harvard University, Physician, Massachusetts General Hospital, Ex officio as Chairman of the Subcommittee on Human Studies of the Committee on Research, Massachusetts General Hospital*; Paul A. Freund, S.J.D., *Carl M. Loeb University Professor, Harvard University*; Franz J. Ingelfinger, M.D., *Clinical Professor of Medicine, Boston University, Editor, New England Journal of Medicine*; John H. Knowles, M.D., *Professor of Medicine, Harvard University, Ex officio as General Director, Massachusetts General Hospital*; Charles P. Price, Th.D., *Plummer Professor of Christian Morals, Harvard University*; Francis O. Schmitt, Ph.D., *Institute Professor, Massachusetts Institute of Technology, Trustee, Massachusetts General Hospital*; Ralph G. Meader, Ph.D., *Deputy Director (Research Administration) and Executive Secretary, Committee on Research, Massachusetts General Hospital*.

† Washington, D.C.: U.S. Government Printing Office 23-24 (1967).

* Boston: The Massachusetts General Hospital 13-14 (2nd ed., 1970). Reprinted by permission.

must therefore be shared with less-concerned but well-informed associates. When the investigator is a member of the faculty of a university, there will be scientists and scholars in his own and in unrelated fields who can provide independent judgments about the quality of his research and the appropriateness of the methods he plans to use. In Government agencies and laboratories and, in fact, in almost every institution, similar peer groups can be established.

The individual investigator must accept the obligation for consulting with appropriate colleagues and senior associates about his work. In addition, the institution itself must accept the responsibility for insuring that the work is done by methods which it is willing to defend, and by investigators whose judgment it is willing to defend. The universities, especially those which have substantial research programs, can provide patterns that will serve as models for other institutions that sponsor research.

Beyond this, the universities, as the chief educators of the next generation of research workers, must accept the obligation to imbue their students with the highest standards in the conduct of research.

A university sometimes finds it difficult to play the role that it would be willing to accept since the individual investigator often establishes his primary relationship with the financing agency. The financial implications of this independence of the investigator and of his relationships with the funding agency have already been referred to in the report of the Wooldridge Committee. The same considerations that apply to fiscal responsibility apply to the propriety of research. When an agency of the Federal Government awards a grant to an investigator, it should assign to the institution where he works the continuing responsibility for insuring that the investigation is carried out in accordance with the highest standards of conduct.

The Public Health Service has recently moved to place this responsibility upon the sponsoring institution. The procedures instituted and the instructions issued should have the very desirable effect of increasing the responsible review of research proposals by institutions. A further benefit of the new procedures used by the Public Health Service is the decentralization of supervision and review from agencies in Washington to institutional representatives who can play a more effective role on a continuing basis.

* * *

NOTE 2.

HAROLD J. LASKI
THE LIMITATIONS OF THE EXPERT*

* * *

[I]t is one thing to urge the need for expert consultation at every stage in making policy; it is another thing, and a very different thing, to insist that the expert's judgment must be final. For special knowledge and the highly trained mind produce their own limitations which, in the realm of statesmanship, are of decisive importance. *Expertise*, it may be argued, sacrifices the insight of common sense to intensity of experience. It breeds an inability to accept new views from the very depth of its preoccupation with its own conclusions. It too often fails to see round its subject. It sees its results out of perspective by making them the centre of relevance to which all other results must be related. Too often, also, it lacks humility: and this breeds in its possessors a failure in proportion which makes them fail to see the obvious which is before their very noses. It has, also, a certain caste-spirit about it, so that experts tend to neglect all evidence which does not come from those who belong to their own ranks. Above all, perhaps, and this most urgently where human problems are concerned, the expert fails to see that every judgment he makes not purely factual in nature brings with it a scheme of values which has no special validity about it. He tends to confuse the importance of his facts with the importance of what he proposes to do about them.

* * *

... However much we may rely upon the expert in formulating the materials for decision, what ultimately matters is the judgment passed upon the results of policy by those who are to live by them. Things done by government must not only appear right to the expert; their consequences must seem right to the plain and average man. And there is no way known of discovering his judgment save by deliberately seeking it. This, after all, is the really final test of government; for, at least over any considerable period, we cannot maintain a social policy which runs counter to the wishes of the multitude.

It is not the least of our dangers that we tend, from our sense of the complexity of affairs,

* London: The Fabian Society 4, 12 (1931). Reprinted by permission.

to underestimate both the relevance and the significance of those wishes. We are so impressed by the plain man's ignorance that we tend to think his views may be put aside as unimportant. . . . But the inference from a knowledge that the plain man is ignorant of technical detail and, broadly speaking, uninterested in the methods by which its results are attained, is certainly not the conclusion that the expert can be left to make his own decisions.

* * *

NOTE 3.

LEO SZILARD
THE VOICE OF THE DOLPHINS*

* * *

"[W]hy not do something about the retardation of scientific progress?"

"That I would very much like to do," Mark Gable said, "but how do I go about it?"

"Well," I said, "I think that shouldn't be very difficult. As a matter of fact, I think it would be quite easy. You could set up a foundation, with an annual endowment of thirty million dollars. Research workers in need of funds could apply for grants, if they could make out a convincing case. Have ten committees, each composed of twelve scientists, appointed to pass on these applications. Take the most active scientists out of the laboratory and make them members of these committees. And the very best men in the field should be appointed as chairmen at salaries of fifty thousand dollars each. Also have about twenty prizes of one hundred thousand dollars each for the best scientific papers of the year. This is just about all you would have to do. Your lawyers could easily prepare a charter for the foundation. As a matter of fact, any of the National Science Foundation bills which were introduced in the Seventy-ninth and Eightieth Congresses could perfectly well serve as a model."

"I think you had better explain to Mr. Gable why this foundation would in fact retard the progress of science," said a bespectacled young man sitting at the far end of the table, whose name I didn't get at the time of introduction.

"It should be obvious," I said. "First of all, the best scientists would be removed from their laboratories and kept busy on committees pass-

ing on applications for funds. Secondly, the scientific workers in need of funds would concentrate on problems which were considered promising and were pretty certain to lead to publishable results. For a few years there might be a great increase in scientific output; but by going after the obvious, pretty soon science would dry out. Science would become something like a parlor game. Some things would be considered interesting, others not. There would be fashions. Those who followed the fashion would get grants. Those who wouldn't would not, and pretty soon they would learn to follow the fashion, too."

* * *

NOTE 4.

FRANCIS D. MOORE
THERAPEUTIC INNOVATION—ETHICAL
BOUNDARIES IN THE INITIAL CLINICAL
TRIALS OF NEW DRUGS AND
SURGICAL PROCEDURES*

* * *

There can be little question that personal ambition, usually for career advancement or public acclaim, underlies much intense motivation in research work and in the trial of new ideas, drugs, operations, or treatment. Such personal ambition is usually well hidden under the sophisticated affect of the dedicated clinical scientist and, far from being remiss, is the sign of a healthy society. While social convention requires its disguise in the masquerade of scientific intercourse, this ambition is not a thing to be ashamed of. Personal ambition for advance and recognition is a far better motive for the work of difficult or protracted clinical investigation than is the seeking of political advancement or financial reward. No matter how deep the urge for pure knowledge, few scientists have not derived some excitement from a general acceptance of their ideas or procedures, particularly if these were of potential social benefit. The possibility of such acceptance provides a more stimulating environment for scientific work than the even temper of an apathetic society where, because of the heavy system of penalties placed upon failure, there is neither a channel for innovation nor an interest in departure from tradition.

But ambition, no matter how praiseworthy,

* New York: Simon and Schuster 100-101 (1961). Copyright © 1961 by Leo Szilard. Reprinted by permission.

* 98 *Daedalus* 502, 518-519 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

can certainly lead individuals astray. A common example is found in the premature publication of scientific results. Personal ambition for recognition has clearly outstripped the cooler judgment of awaiting more definitive data. The active collaboration of scientists provides the best way of harnessing these fine qualities of excitement and ambition so as to maintain their force for forward motion and yet prevent them from running wild. For this reason, a collaborative group with open discussion, avoidance of secrecy, and frequent review of plans and policies seems far more important than the short-term arbitrary review of some one drug or operation by a formal panel with a strictly *ad hoc* mission. Such formal panels are usually composed of individuals who know little of the work contemplated, and they may even come to include individuals who for reasons of jealousy or ignorance would rather not see the old order challenged anyway. The ethical acceptability of therapeutic innovation documented in a research application, for example, is far better attested by the nature of the scientific consultants working on the project than it is by the nature of the hospital panel that is to review each case.

* * *

NOTE 5.

IRVING L. JANIS
PROFESSIONAL ROLES, NORMS, AND ETHICS—
A SOCIAL PSYCHOLOGICAL VIEWPOINT*

* * *

... I have heard some informal discussions in which a team of research workers puts forth a simple formula that all of them agree upon as an adequate justification, absolving themselves of responsibility for any potentially untoward effects of their human experiments: e.g., "You can't do scientific research on important human problems without taking risks." Research teams, like any other face-to-face work group, seem to be quite capable of developing shared rationalizations that give the members moral support in carrying out questionable actions—actions that, in any other social context, each individual would be inclined to forego. In extreme instances, a cohesive local group develops an informal code of its own that deviates from the norms of the superordinate organization and the community at large.

* 6a *The Canadian Psychologist* 143, 148 (1965). Reprinted by permission.

One major factor that must be taken into account in this connection is the attitude conveyed by the local leaders. Obviously, when a group of psychologists has a strong department chairman or clinical director who openly opposes the norms of the professional organization, the chances are greater that the group working under him will develop an informal code that deviates from the professional organization's norms. . . .

* * *

NOTE 6.

BERNARD BARBER
SOME "NEW MEN OF POWER"—THE CASE
OF BIOMEDICAL RESEARCH SCIENTISTS*

* * *

[T]he matter of outsiders is one that I consider particularly important. One of the possible defects of formal review committees is that even they, like informal groups, are too ingrown, too particularistic, too narrow in their perspectives, to function as well as they might. In view of these possibilities, I should like to see two kinds of outsiders mandated as members of all review committees. One kind is relevant biomedical research experts from institutions other than the one where the review committee functions. Such expert outsiders would carry from Harvard to Texas, or from Kansas to Cornell, for instance, a different perspective and an impersonal objectivity that is harder to provide from the inside. A second kind of outsider should be the sociological-legal-ethical expert, fairly knowledgeable about biomedical research, but, rather, an expert in such problems as the nature of social norms, the problems of fair or judicial procedure, and the relevance of public feelings, values, and knowledge to the ethical matter in hand. Indeed, with this kind of outsider in mind, I foresee a whole new social role, one in which people with various kinds of social science and legal training undergo further formal and on-the-job training to qualify themselves to serve on ethical review committees in biomedical research institutions. It is not sufficient to have a slightly trained person in this role. Some members of the clergy can fill it, but not all, and even those who are suited should have further training. Some members of the general public might fill it,

* 169 *Annals of the New York Academy of Sciences* 519, 521 (1970). Reprinted by permission.

but, once again, only if they have special sociological-legal skills and further training.

* * *

NOTE 7.

KENNETH L. MELMON, MICHAEL GROSSMAN,
AND R. CURTIS MORRIS, JR.
EMERGING ASSETS AND LIABILITIES OF A
COMMITTEE ON HUMAN WELFARE
AND EXPERIMENTATION*

* * *

The Committee [on Human Welfare and Experimentation of the University of California at San Francisco] realized that the number of applications, the diversity of subject matter and the seriousness of the task would preclude meaningful review of consistent and high quality by a small fixed group. Therefore, the Committee established itself as parent group to three-man ad hoc review committees it appointed for each submitted protocol. Members of the parent committee could review some applications and take "administrative action," or they could serve on ad hoc committees. Members of the ad hoc groups were chosen by the Committee on Human Welfare and Experimentation from the faculty at large. Each member was chosen for his objectivity, morality, expertise in some area related to the research protocol, ability to communicate critical information to the investigator and lack of personal involvement in the research project.

* * *

The chairmen of ad hoc committees were asked to file a written report to the parent committee within 10 days of its assignment to the ad hoc committee. Disagreement by any member on any of the six points used for review was interpreted as a potential disapproval and required that the parent committee transmit recommendations for revision to the investigator. Re-examination of the revised protocol by the parent committee could then result in approval. If the ad hoc group disapproved unanimously of any of the six points, revision became mandatory, and the protocol could be accepted only with the unanimous approval of the ad hoc committee. In response to disapproval, an investigator could withdraw the request, alter the protocol to comply with recommendations or request an-

other ad hoc committee that would review the protocol de novo. No more than two ad hoc committees could review an unaltered protocol.

Administrative approval was given by the chairman of the Committee on Human Welfare and Experimentation under two circumstances. When an unanticipated opportunity for research arose and required immediate response, the investigator could submit a written request for a single study. The permission for such a study could be granted without committee action, but additional studies could not be done before formal approval by an ad hoc committee. Administrative approval could also be granted for studies involving routine tests or minimal risk. The great majority of such requests were for venous-blood sampling totaling less than 50 ml from nonanemic volunteers or patients. No protocols could be finally rejected by administrative action alone.

The first-year and second-year experiences were compared on the basis of the following criteria: Was there compliance with the questions listed above? Could evolutionary patterns of committee function be appreciated? Did aspects of protocol procedure affect an ad hoc committee's action? What were the judgments or philosophies of the reviewers on the ad hoc committees, and were changing or unanticipated factors operating in decision making?

Difficulties are many and perhaps obvious in such an evaluation. Protocols vary widely in the care with which they are prepared, reviewers may be internally inconsistent, and various reviewers approach the evaluation with different standards. In view of such considerations, it is perhaps surprising that useful information could be gleaned from the review of the data.

* * *

New applications averaged greater than three per week and the number in the second year was greater than in the first. This trend has continued. In the first six months of the third academic year of committee function, 265 applications have been received for a projected total of greater than 500 for the third year. In each of the first two years, the number of applications assigned to ad hoc committees remained approximately the same, but initial rejections increased from 12 to 20 and final rejections tripled (from four to 13) in the second year. An increasing seriousness of approach to review by the ad hoc committees can be inferred from the increased percentage of unqualified dissensions in the sec-

* 282 *New England Journal of Medicine* 427, 428-431 (1970). Reprinted by permission.

ond year. Similarly, the standards of the ad hoc committees approximated more closely those of the representatives of the parent committee (and of the entire parent committee, whose members have not changed). Inconsistencies were fewer in the second year than in the first. Literature citations were more carefully selected, and greater care was taken to explain the objectives and methods in both the protocol and the consent form. During the second year, progressively more disagreement arose within ad hoc committees regarding the appropriateness of the way in which consent was secured and risk described.

All 17 rejected protocols were reviewed by at least two ad hoc committees. A striking finding is that each protocol rejected initially was rejected by a second committee that was unaware it was reexamining a previously rejected protocol. Seven protocols were rejected because risk benefit could not be assessed from the description of objectives and methods. None of the seven decisions were contested. Eight protocols were rejected because of inadequate precautions, and the remaining two rejections were because of unacceptable risk.

When a sample of seven rejected protocols was compared to acceptable proposals by the same authors, striking differences were apparent in the care of preparation of the protocol (including length, number of references, number of misspelled words and uncorrected typographical errors). Although this was a subjective appraisal, there seemed little doubt that investigators had given considerably less thought and care to the protocols that were rejected than to those approved.

Most of the reviewers interviewed believed that protocols should be submitted anonymously; some admitted that they were swayed by the academic status of the investigator. A distinct minority admitted that incomplete protocols were more likely to be passed if submitted by a full professor with a "good reputation" than if submitted by a younger, "less established" faculty member. Of note was the fact that all rejected protocols were submitted by University of California tenure faculty members. The majority (58 per cent) of total applications were submitted by nontenure faculty.

The majority of reviewers, who also serve as referees or editors to scientific journals or members of National Institutes of Health study sections, observed that time expended on an average review during the second year was considerably greater than during the first; the aver-

age time necessary for a review of a protocol for the ad hoc committee was greater than that spent on an average paper reviewed for a journal. The reviewers all suggested a larger pool of reviewers, but only one preferred not to continue.

None of the reviewers interviewed knew of flagrant violations of committee policy (investigators who had proceeded without approval from the committee), and yet two probable violations were discovered during the second year. Neither violation was detected as a result of policing, but each became evident upon casual observation by faculty either previously involved in evaluations or concerned with standards of human experimentation. Such an observation may imply that formal policing may not be necessary as long as a broad spectrum of faculty participates in reviewing protocols. There is a clear division of opinion over whether policing should be instituted, but many agree that a high-level administrator should be apprised of all detected violations. Such a policy might influence the quality of applications by some and the adherence to regulations by others. Now, infractions of policy are brought to the attention of the involved department chairman and sent to a research policy committee of the school in which the infraction has been involved. Action by this committee is not included in the files of the Committee on Human Welfare and Experimentation. Although preliminary investigation can be undertaken by the parent committee, it is convinced that definitive decisions on punitive action should not be within its purview. Such judicial action could severely and unduly prejudice future reviews of projects proposed by the same investigator, would be unrelated to measures taken after other violations of campus policy, and could alter the focus of the function of the Committee on Human Welfare and Experimentation.

* * *

The most difficult tasks for the Committee on Human Welfare and Experimentation were as follows: to disseminate convincing information that there is a legal as well as a moral obligation for investigators with any affiliation to the University of California to submit protocols on investigations in human beings for peer-group evaluation; to establish a guide for investigators that clearly stated that objectives of peer-group review and the requirements of an actual application; to emphasize the importance of specific criteria by which the risk-benefit ratio could be assessed; to help create useful written consent

forms; to be certain that fail-safe methods were provided to reverse or terminate an experimental procedure; and to educate the investigators to recognize when new or old investigational drugs were being used. We think that such problems have been overcome to a large degree.

A majority liability lies in the long-term consistency and beneficial evolution in policy. We believe that slow rotation of the membership of the Committee on Human Welfare and Experimentation, slow progress of a member to chairmanship and overlapping terms of service will provide consistency in policy. We strongly endorse the ad hoc committee concept both for its flexibility in providing the best reviewers for each situation and for continuously and painlessly expanding the number of faculty informed on and concerned with policy on investigation in human beings. Broadening of the base of faculty awareness of the needs for high standards in human experimentation should also obviate the need for specific policing procedures.

Committee function has evolved steadily and has led to alterations of policy and suggestions for the future. We believe that ad hoc committees of experts should be selected on a randomized basis to evaluate each protocol. Such randomization of reviewer selection can be accomplished by the following steps: establishing separate categories requiring expert evaluation; listing eligible qualified reviewers recommended by department chairmen; determining categories from which reviewers should be picked; having the secretary of the committee draw names from each category as designated by the chairman; and establishing a rotation for reviewers. In addition, an attempt should be made to ensure anonymity of the investigator by coding protocols.

NOTE 8.

BERNARD BARBER, JOHN LALLY,
JULIA MAKARUSHKA, AND DANIEL SULLIVAN
THE STRUCTURE AND PROCESSES OF
PEER GROUP REVIEW*

* * *

Evidence from our interviewing of bio-medical researchers at University Hospital and Research Center and at Community and Teaching

* A preliminary version (1970) of *Experimenting with Humans: Problems and Processes of Social Control in the Bio-Medical Research Community*. New York: Russell Sage Foundation (forthcoming). Printed by permission of the authors who retain all rights.

Hospital indicates that even in institutions where there is a peer review committee presumably reviewing *all* research, there is another perhaps important minority of research activities which is not submitted to peer review. In these two institutions where we interviewed researchers, 9 percent of them *volunteered* the information that one or more of their investigations using human subjects had not been reviewed by the peer review committee. A few more informed us that they knew of what they called "ad hoc" or "non-systematic" human research by others which was not reviewed by the committee.

Those who volunteered this information about unreviewed research by themselves or others suggested two structured sources for such bypassing of the review committee. First, what is considered "delay" in the reviewing process may generate evasion techniques. At University Hospital and Research Center, it takes about a month from the time a protocol is submitted to the time it is considered by the review committee. Researchers racing to establish priority of discovery or those who feel that some case or situation presents them with "now or never" opportunities to do research both may feel that this is an unacceptably long time to wait. Instead of waiting, they go ahead without submitting a protocol for review at all or, alternatively, submit a protocol but go ahead before it is approved. . . . Procedures for especially speedy review where the researchers were afraid of undue delay would probably be necessary only in a minority of cases and would cut down the evasion that is caused by these exigencies in bio-medical research.

A second structural source of evasion of, or indifference to, peer review procedures arises from the genuine and not infrequent ambiguity regarding what is "research" and what is a small, everyday variation on standard medical or surgical procedures. Evidence on this ambiguity is available in the responses to a question we asked in our national sample survey. We asked our respondents whether the following definition of research was "personally acceptable to you without addition or deletion?"—

Clinical Research or Investigation: Anything done to a person which is as yet not established, by clinical experience or scientific research, as being for his direct therapeutic benefit or as contributing to the diagnosis of his disease. (What is done may eventually, of course, be for the person's own direct or indirect therapeutic benefit and/or for the eventual therapeutic benefit of the population at large.) Inves-

tigations which involve the analysis of human substances collected as a by-product of established diagnostic or other procedures should be included here as clinical research.

While 75.2 percent (299) of our respondents agreed with this definition, 24.8 percent did not. Those who disagreed with our definition suggested alternative definitions. Some were more inclusive than ours, and some were more exclusive. Until definitional ambiguities are reduced, it is inevitable that a certain amount of research may not be defined as such and may be carried out without peer review.

* * *

As might be expected from the recency of its development, and as the data from our national sample survey of bio-medical research institutions indeed confirm, the peer review committee in its typical structure is still not highly differentiated or specialized. . . . 68 percent of the respondents said their peer review committees were not specialized in any way. 15 percent indicated that there were other review committees in their institutions, either at some higher or lower level of the structure or at some affiliated institution. Only 9 percent report specialization into subcommittees, and only 5 percent report specialized departmental committees. Only 8 percent of the institutions have executive committees for their peer review groups. Only 5 percent of the institutions claim that they have any members at all who spend "full time" in the activities of the peer review committee, and in every instance these "full-time" people were clerical.

As might be further expected from such relatively undifferentiated groups, the number of members is typically small: 27 percent of the institutions reported 1-5 members; another 48 percent reported 6-10; and 25 percent report 11-40.

A further indication of the lack of differentiation in peer review committee structure is the admixture of other functions besides that of ethical review. In 22 percent of the responding institutions, for example, the peer review committee also allocates the institution's research funds to its clinical investigators. In about two-thirds of our sample, the peer review committee also evaluates the scientific merit of proposed clinical research. Since scientific merit (e.g., representativeness and size of sample) is often related to ethical issues (e.g., too small a sample merely puts subjects at risk unnecessarily, too

large a sample may put too many subjects at risk), it is often not desirable to separate the reviewing of ethical and scientific issues. But insofar as a committee is not relating scientific merit to ethical concerns, its lack of differentiation may reduce its competence with either one of these two issues. One respondent even informed us that his peer review committee reviewed the cost-effectiveness of all proposed researches. While again this may sometimes be related to ethical matters, it is often quite another and related issue which should be left to other committees.

As to rank of peer review committee members in the formal hierarchy of their institutions, here again the typical structure seems to be less differentiated than it might be. Four-fifths of the institutions report that most of the members of their peer review committees come from the highest level of the formal institutional hierarchy, including the clinical, administrative, and academic. In the other institutions, the majority of the peer review members are from the intermediate level. Nowhere is a majority from the lower levels. A different mixture of members from different levels might give the peer review committees a more differentiated set of viewpoints on the ethical issues they are required to screen.

Finally, the relative lack of differentiation of the structure of review committees is manifest in the categories of types of activities, specialties, and occupational roles that their members are selected from. There is a heavy emphasis on members with experience in clinical research, as there of course needs to be, though perhaps somewhat too much so at the expense of other types of members who have other knowledge and viewpoints to bring to the decisions of the committee. 15 percent of the responding institutions report that they have only persons who engage in clinical research on their peer review committees. Overall, 91 percent of the institutions report members from among those who actually engage in clinical investigations. 27 percent report M.D. members who do not do clinical research. 43 percent report that they have pathologists either as members or as consultants. 59 percent report administrators as members, probably in recognition of the administrative responsibility of the institution for complying with P.H.S. regulations. 18 percent say that nurses are members. And then there is a scattering from other types of roles: 10 percent use lawyers employed by the institution, 8 percent have members of the board of trustees as members, 9 per-

cent use basic scientists, 9 percent use social scientists (a term which includes social workers and psychologists), and 2 percent have pharmacologists or pharmacists as members.

As for outsiders of various kinds, that is, outsiders who are either clinical research specialists in other institutions or outsiders who have non-medical roles in the larger community, the typical peer review committee has small place for them. 9 percent of the responding institutions said they had members on their peer review committees from other institutions who do clinical research in the general areas in which members of the institution do research and 9 percent also use M.D.'s from other institutions who do no clinical research in the institution's areas of specialization. Only 4 percent use outside lawyers; only 4 percent use outside social scientists; and only 4 percent use clergymen. Only one institution has a patient sitting on its peer review committee. Thus, very few peer review committees use outsiders as regular members either to bring them kinds of expertise they might want or to provide what is probably even more important, namely, the universalistic standards that may often be hard for members of a particular institution to apply to one another just because they are caught up inevitably in a web of personal and particularistic relationships with many of their colleagues. Some institutions do use outside consultants on an irregular basis, but we do not have data on this practice.

... We were interested ... in the intensiveness of the review process, so we asked if there were any kinds of pre-review before the whole committee met and we also asked if indeed the whole committee did meet. 77 percent of the respondents reported some kind of pre-review, that is, by all the individual members, or by a few of them, or by at least one. This procedure is obviously a more intensive kind of review than that engaged in by the 15 percent of our respondents who indicated that there was no pre-review at all before the committee met as a whole. 8 percent of our respondents, further, indicate that the committee does not meet as a body. Instead, one or more individual members perform the review and a decision is reached after communication among the chairman and the members by phone or mail only. In such cases, the degree of intensiveness of consideration which might come from face-to-face interaction among the members of the peer review committee is obviously lacking.

In that large majority (92 percent) of the

responding institutions where the committee does meet as a body, either with or without pre-review, a varying number of meetings is required to handle the work-load. 56 percent of these committees that meet as a body come together 1-10 times a year; 37 percent meet 11 times or more; and 7 percent are indefinite, indicating only that they come together "as required." Of the committees meeting as a body, 37 percent report an average of no more than one proposal considered per meeting; 39 percent indicate 2-3 proposals; and 24 percent report 4 or more proposals.

... 41 percent of the responding institutions said their procedures required unanimity; 25 percent, a simple majority; 6 percent, a two-thirds majority; and 27 percent, no specific proportion stipulated in their procedure. These data show some considerable tendency toward that large degree of consensus, even toward unanimity, that we expected from groups that define themselves as "collegial," that is, as a company of near-equals sharing a single set of values, rather than as "political," that is, a group of unequals with divergent values and interests. In the former type of group, there would be a greater tendency to unanimity; in the latter, a simple majority would tend to be adequate for deciding among somewhat different interests and values.

* * *

... In well-differentiated systems for making adjudicatory decisions, there is some mechanism for those whose cases are being adjudicated to make an appeal from what they consider erroneous decisions. In this respect, again, we find that the review committee system has not moved all the way toward adequate functional differentiation. In response to our question on this matter, only 47 percent of the responding institutions reported that they have any formal procedure by which a negative decision can be appealed from the review committee to some other body.

* * *

[R]espondents were slightly more likely to say the committee at their institution was less than "very effective" if there were no additional controls over the ethical aspects of research at that institution. (It will be remembered that these additional controls were approval by department chairmen, board of trustees, or some other person or group.) This finding supplements our earlier finding that, in institutions where there were no additional controls, the peer review commit-

tee was less likely to request revisions or make rejections of research proposals. Our respondents' estimates seem to coincide with the facts about actual decisions. . . .

We also found . . . that our respondents viewed their committees as less effective when it was not committee policy to review all research as opposed to just that research funded by P.H.S. Once again . . . these estimates coincide with the facts about decisions.

The presence of continuing review is also connected with respondents' estimates of effectiveness. [R]espondents who considered their committees less than very effective were more likely to be from institutions without continuing formal or informal review.

* * *

NOTE 9.

OSCAR D. RATNOFF AND MARION F. RATNOFF
ETHICAL RESPONSIBILITIES IN
CLINICAL INVESTIGATION*

* * *

The urge for [human experimentation] is fostered, too, by the practical needs of academic life. Despite miles of verbiage about the need to recognize fine clinical teachers, the route to promotion is all too often dependent upon the production and publication of experimental results. Even disregarding promotion, the economic well-being of the member of a clinical department may be inextricably hitched to his ability to carry out experimental work. In a period of gradual inflation, the proportion of a departmental budget which is in the form of "hard money" is inevitably, shrinking. The beleaguered departmental director must apply pressure upon his colleagues to include substantial portions of their salaries in their applications for research grants. "You are expected to generate a portion of your own salary," is the euphemism in a letter offering one of our colleagues an otherwise fine position. Research, it would seem, must be conducted not only for its own sake but to gain both salary and advancement. No wonder the desire for short cuts to attractive answers blunts the investigator's judgment about what is and what is not appropriate.

* * *

* 11 *Perspectives in Biology and Medicine* 82, 84 (1967). Copyright 1967 by the University of Chicago. Reprinted by permission.

[iv]

*Food and Drug Administration Institutional Committee Review of Clinical Investigations of New Drugs in Human Beings**

In the *Federal Register* of August 22, 1969. . . . a notice was published in which the Commissioner of Food and Drugs proposed that § 130.3 be amended to assure that clinical investigations of new drugs on institutionalized human subjects are appropriately supervised in and approved by such institutions and to assure adequate safeguards for the health, safety, and welfare of the human subjects during all phases of clinical studies of new drugs. . . .

Comments were received from more than 20 representatives of the drug industry and from interested individuals. . . .

* * *

C. The National Academy of Sciences—
National Research Council, Drug Review Board,
suggests that:

* * *

2. Changes in protocol are often required as a given investigation proceeds; however, the present peer group proposal does not make clear under what circumstances these changes would require a rereview by the peer group. It is clear that only substantial changes in protocol ought to require this additional review.

3. If foreign investigators conduct studies in other countries under IND's, they should be required to follow the procedure set forth for investigators in the United States.

4. The Code of Helsinki ought to be a minimum basis for the decisions reached by the peer committees.

D. An individual physician suggests that:

1. Peer group committees must not set themselves up as censoring groups except insofar as they function to safeguard patients or volunteers from irresponsible and careless investigators.

2. Some of the suggestions made for expanding the activities of these committees are not realistic in terms of how much work is involved and what the effect may be on the performance of research.

3. A 1-day meeting be held of lawyers,

* Charles C. Edwards, Commissioner of Food and Drugs. 36 *Federal Register* 5037-5038 (1971).

judges, consumer group representatives, the FDA, the drug industry, etc., to bring out all the ramifications and complexities and to develop a workable, realistic program that will protect the public without needlessly hamstringing researchers.

E. The American Society of Hospital Pharmacists, Washington, D.C., suggests that the regulation be changed to indicate that there be pharmacy representation in the peer committees and to provide for the designation of pharmacy and therapeutics committees as peer group committees.

The Commissioner of Food and Drugs, having considered the comments, finds that:

1. To achieve a balanced review of a study that will take into consideration the nature of the research as well as the acceptability of the research in terms of relevant law and community acceptance, varying backgrounds of committee members are essential. The need for broad considerations of the ethical and moral aspects of research in humans, in addition to the scientific justification, is too important to limit review of such proposals to individuals with the same areas of interests, training, and background.

2. In view of the need for committee members with varying backgrounds, referring to the review committee as a "peer committee" is inappropriate. The designation "institutional review committee" is more appropriate.

3. The approval or disapproval of a study is the committee's responsibility. The review by the Food and Drug Administration is in addition to the committee review for those studies that are approved by the committee.

4. The requirement for institutional committee review applies to all three phases of clinical studies on institutionalized human subjects and to studies conducted by an individual investigator affiliated with an institution which agrees to assume responsibility for the study to assure adequate protection of the patient's or subject's interests. The requirements of the regulation as amended below do not extend to clinical studies conducted by an individual investigator independent of any institution. . . .

* * *

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act . . . and under authority delegated to the Commissioner § 130.3 *New drugs for investigational use in human beings; exemptions from section 505(a)* is amended. . . .*

* * *

NOTES

NOTE 1.

COUNCIL OF HEALTH ORGANIZATIONS
COMMENTS ON PROPOSAL FOR PEER GROUP
COMMITTEE REVIEW OF CLINICAL
INVESTIGATIONS OF NEW DRUGS ON
HUMAN BEINGS (1969)†

* * *

[S]ignificant questions are raised by the FDA's use of the Public Health Service peer group committee model, since those committees are specifically designed for the universities, research institutions, and hospitals which do research with NIH funds. There is reason to doubt that the same model without modification would suit the prisons, orphanages, or homes for the aged where new drugs are often tested. The NIH-PHS program is grounded on the assumption that all members of the hospital community share a professional concern about experimentation with human subjects. As a result, the staff has the competence and motivation to make certain that the hospital selects a knowledgeable, concerned, and objective review committee. There is no evidence that any similar widespread concern and competence exists in other kinds of institutions. As a result, an investigator operating in a prison or orphanage might have inordinate influence in choosing the members of the committee. Furthermore, if the committee members come from within the institutions—as the NIH-PHS committee members often do—there is little likelihood that they would have either the requisite interest or competence. It is unclear who on the staff of a prison, for example, is a "peer" of the investigator. In our view, to speak of a "peer group" in a prison is a non sequitur.

* * *

Commissioner Ley suggested in his testimony before Senator Nelson's Subcommittee on Monopoly of the Select Committee on Small Business on August 12 that the review committees would . . . provide a check on a test's scientific adequacy and necessity. This aspect of the review committee's role is totally ambiguous in the FDA proposal. The scientific quality of new drug testing badly needs to be improved, and

* The text of Section 130.3, as amended, is set forth at pp. 862-873 *supra*.

† Reprinted by permission of Paul Lowinger, M.D., Chairman.

some consideration of the scientific adequacy and necessity of a new drug test is essential to a consideration of the rights and welfare of test subjects.

* * *

[A]ssessment of the relative benefits against risks also calls for some scientific expertise and understanding of the particular area of medicine in which the experimentation is taking place.*

The review committees will have to be especially vigilant to insure that . . . "adequate and appropriate" methods are "used to obtain informed consent." Major problems were left unresolved by the FDA regulations adopted in 1967 (section 130.37) concerning consent by test subjects. For example, obtaining the consent of children in orphanages and the senile in homes for the elderly is a delicate matter at best. Often their legal guardian is the state. Members of such groups would benefit from a review committee acting in their interest to make sure that the state safeguards their rights. . . .

* * *

The most glaring omission of the proposed regulation is the failure of the FDA to deal with phase 3 testing problems or to provide a review mechanism for noninstitutional tests of new drugs. Any comprehensive scheme adopted by the FDA to safeguard the rights of human subjects on whom new drugs are tested must deal with phase 3 problems as well as phase 1 and phase 2. In addition, the FDA should devise a method of bringing noninstitutional investigators under the surveillance of a review committee, perhaps through regional review committees.

* * *

NOTE 2.

HOFFMANN-LA ROCHE, INC.

COMMENTS ON NOTICE OF PROPOSED
RULEMAKING (1969)†

* * *

The August 22 notice applies the peer group concept to Phase III studies. . . . We believe that

* The Council believes that it can never be ethical to ask a person to take the risks associated with new drug testing if the tests themselves are unnecessary or will not, because of their design, yield significant results. Hence, any committee charged with protecting the rights and safety of test subjects must have the capacity to review the scientific aspects of the tests.

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the peer group concept should not be applied to Phase III studies for the following reasons:

First, Phase III studies are less hazardous than Phase I and Phase II studies. By the time the drug reaches Phase III, considerably more is known about its toxicology, pharmacology, and safety.

The question of whether a drug can be allowed to proceed to Phase III testing is reviewed and answered before such testing starts. It should be noted that normally the FDA must be supplied with a protocol before Phase III studies begin. Also, while Phase III studies are in progress, progress reports must be submitted to the FDA at not more than yearly intervals.

The sponsor is also required to submit immediately to the FDA any alarming findings received from investigators relative to the safety of the drug.

Second, peer group committees would not have enough time to monitor all Phase III studies. As an investigational drug moves from one phase to another, the number of investigators involved pyramids. In comparison to the number of investigators involved in Phase I and Phase II studies, the number of Phase III investigators is quite large. We do not believe that institutions would be able to impose the administrative burdens required by the proposed regulation on their expert committees. As a consequence, many institutions would not accept Phase III work which . . . would be detrimental to drug research.

* * *

[T]he proposed regulation speaks in terms of committee members of "varying backgrounds." This language is indefinite as to whether it refers only to persons with scientific backgrounds, e.g., pharmacologists, internists, physiologists, etc., or whether the committee is also to be composed of persons from non-scientific pursuits, e.g., clergymen, lawyers, etc.

The primary concern of a peer group committee, as we understand it, is to supervise investigational drug work to help insure that the risks to the patient will be minimized as much as possible. This supervision should be based primarily on the scientific aspects of the studies being conducted at the institution. Such supervision, we believe can be handled only by persons trained in the type of work involved, e.g., physicians, pharmacologists, physiologists, etc.

A committee composed of persons particularly suited for such supervision could ask clergymen and lawyers for advice on any moral and legal issues which might arise. However, whether

the study should proceed should be governed basically by scientific issues and only persons trained in scientific fields should have voting power in deciding whether a study should be conducted.

Therefore, we suggest that the proposed regulations be amended to reflect that the committee need only be composed of persons qualified in areas directly related to drug research.

* * *

[W]e believe that the August 22 notice should be revised in regard to the relationship of the investigator with the committee. . . .

. . . Oftentimes, the investigator conducting the study is the most expert person at the institution relative to the study being conducted, or he is at least as expert as the members of the committee.

To relegate an investigator to being a mere conduit of information demeans the investigator's position as an expert.

His opinions are as vital to an investigation as those of the committee members inasmuch as the investigator has a closer relationship to persons involved in the study and to the data that the study are constantly developing.

We believe that the investigator involved in the study must be a member of the peer group committee. Since an investigator may be prominent enough to exert influence on the committee, we suggest that in order that undue influence by the investigator be avoided, the investigator be a non-voting member of the committee. In any event, the investigator's comments and opinions, as well as information regarding the study, are vital to any decision made by a peer group committee.

* * *

NOTE 3.

FOOD AND DRUG RESEARCH LABORATORIES, INC.
PEER GROUP COMMITTEE REVIEW
OF CLINICAL INVESTIGATIONS OF NEW
DRUGS IN HUMAN BEINGS (1969)*

* * *

The proposals developed by the FDA . . . seem to be an unnecessarily complicated and time-consuming approach to the problem and likely to act as a bottleneck in the development of drug research. As a more workable approach

to the problem, I would suggest devising a means for rapidly reviewing by computer the Forms 1571 as they are received, and that submission of Forms 1572 and 1573 be required for a similar review. This would enable the FDA to quickly evaluate the qualifications of every proposed investigator and to decide whether sufficient safeguards have been incorporated in the study design.

Furthermore, routine computerized cross-tabulations would pinpoint those investigators who had run into difficulties in the past or who were undertaking too many clinical studies to supervise them all adequately, probably a major factor contributing to the poor quality of some investigations. Such a procedure, coupled with the requirement for reporting immediately any unexpected untoward reactions, would, in my opinion, provide more efficient control of the quality and safety of clinical investigation than review by peer committees.

* * *

C.

Should Research Design and Scientific Merits Be Evaluated?

[i]

David D. Rutstein

*The Ethical Design of Human Experiments**

* * *

It may be accepted as a maxim that a poorly or improperly designed study involving human subjects—one that could not possibly yield scientific facts (that is, reproducible observations) relevant to the question under study—is by definition unethical. Moreover, when a study is in itself scientifically invalid, all other ethical considerations become irrelevant. There is no point in obtaining "informed consent" to perform a useless study. A worthless study cannot possibly benefit anyone, least of all the experimental subject himself. Any risk to the patient, however small, cannot be justified. In essence, the scientific validity of a study on human beings is in itself an ethical principle.

How, then, can the experimental human subject be protected from incompetent investigators so that he will not become a victim in feckless studies? There are two lines of defense. The

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* 98 *Daedalus* 523, 524, 527-528 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

research committee of a medical school, institution, or hospital must be concerned with the ethical principles as well as the scientific validity of the proposals placed before them. To perform this task effectively, every committee must have among its membership a biostatistician to insure scientific validity and an expert (for whom there is as yet no name) who is concerned with the ethical aspects of human experimentation. The biostatistician can assist the committee in evaluating the scientific quality of the proposed investigation and make recommendations for improvement of the scientific aspects of the study design. Experiments on human beings must not be performed without a carefully drawn protocol, which in turn can best be prepared in consultation with experts in study design. In the same way, experts in the ethical aspects of human experimentation should assist the committee in passing on the ethical issues of proposed studies and in recommending modifications that might make the studies ethically acceptable.

* * *

The design of an experiment depends at first on the question asked by the investigator. Some questions are in themselves unethical. One cannot ask whether plague bacilli are more virulent in human beings when injected into the bloodstream than when they are sprayed into the throat. One may obtain hints as to the answer to such a question by epidemiologic comparison of the spread of pneumonic plague (spread from the lungs into the air) and bubonic plague (spread by insect bite). Anecdotal information on the spread of plague can also be obtained through the study of laboratory accidents. But a deliberate experiment to answer this question cannot be performed.

The human experiments performed by the Nazis during World War II horrified the world because they were designed to answer unethical questions. "How long can a human being survive in ice cold water?" will, it is to be hoped, never again be a question to be answered by a scientific experiment. Thus, as a first step in the design of any human experiment, we must first be sure that the question itself is an ethical one.

Moreover, an unethical experiment can sometimes be converted into an ethical one by rephrasing the question. In drug testing, for example, it is not ethical to design an experiment to answer the question: "Is treatment of the disease with the new drug more effective than no treatment at all?" In answering such a question,

the patients in the control group would literally have to receive "no treatment" and that is completely unacceptable. Instead, if the patients in the control group are given the best possible current treatment of the disease, we may now ask an ethical question: "Is treatment with the new drug more effective than the generally accepted treatment for this particular disease?"

We faced this problem in the design of the United States-United Kingdom Cooperative Rheumatic Fever Study, which was concerned with measuring the relative effectiveness of cortisone and ACTH in the treatment of that disease. We could not give rheumatic fever patients in the control group "no treatment." We would have had to go so far as to prohibit bed rest, which in itself may be helpful to rheumatic fever patients, because patients in bed have a slower heart rate. Instead, we asked the question: "Is treatment with ACTH or cortisone better, worse, or the same as the best generally accepted drug treatment for this disease?"

* * *

[ii]

John R. Platt
*The Step to Man**

Scientists tend to keep up a polite fiction that all science is equal. Outside of the misguided opponent whose work we happen to be refuting at the time, we speak as though every scientist's field and methods of study are as good as every other scientist's, and perhaps a little better. This keeps us all cordial when it comes to recommending each other for government grants.

But I think anyone who looks at the matter closely will agree that some fields of science are moving forward very much faster than others. . . .

Why should there be such rapid advances in some fields rather than others? I think the usual explanations that we tend to think of—such as the tractability of the subject, or the quality or education of the men drawn into it, or the size of research contracts—are important but inadequate. I have begun to believe that the primary factor in scientific advance is an intellectual one. These rapidly moving fields are fields where a particular method of doing scientific research is systematically used and taught, an accumulative

* New York: John Wiley & Sons 19-20, 23-24, 35-36 (1966). Copyright 1966. Reprinted by permission of John Wiley & Sons, Inc.

method of inductive inference that is so effective that I think it should be given the name of "strong inference". . . .

In its separate elements, strong inference is just the simple and old-fashioned method of inductive inference that goes back to Francis Bacon. The steps are familiar to every college student and are practiced, off and on, by every scientist. The difference comes in their systematic application. *Strong inference consists of applying the following steps to every problem in science, formally and explicitly and regularly:*

- (1) *devising alternative hypotheses;*
- (2) *devising a crucial experiment (or several of them), with alternative possible outcomes, each of which will, as nearly as possible, exclude one or more of the hypotheses;*
- (3) *carrying out the experiment so as to get a clear result; and*
- (1') *recycling the procedure, making sub-hypotheses or sequential hypotheses to refine the possibilities that remain; and so on.*

* * *

This analytical approach to biology has sometimes become almost a crusade, because it arouses so much resistance in many scientists who have grown up in a more relaxed and diffuse tradition. At the 1958 Conference on Biophysics at Boulder, there was a dramatic confrontation between the two points of view. Leo Szilard said: "The problems of how enzymes are induced, of how proteins are synthesized, of how antibodies are formed, are closer to solution than is generally believed. If you do stupid experiments, and finish one a year, it can take 50 years. But if you stop doing experiments for a little while and *think* how proteins can possibly be synthesized, there are only about 5 different ways, not 50! And it will take only a few experiments to distinguish these."

One of the young men added: "It is essentially the old question: How *small* and *elegant* an experiment can you perform?"

These comments upset a number of those present. An electron microscopist said, "Gentlemen, this is off the track. This is philosophy of science."

Szilard retorted, "I was not quarreling with third-rate scientists: I was quarreling with first-rate scientists."

A physical chemist hurriedly asked, "Are we going to take the official photograph before lunch or after lunch?"

But this did not deflect the dispute. A dis-

tinguished cell biologist rose and said, "No two cells give the same properties. Biology is the science of heterogeneous systems. . . ." And he added privately, "You know there are *scientists*; and there are people in science who are just working with these oversimplified model systems—DNA chains and *in vitro* systems—who are not doing science at all. We need their auxiliary work: They build apparatus, they make minor studies, but they are not scientists."

To which Cy Levinthal of M.I.T. said: "Well, there are two kinds of biologist, those who are looking to see if there is one thing that can be understood, and those who keep saying it is very complicated and that nothing can be understood. . . . You must study the *simplest* system you think has the properties you are interested in."

As they were leaving the meeting, one man could be heard muttering, "What does Szilard expect me to do—shoot myself?"

* * *

. . . I will mention one severe but useful private test—a touchstone of strong inference—that removes the necessity for third-person criticism, because it is a test that anyone can learn to carry with him for use as needed. It is our old friend the Baconian "exclusion," but I call it "The Question." Obviously it should be applied to one's own thinking as much as or more than to others'. It consists of asking in your own mind, on hearing any scientific explanation or theory put forward:

"But sir, what experiment could *disprove* your hypothesis?" Or on hearing a scientific experiment described:

"But sir, what hypothesis does your experiment *disprove*?"

This goes straight to the heart of the matter. It forces everyone to refocus on the central question of whether there is a testable scientific step forward or not.

If such a question were asked aloud, many a supposedly great scientist would sputter and turn livid and would want to throw the questioner out, as a hostile witness! Such a man is less than he appears, for he is obviously not accustomed to think in terms of alternative hypotheses and crucial experiments for himself; and one might also wonder about the state of science in the field he is in. But who knows, the question might educate him, and the field too!

On the other hand, I think that throughout most of molecular biology and nuclear physics,

the response to The Question would be to outline immediately not one, but several tests to disprove the hypothesis!—and it would turn out that the speaker already had two or three graduate students working on them!

I almost think that government agencies could make use of this kind of touchstone. It is not true that all science is equal, or that we cannot justly compare the effectiveness of scientists by any method except by a mutual-recommendation system. The man to watch, the man to put your money on, is not the man who wants "to make a survey" or a "more detailed study," but the man . . . with the alternative hypotheses and the crucial experiments; the man who knows how to answer your question of disproof, and is already working on it.

* * *

NOTES

NOTE 1.

ROBERT H. GIFFORD AND ALVAN R. FEINSTEIN
A CRITIQUE OF METHODOLOGY IN
STUDIES OF ANTICOAGULANT THERAPY
FOR ACUTE MYOCARDIAL INFARCTION*

Despite two decades of statistical studies, anticoagulant therapy for acute myocardial infarction remains a controversial issue. The persistence of controversy can be explained either by the claim that nature is inscrutable or by the suspicion that man's best efforts to understand it have not been very good. A particular focus of suspicion is that the existing statistics were obtained without adequate attention to fundamental principles of clinical science. The work reported here was done to test that suspicion.

We used three criteria in selecting papers for review in this study: to simplify the language problem, we examined only papers that had been English . . . we confined our attention to reports of anticoagulant therapy for the acute phase of myocardial infarction; and to assess the validity of "control" groups, we chose only investigations in which a specific comparison had been made between different modes of therapy—either one type of anticoagulant vs another or anticoagulants vs no anticoagulants.

From the literature published between 1948 and 1966, we found 32 reports that fulfilled these three criteria. In the first 27 reports patients

treated with anticoagulants were compared with a "control" group not receiving anticoagulants; and in the last five reports, one type of anticoagulant treatment was compared with another type.

. . . We . . . established a series of eight methodologic standards that would be generally regarded as scientific necessities for ensuring comparability of treated patients in a clinical investigation of therapy. . . .

Diagnostic criteria for myocardial infarction. The first scientific requirement in any investigation of therapy is a clear, precise statement of diagnostic criteria for the disease under study. . . .

. . . Our sole concern was for the authors to state their interpretational criteria clearly enough so that another investigator could use them with scientific reproducibility.

* * *

[O]nly eight (25 per cent) of the 32 reports contained a satisfactory statement of the evidence used for making a clinical diagnosis of acute myocardial infarction. In 13 papers, the criteria were described equivocally, and in 11 (34 per cent), no criteria were stated.

* * *

Concurrent controls. If treatment is to be compared in two groups of patients who have not been studied experimentally, they should have been treated during approximately the same years in the calendar. If patients from one era are compared, in a survey, with those from another, the group treated later may have better results not because of the improved therapeutic agents but because of improvements, with advancing time, in methods of diagnosis and of ancillary therapy. . . . Thus, if anticoagulant-treated patients are compared with "controls" taken from medical records of the earlier era before anticoagulant therapy, the better results of the later group may have little or nothing to do with the anticoagulant therapy.

* * *

[O]nly 72 per cent of the investigators rigorously observed the principle of concurrent controls.

Hospital coordination. Comparisons of treatment should preferably be concurrent not only in time, but also in space. If the comparison extends to patients managed in more than one hospital, the ancillary treatment used at the different hospitals should be co-ordinated so that

* 280 *New England Journal of Medicine* 351-357 (1969). Reprinted by permission.

elastic stockings, chair rest, early ambulation, tactics in nursing care and other nonpharmaceutical therapeutic maneuvers are carried out in a comparable way for all patients. . . .

In 24 of the 32 investigations reviewed here, the work was "coordinated" because it was all done at a single hospital. The other eight reports combined data from different hospitals, often widely separated geographically. . . .

* * *

Random allocation. The next principle deals with the random allocation of treatment, which is intended to ensure against bias when the modes of therapy are assigned in a trial. Unless this principle is observed, the investigator's conscious or unconscious bias may affect the assignment of treatment so that patients with a milder form of the disease and a better prognosis receive one mode of therapy, and the other agent is given to a more severely ill or "poor-risk" group.

* * *

[O]nly four of the 32 reports in this review used a strictly random method of allocating treatment. These four reports constitute 31 per cent of the 13 investigations that were performed as experimental clinical trials.

* * *

Diagnostic criteria for thromboembolism. If anticoagulants are being used to prevent thromboembolic phenomena, an investigator should specify the way the phenomena were diagnosed. A thromboembolism can be manifested by symptoms or signs in a leg, by certain clinical findings in the chest or brain, by roentgenographic silhouettes or by various other items of evidence. These findings can be given such diagnostic names as "pulmonary embolus," "thrombophlebitis," "cerebrovascular accident" or "mural thrombus," but each such diagnosis requires criteria to state the prerequisite evidence. . . .

. . . In the 32 reviewed reports, thromboembolic phenomena had not been assessed in eight. . . . We searched the remaining 24 reports for statements of their diagnostic criteria for thromboembolism [but] none of the investigators made a specific statement. . . .

Double-blind procedure. In a double-blind procedure, neither the patient nor the doctor knows which drug is being given. The double-blind procedure helps eliminate the bias in selection of cases that may occur if treatment is as-

signed by someone who knows the identity of the therapeutic agents. After a trial is under way, the double-blind procedure helps preserve the objectivity of the investigator when he evaluates clinical and other evidence for such diagnoses as thromboembolism, particularly if precisely defined criteria are not used for those diagnoses.

* * *

[O]nly one of the 32 investigations cited here was done with a double-blind procedure.

* * *

Therapeutic conclusions. [W]e have cited the therapeutic conclusions reached in each of the 32 reports; we listed the anticoagulants as "significantly better" only when the authors had expressed this conclusion. In the last five reports, the comparison was either between strict and nonstrict methods of anticoagulant regulation, or between oral and parenteral methods. Since so much controversy has developed about the issue of anticoagulants vs nothing, the remainder of our analysis is confined to the 27 reports in which such a comparison was performed.

Of these 27 reports, 14 concluded that anticoagulants were superior, and 13 did not. To examine this issue in greater detail, we correlated the therapeutic conclusions of each investigation with the methodologic standards that had been used in that investigation. [F]or each of the cited methodologic standards, anticoagulant therapy was found superior to no treatment more often in the reports that did *not* observe the standard than in those that did. Moreover, the differences are particularly striking for the standards that are most likely to eliminate bias in comparability of cases—random allocation, stratified prognostic correlation and double-blind procedure.

* * *

Our purpose in this review is not to single out any investigations for adverse criticism, and we apologize to any investigators whose methods we may have misinterpreted. . . . Instead, we want to call attention to certain clinical and scientific principles that are the basis for sound statistical appraisals of treatment. The violation of these principles seems to be the source of the current controversy about anticoagulant therapy. . . .

. . . As clinicians and statisticians collaborate in planning future research projects, an

important point to be recognized is that treatment is an act of clinical medicine, and that valid statistical inferences must be based on this clinical context; accordingly, the critical features of scientific design for therapeutic experiments must be clinical and not merely statistical. Among the needed improvements are better clinical methods for selecting, classifying, specifying and comparing the patients who are the "experimental material."

NOTE 2.

YALE REPORTS
ETHICS AND MEDICINE—
CONTROL OF HUMAN EXPERIMENTATION*

* * *

MR. CALABRESI: [T]he first thing that [the review committee should] look at is whether the plan of research is adequate and whether experiments on animals have been made beforehand. . . . After that, you study the question of whether consent was adequately sought, and beyond that you impose a kind of control which is supposed to be a judgment essentially by other physicians as to whether this experiment, involving the risks it does, is in the interest of society at large. Now, it is this last part which is most interesting to me because it says: consent is not enough, we have to have another judgment. What is interesting to me is that this other judgment is made by physicians for society, they are the ones who are asked to represent the decision, if you want, between future lives and present lives. I can perfectly well see that it would not be desirable to have some kind of central governmental group making this decision, but is it really sensible to think that physicians, and especially physicians in the same institution who have so many relationships with the experimenter, are the best suited to make this kind of judgment? Would it not be better if, at least as a start, one had physicians from other institutions who had no particular interest or relationship with the experimenter and perhaps people from other disciplines involved in such a committee?

* * *

* A weekly broadcast review presented by Yale University and *WTIC*, March 3, 1968. Participating were Guido Calabresi, Professor of Law; Morton Kligerman, Chairman, Department of Radiology, Yale Medical School; and Jay Katz, Professor (Adjunct) of Law and Psychiatry. Reprinted by permission.

DR. KLIGERMAN: . . . As you indicated, those of us who are involved professionally in doing a certain job, although we are experts in the ability to do this job (to make judgments about the manner in which the job is being done), hopefully, we are experts in making decisions on how to improve the teaching and the execution of our specialties. When it comes to making a decision as to what is good for society, the very fact that we say: "What is good for society" takes it out of our hands and must put society, that is the non-specialists, in. I think in this instance the specialist becomes the adviser to society's representatives. He is an expert witness, but he alone probably often is not the best one to make the decision about whether something should be done. It would be burdensome, I think, if one had a committee which decided on scientific merits, and then the question would be sent to another committee to have a decision as to whether society can tolerate the experiment at all.

I think that the way to do this is similar to the way the National Institutes of Health have solved the problem of their advisory councils. For instance, the National Advisory Cancer Council does not have solely scientists on its board; there are physicians, there are biologists, and other scientists, but then there are lay people on it. I would, therefore, like to suggest that a committee which reviews proposals for clinical investigation have community representatives in addition to scientists on its board.

MR. CALABRESI: I think that you would probably find that such a committee would be, if anything, more lenient with experiments than one made up only of physicians because sometimes I think that physicians are concerned with not hurting the profession, and, therefore, are more careful than society's interest might dictate.

DR. KATZ: I am not certain whether our committee should evaluate the design of the experiment. [As yet] we have not delegated to members of the committee the specific task of evaluating either the merits or the design of the experiment. Perhaps, this should be done. We do have one additional safeguard; before an experiment is submitted to us, it has to be reviewed by the Department Chairman, and we hope that the Department Chairman will pay some attention to that particular problem.

[I]n the light of a year's experience, I have been impressed by the fact that we have not re-

ceived an experiment which raises the question should this experiment be done? Is it, for example, so risky that we have to evaluate societal interests? If we had in addition to our committee, another committee which has a much broader representation (including people from the community, law, sociology, etc.) that would address itself to these issues, maybe then experimenters would feel much freer to think about doing these kinds of experiments [and] submit them [for review] to such a group. It may be that the absence of such a group precludes experimenters from even considering such experimentation.

MR. CALABRESI: I think so. And especially I think it would be useful if there were someone who could pass on such things as [the] design [of the] experiment. I frankly was a little bit worried by your comment that that is one of the things you don't examine and you leave it up to the Department Chairman. The Department Chairman is not the ideal person for making this decision. After all, he has made his own way by making experiments. He feels a great many qualms about keeping back his able men in a situation where some really significant experiment might be made, especially where someone in another medical center may get permission to do it. A whole series of pressures come on him so that I would rather have it be scientists in the same general area who are not so related to this particular experiment.

* * *

DR. KLIGERMAN: I agree with Guido and I think there would be a very easy mechanism to do that. You would simply select two other individuals, even from within our school, because I do feel that people will, when asked to put on paper their reasons for support or non-support of a subject, be very, very careful to do the right thing. By the way, even if they didn't have to sign it, they would want to do the right thing anyway. No one wants to see his colleague do the wrong thing; no one wants to see a patient harmed. And I think then that your committee should select two people who would be, (shall we call them primary reviewers?) in a field of relevance. By the way, I am certain that on some occasions, it would include a member of your committee, and that they would then present their opinion at least about the scientific merits of the situation to your committee which then could look at the other aspects that you are charged with.

* * *

NOTE 3.

BRITISH MEDICAL RESEARCH COUNCIL
MEMORANDUM ON CLINICAL INVESTIGATION*

* * *

... In such a diverse and rapidly expanding subject as clinical research it is impossible to frame a code of general advice which would adequately cover the ever changing circumstances which arise. In any particular case—so specialised has medical knowledge become—only a small group of experienced investigators, who have devoted themselves to this branch of medicine, are likely to be competent to pass an opinion on the advisability of undertaking any particular investigation. But in every branch of medicine such a group of investigators exists. It is upon them, and the specialised scientific societies to which they belong, that the medical profession must mainly rely for the creation of the body of precedents and the climate of opinion which shall guide investigators in clinical research. Hitherto no deliberate attempt to provide guidance in this way has been made: but it is important that it should be. The Medical Research Council feel, therefore, that they must clearly express their belief that it is incumbent upon the medical scientific societies to accept this responsibility and, by encouraging critical discussion on the communications presented to them, help to resolve doubts and to form a body of opinion of what is necessary, desirable and justifiable to guide investigators in their field.

* * *

NOTE 4.

RENÉ TATON
REASON AND CHANCE IN SCIENTIFIC DISCOVERY†

* * *

One of the saddest examples of a scientist falling a victim to his own discovery is that of the Hungarian physician Ignaz-Philipp Semmelweis (1818–1865), who, after having discovered the cause of puerperal infection, tried, but unfortunately without success, to introduce the general use of antiseptics. The factors surrounding his discovery give a clear illustration of his scientific rigour, and thus merit our attention.

* Memorandum M.R.C. 53/649 (October 16, 1953). Reprinted by permission. See p. 847 *supra*.

† Translated by A. J. Pomerans. New York: Philosophical Library 153–154 (1957). Reprinted by permission.

In the middle of the nineteenth century puerperal fever was so rampant in maternity hospitals that women in labour were truly terrified. At the time speculations on its causes were fantastic rather than scientific; we need but mention the assumed influence of some food-stuffs and even of scents. During the autopsy of a laboratory assistant, who had died of an infection that he had contracted during a dissection, Semmelweis noticed that some anatomical and pathological symptoms were similar to those observed in women who had died of puerperal fever. From this he concluded that both diseases had similar origins, and he was confirmed in this idea by his discovery that deaths from puerperal fever were much more common in clinics where students did their obstetrics without taking any of the precautions that today are a matter of routine. He immediately communicated his observations and ideas to the Medical Council of Vienna, and stated that puerperal fever was due to blood poisoning caused by the absence of antiseptic precautions. The rapid drop in mortality which followed upon the implementation of his advice that all who came into contact with women in labour should take care to wash their hands, and that wards should be disinfected by chlorination, was a remarkable justification of Semmelweis's point of view.

However, the leading obstetricians of Vienna fought so bitterly against this thesis that Semmelweis had to leave the hospital where he practised. In 1855 he was appointed professor at the University of Budapest, where he continued propounding his ideas. In 1861 he published his *On the etiology, the pathology, and the prophylaxis of puerperal fever*, in which these ideas were developed further and based on new observations. Refusing to accept clearly established facts, his adversaries redoubled the violence of their attacks to such a point that Semmelweis had to abandon his Chair. Broken by such obstinacy and by the most vicious abuse, the Hungarian doctor some years later died a sad death in a lunatic asylum.

However, the work of Pasteur and the unquestionable triumph of the great English surgeon, Joseph Lister (1827-1912), slowly overcame the obstinacy of those who opposed antiseptics in the prevention of infectious diseases, and some twenty years later the correctness of the ideas of Semmelweis was finally recognized and antiseptic methods were applied successfully to the prevention of puerperal fever. The statue that the city of Budapest erected in

1894 in honour of the great Hungarian physician, pioneer and genius, and martyr to his own discovery, unfortunately does not erase the memory of his tragic death, and of the thousands of innocent victims who had to pay with their lives for the blind obstinacy of orthodox medicine of the time.

* * *

NOTE 5.

FIORENTINO v. WENGER
19 N.Y.2d 407, 227 N.E.2d 296 (1967)

BREITEL, JUDGE:

* * *

It should be evident that a hospital generally cannot be held liable, other than derivatively, for another's malpractice. Thus, where, as here, there is no vicarious liability, the plaintiff must establish that the hospital, through its own agents, was guilty of malpractice or other tort occurring in causing the harm. Where a hospital's alleged misconduct involves an omission to act, the hospital will not be held responsible unless it had reason to know that it should have acted within the duty it concededly had. . . . More particularly, in the context of the present case, a hospital will not be held liable for an act of malpractice performed by an independently retained healer, unless it had reason to know that the act of malpractice would take place. . . . As Mr. Justice Lazansky noted, dissenting in the Appellate Division in *Hendrickson v. Hodkin*, "[A hospital] is not required to pass upon the efficacy of treatment; it may not decide for a doctor whether an operation is necessary, or, if one be necessary, the nature thereof; but it owes to every patient whom it admits the duty of saving him from an illegal operation or false, fraudulent, or fictitious medical treatment." (250 App. Div., p. 621, 294 N.Y.S., p. 984.)

To be sure, Dr. Wenger stands responsible for proven acts of malpractice on this record, but not because a spinal-jack operation is per se an act of malpractice. Hence, the mere fact that the hospital knew the surgeon was to perform a spinal-jack operation does not charge it with a tort. The surgeon's responsibility stemmed from his failure to obtain an informed consent from the boy's parents, and perhaps for some of the incidents of the operation about which proof was made with the contention that he had been negligent. But none of these acts or omissions are chargeable to the hospital. Only if, because of the nature of the operation, the hospi-

tal was required to obtain a further consent from the patient or his parents or to verify in some other way that the surgeon had done his duty in that respect could liability attach to the hospital.

Moreover, it would not be just for a court, having the benefit of hindsight, to impose liability on a hospital for its failure to intervene in the independent physician-patient relationship. That relationship is always one of great delicacy. And it is perhaps the most delicate matter, often with fluctuating indications, from time to time with the same patient, whether a physician should advise the patient (or his family), more or less, about a proposed procedure, the gruesome details, and the available alternatives. Such a decision is particularly one calling for the exercise of medical judgment. . . .

In the exercise of that discretion, involving as it does grave risks to the patient, a third party should not ordinarily meddle. . . .

* * *

[iii]

*Ninety-first Congress, Second Session
An Act to Amend the Act of August 24, 1966,
Relating to the Care of Certain Animals Used
for Purposes of Research, Experimentation,
Exhibition, or Held for Sale as Pets**

* * *

SEC. 14. Section 13 of such Act† is amended to read as follows:

"SEC. 13. The Secretary [of Agriculture] shall promulgate standards to govern the humane handling, care, treatment, and transportation of animals by dealers, research facilities, and exhibitors. Such standards shall include minimum requirements with respect to handling, housing, feeding, watering, sanitation, ventilation, shelter from extremes of weather and temperatures, adequate veterinary care, including the appropriate use of anesthetic, analgesic or tranquilizing drugs, when such use would be proper in the opinion of the attending veterinarian of such research facilities, and separation

* Act of December 24, 1970, Pub. Law No. 91-579, 84 Stat. 1560; see 7 U.S.C. § 2143 (1971).

† The regulation of laboratory animals' care and handling was the subject of a number of bills in the Eighty-ninth Congress. One of these (H.R. 3036), which was not adopted, is set forth at pp. 840-842 *supra*; another (H.R. 13881) was enacted on August 24, 1966, as Public Law No. 89-544, which is incorporated in 7 U.S.C. §§ 2131 *et seq.* (1971).

by species when the Secretary finds such separation necessary for the humane handling, care, or treatment of animals. In promulgating and enforcing standards established pursuant to this section, the Secretary is authorized and directed to consult experts, including outside consultants where indicated. Nothing in this Act shall be construed as authorizing the Secretary to promulgate rules, regulations, or orders with regard to design, outlines, guidelines, or performance of actual research or experimentation by a research facility as determined by such research facility: *Provided*, That the Secretary shall require, at least annually, every research facility to show that professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, during experimentation are being followed by the research facility during actual research or experimentation."

* * *

d.

Should Consent Be Supervised?

[i]

*Louis Loss
The Role of Government in the Protection of
Investors**

[S]ecurities are, in a phrase used by a committee of our Congress in 1934, "intricate merchandise." Although one cannot imagine a system of private capital without them, it is a regrettable fact that their very nature makes them a ready device by which people of questionable morals may prey upon the unsophisticated and the gullible. An English historian named John Francis, who wrote on the Bank of England in 1862, claimed to have seen with his own eyes a prospectus issued in 1825 by a company formed "to drain the Red Sea in search of the gold and jewels left by the Egyptians in their passage after the Israelites." A spiritual descendant of those promoters was convicted in one of our federal courts just a few years ago on a charge that he had obtained more than \$100,000 from persons in several midwestern states and Canadian provinces by means of a fraudulent scheme which was no less fantastic. . . .

* * *

. . . If the period 1890-1914 which produced our two great anti-monopoly statutes had

* Address Delivered at the Mexico Stock Exchange 3-4, 8-13 (1957). Reprinted by permission.

also seen the promulgation of federal controls over securities, there might never have been any substantial state legislation in this area. But federal regulation of securities—like the federal social legislation and much of the federal labor legislation now on the books—dates only from President Roosevelt's New Deal in 1933. Indeed, although there had been agitation for securities legislation from the turn of the century, this much at least of the New Deal might never have eventuated except for the stock market crash of 1929.

This left the states free to act in the first third of the century, and they did. Actually there was sporadic state legislation much earlier. But it applied only to railroads and public utilities. . . .

General securities legislation at the state level dates from the second decade of this century. Some of the frauds practiced by promoters in those days were so brazen that someone said they would sell building lots in the blue sky. The state securities statutes thus became popularly known as "blue sky laws." And the fashion soon spread to the point where blue sky laws of one kind or another were found in every one of our forty-eight states except Delaware and Nevada, as well as in Hawaii and every one of the ten Canadian provinces.

Except in a handful of states, these statutes went considerably beyond the philosophy of the English Companies Act. . . . The English philosophy is one of disclosure. There is no government agency comparable to the securities commissions of our countries. Prospectuses are merely filed with the Registrar of Companies in the Board of Trade. They are not examined. It is a criminal offense to fail to give a prospectus to a person who is asked to purchase shares or debentures. But there are no criminal or administrative sanctions for misstatements in the prospectus. The sanction is a civil liability which is imposed upon every director or promotor individually and the liability is to pay the buyer any damage sustained by reason of an untrue statement included in the prospectus.

The theory, in short, is that government should not attempt to dictate which securities may and which may not be offered to the public. It should merely see to it that full and fair disclosure is made to those who are asked to buy. Then, if a prospective investor does not take the trouble to inform himself before risking his money, he has no one to blame but himself. If government were to do more in this area, the

Lord Davey Committee said in 1895, "It would be an attempt to throw what ought to be the responsibility of the individual on the shoulders of the State, and would give a fictitious and unreal sense of security to the investor, and might also lead to grave abuses."

There is a simple grandeur about this philosophy. It has an aura of Plato's *Republic* and of what we in my country like to call Jeffersonian democracy. "All men are created equal," and "The truth shall make you free." But, of course, if all men have an inalienable right to equality before the law, they are not endowed by their Creator with equal wisdom. The question remains whether the ordinary investor will take the trouble to study a modern corporate prospectus, down to the vital footnotes to the financial statements, or will be able to understand what he reads in any event. The typical prospectus does not make light bedtime reading.

With few exceptions, the state legislatures decided that their citizens needed something more than mere disclosure. The forty-seven statutes vary greatly in their terms. But they do embody three general philosophies. The first is the so-called "fraud" approach: the attorney-general or the securities administrator is given broad authority to investigate frauds, to sue in the courts for injunctions, and to prosecute criminally. The second approach requires the registration of brokers and dealers, as well as investment advisers more recently. The third approach requires the issuing corporation or an interested dealer to register the securities themselves—not on the basis of a simple disclosure test, but under various substantive standards. That is to say, the securities administrator is directed by the legislature to examine the registration statement and to permit it to become effective only if he finds that the offering "would not tend to work a fraud," or that the terms of the offering and the proposed plan of business are "fair, just and equitable," or that it is not proposed to issue an excessive amount of securities in payment for physical property or intangible assets such as good will. There are many similar standards, which vary from state to state. In a few states there is a broad standard which simply speaks in terms of "public interest."

These three regulatory philosophies—the fraud approach, registration of dealers, and registration of securities—are not mutually exclusive. Most states follow all three. This is not to say that the blue sky laws and their enforcement

are equally stringent in their application throughout most of the country. . . .

* * *

When Congress finally entered the scene in 1933, it decided that federal legislation was essential because the state statutes were inadequate for what had become very largely an interstate economy. The first major decision which Congress faced was whether to follow the disclosure philosophy of the English statute or the more stringent regulatory philosophy of the states. . . . The latter choice would clearly have been more consistent with the idea of a planned economy which underlay the National Industrial Recovery Act, with its codes for various industries. But philosophical consistency is not an outstanding characteristic of legislation in a democracy. At any rate, Congress chose the milder disclosure philosophy of Great Britain rather than the substantive controls of the state blue sky laws.

The man who was perhaps most responsible for this choice was the great Supreme Court Justice, Louis D. Brandeis. . . . In *Other People's Money*, published in 1914, he had strongly urged publicity as a remedy for social and industrial disease generally, and excessive underwriters' charges specifically: "Sunlight is said to be the best of disinfectants; electric light the most efficient policeman." At the same time, the law should not try to keep investors from making bad bargains; it should not even undertake (except incidentally in connection with railroads and public-service corporations) to fix bankers' profits. He cited the Pure Food Law as an example: it does not guarantee quality or prices, but it does help the consumer to judge quality by requiring the disclosure of ingredients.

* * *

. . . Brandeis . . . cautioned in [*New State Ice Company v. Liebmann*, 285 U.S. 262 (1932)]: "Denial of the right to experiment may be fraught with serious consequences to the Nation. It is one of the happy incidents of the federal system that a single courageous State may, if its citizens choose, serve as a laboratory; and try novel social and economic experiments without risk to the rest of the country." Whether out of this spirit of federalism to which both our countries are attached or out of considerations of political feasibility—perhaps it was a little of both—Congress did not interfere with the more drastic blue sky laws of the states.

The Brandeisian philosophy which prevailed at the federal level was not without its critics. The present Justice Douglas, who was destined to become Chairman of the Securities and Exchange Commission and then to succeed Brandeis on the Supreme Court, wrote as a Yale law professor in 1934 that the Securities Act of 1933 was "superficial." It was essentially, he said, a "nineteenth-century piece of legislation" which unrealistically envisaged a return to the simpler days of small business units. Douglas did not favor a federal statute of the "blue sky" type either. That type of control on a nationwide basis, he thought, would be far too complex. What he advocated was a philosophy which would combine self-regulation by industry with supervision by government—something, in short, like the then current industrial codes under the National Recovery Administration, which was soon to be declared unconstitutional by the Supreme Court.

* * *

. . . I shudder at the thought of giving a federal agency life-and-death power over virtually the entire industry of the country by subjecting all public financing to such vague tests as "fair, just, and equitable" or "sound business principles." Although the disclosure philosophy has its inadequacies, it has turned out to be considerably more potent than many people anticipated. It may be permissible in theory for a company to offer shares in a venture which is nothing more than "a hole in the ground," or to pay promoters exorbitant amounts of stock for good will or promotional services. But the practicality of doing this sort of thing on the basis of the disclosure which the Commission requires is another matter. And, if not too many investors read or could understand prospectuses, the information on file in Washington seeps down to them through their advisers and the financial publications. . . .

* * *

Our Securities Act of 1933, with certain exceptions, requires the federal registration of all new issues of securities which are offered to the public by use of the mails or any instrumentality of interstate or foreign commerce. . . . The registration requirement also applies to secondary distributions of outstanding securities by persons who are in a relationship of control with the issuer. And a prospectus containing

the basic information in the registration statement must be given to each buyer.

The Act includes a civil liability provision which was largely modeled on the English Companies Act. But it also contains administrative machinery which is not found in England. The prospectus and various other documents, which are collectively called the registration statement, are carefully examined by the Securities and Exchange Commission. The Commission has no power to pass on the merits of securities, and it is a criminal offense to represent that it does. But it may issue a so-called stop order, subject to judicial review in a federal appellate court, upon a finding that the registration statement is incomplete or misleading. Since this administrative power exists, it seldom has to be exercised. An informal procedure has been developed whereby the registration statement is examined by a group of financial analysts, accountants, lawyers, and engineers on the Commission's staff and then amended to repair any deficiencies which are thus found. This detailed examination, if it frequently proves annoying to registrants and their lawyers, is essentially welcomed by the financial and legal communities as a cheap form of insurance against what might otherwise be disastrous civil judgments.

The Securities Act of 1933 was the first, but by no means the last, of the federal statutes. Almost annually for the next seven years Congress added a new statute, until there are now seven under which the SEC functions.

The Securities Exchange Act of 1934, the second statute in the series, is concerned with trading in securities already issued rather than the process of capital formation. Every stock exchange must be registered with the Commission, which has certain supervisory functions with respect to their rules. Every security which is listed for trading on a stock exchange must likewise be registered. Annual and other periodic reports must be filed to keep the registration data current. The Commission has a quasi-legislative power to adopt rules regulating the solicitation of proxies. Directors, officers and ten-percent stockholders must file monthly reports of their holdings, and must surrender to the corporation any profits they make from trading in their corporation's securities within any period of six months.

These several provisions apply only to securities listed on exchanges. So far as the over-the-counter market is concerned, the securities themselves are not registered unless they are the

subject of a distribution which falls within the 1933 statute, but brokers and dealers in the over-the-counter market must be registered and file annual financial statements. Moreover, the Commission has very broad powers to define fraudulent practices by rule; to enforce the statute and the regulations by investigation, injunction, and criminal prosecution; to control various stock exchange practices such as short selling, stabilization, floor trading, and the hypothecation of customers' securities; and to suspend or expel stock exchange members, as well as to revoke the registration of over-the-counter brokers and dealers, for illegal conduct.

All this regulation is supplemented on an ethical plane by the National Association of Securities Dealers, an organization of over-the-counter brokers and dealers which has semi-official status. And the 1934 statute also attempts to control the amount of the nation's credit which is channeled into the securities markets by authorizing the Board of Governors of the Federal Reserve System to promulgate margin rules, which are enforced by the Commission.

* * *

[ii]

*Kenneth L. Melmon, Michael Grossman, and
R. Curtis Morris, Jr.*

*Emerging Assets and Liabilities of a Committee
on Human Welfare and Experimentation**

* * *

... This report examines the operations of the Committee on Human Welfare and Experimentation of the University of California at San Francisco in the first two years of its existence and attempts to evaluate the Committee's past and current effectiveness.

* * *

Acceptability of the protocol was at first judged on a number of points, the first being the question, *Will the rights and welfare of the subject be protected?* Attempts were made to assess the manner in which subjects were sought, the enticement offered, the explanation of means by which the subject could withdraw from the study, the manner in which studies were to be monitored, the expressed provisions protecting the subjects from potential harm, the feasibility relating to time factors, drug doses and availability of antidote, the expressed clinical criteria

* 282 *New England Journal of Medicine* 427-428 (1970). Reprinted by permission.

for termination of an experimental procedure, the degree of experience and sophistication of an investigator in the area to be studied, and the applicability of the cited references to the substance of the proposal as an index of the care and seriousness of the exposition of the protocol. As a second point, the question was asked, *Are the methods used to obtain a subject's informed consent appropriate?* Are subjects approached only by physicians involved in the experimental procedure? If so, there could be no guarantee that an objective and unbiased explanation of the protocol would be made to the patient. Therefore, some specific mention is required of the presence of an impartial but knowledgeable witness to judge the suitability of the explanation to the subject of the experimental procedures. Such witnesses are also required to sign the consent form. Are subjects fully informed of their rights to withdraw and realistically told of the risks? Are subjects told which of the agents or procedures are experimental and what experience with these the principal investigators have had? The third question was, *Are the potential scientific benefits of the procedure proportionate to the risks involved?* This question is perhaps the most difficult to answer. All would agree that the risk-benefit ratio is low if only 10 ml of venous blood needs to be withdrawn from a single normal volunteer and results of experimentation would reveal a cure of an otherwise fatal disease. The question of risk benefit is usually considerably less clear. However, protocols were rarely rejected because of unacceptable risk.

After the first year, three additional questions were considered necessary because unanticipated inconsistencies arose in the judgment made by the parent committee as opposed to ad hoc committees. *Is the informed patient consent form to be used appropriate for the type of patients involved?* The question became necessary because of discrepancies between the subject's understanding of the experimental procedure and its realities. *Are the risks described completely and in reasonable language? If not, why? Does the project require the use of investigational or new drugs?* Eight of 80 randomly selected protocols in the second year elicited partial, and two complete, disagreement on whether a drug to be used was new. Yet, in the first year, the question was not put because the parent committee did not anticipate serious difficulties in an investigator's ability to identify new drugs. . . .

* * *

NOTES

NOTE 1.

T. T. BRÜCKE
CLINICAL RESEARCH IN AUSTRIA*

* * *

In Austria therapeutic experiments are permitted in university clinics, but the law forbids them in other hospitals. Thus the patient admitted to a university hospital knows that new procedures not yet in current use may be used for his benefit. This being the case, it is unnecessary to inform him fully; nor is it possible when a new procedure is being utilized. In any case the surgeons, even in current practice, do not tell their patients that an accident occurs in every 10,000 cases. It is undesirable that the patient should know everything, and that is indeed the problem involved in his being informed of a trial to be carried out on him.

NOTE 2.

OTTO GUTTENTAG
THE PROBLEM OF EXPERIMENTATION WITH
HUMAN BEINGS†

* * *

Present types of experimentation on the sick clearly challenge tremendously the basic concepts of the original patient-physician relationship. . . .

Perhaps a glance at the way the legal profession meets the moral and technical demands of society and the individual when a conflict arises between the two will offer a clue to a solution of our problem. As we all know, that profession provides each of the two with a representative of equal stature: there, the prosecuting attorney and, here, the defense attorney. Similar arrangements may have to be developed in the field of human experimentation, performed not for the good of the individual patient but made to confirm or disprove a doubtful or suggested biological generalization. Research and care would not be pursued by the same doctor for the same person, but would be kept distinct, the physician-friend and the physician-experimenter would be two different persons as far as a single

* V. Fattorusso, ed.: *Biomedical Science and the Dilemma of Human Experimentation*. Paris: Council for International Organizations of Medical Sciences 38 (1968). Reprinted by permission.

† 117 *Science* 205 (1953). Reprinted by permission.

patient is concerned—for instance, my patients would become research objects for someone else, and I would be permitted to experiment only with the patients of another physician. The responsibility for the patient would rest, during the experimental period, with the physician-friend, unless the patient decided differently. Retaining his original physician as personal adviser, the patient would at least be under less conflict than he is at present when the question of experimentation arises.

* * *

. . . A given situation may demand that the attitude of the physician-experimenter and that of the physician-friend be embodied in one person. Unless we recognize the basic differences of the two attitudes, each will suffer, as demonstrated by the confused concept of the "hopelessly incurable"; or one will be needlessly neglected, as demonstrated by our failure to supplement forms requesting consent from a patient with some corresponding affirmation of utmost concern for his welfare on the part of the attending physician.

e.

Should Ongoing Research Be Monitored?

[i]

*Senate Committee on Government Operations
Interagency Drug Coordination**

* * *

The tragedy of thalidomide was not that a drug caused a deformity, but that it continued for so long to cause deformities in the thousands before notice was taken and the cause tracked down.

Recording and evaluation of birth defects was inadequate in the countries where the epidemic first occurred; months went by before significant suspicion was aroused. This was despite the fact that the pattern of malformations was so rare that it should have promptly evoked strong curiosity.

As early as October 1960 the first two cases of "grossly deformed" babies with *seal-like deformities* were presented in a medical exhibit in West Germany.

These cases were described in a later article by Helen B. Taussig, M.D., School of Medicine, Johns Hopkins University. Dr. Taussig is

the distinguished American physician who, on hearing of the early defects from a German colleague, journeyed to West Germany to study the problem at first hand. It was Dr. Taussig who, on return, alerted the United States to the drug's danger.

Later, Dr. Taussig wrote of the two initial cases in the medical exhibit of October 1960:

* * *

But over a year was to elapse before the cause of what had become an epidemic was traced.

* * *

Like so many other drugs with a strong market potential, Thalidomide naturally became available in a number of countries through a system of licensing, export of bulk supplies, and other arrangements. The news of side effects of the drug did not, however, proceed through systematic channels between the interested companies of the various nations.

* * *

Many months after the first report on peripheral neuritis, the news of an infinitely more serious nature came. Thalidomide had been withdrawn from the market in West Germany on November 25 because the drug was suspected of responsibility for deformity of babies.

The news from West Germany broke the "dam." A full flood of similar news began to break in country after country. Doctors reported scores and hundreds of deformed babies.

But no intergovernmental action ensued. No international resource, such as the World Health Organization, was informed, consulted, or used so as to minimize the disaster.

* * *

Exchange of information was (and is) handicapped by the fact that a single drug may be called by any one of five or more types of names—by a code name, a chemical name, a generic, an official, and a proprietary name. Within the single "proprietary" category, a drug may be known by dozens or scores of brand names in any one country and by hundreds of

* Senate Report No. 1153, 89th Congress, 2d Session 8-25 (1966).

such names in many countries. Thalidomide was the generic non-brand name. A physician, reacting to news about the danger of "thalidomide," might unwittingly continue to prescribe the very same chemical ingredient under any one of dozens of trade names.

* * *

The international practice of identifying prescription drugs to laymen by number, not by name, lowered the chance of the public getting rid of the drug, once its hazards became known.

Dr. Taussig wrote in her July 1963 article:

Some pills which were prescribed in good faith by physicians, are now tucked away in many a medicine closet, with only a prescription number and no name. The serious consequence of this well-established custom of filling prescriptions by number is illustrated by one unfortunate woman who, because the bottle was unlabeled, unwittingly took Distaval (a trade name for thalidomide in Great Britain—ed.), during two successive pregnancies and has two children with phocomelia.

The New England Journal of Medicine editorialized:

Dr. Taussig carries her reasoned apprehension beyond the matter of proprietary versus generic names and raises the question whether physicians' prescriptions, which usually bear on the label no other identification than a number, should not also carry the name of the drug or drugs embodied in them. After all, the less secrecy with which the business of administering medicines can be surrounded, the safer it will become.

Upon her return from studying the deformities in Western Germany, Dr. Taussig sought to report her findings promptly to American physicians. Her report did not, however, appear in any medical journal until 3½ months after the investigational use in the United States had ended.

A memo by Dr. [Frances] Kelsey to the file discussed her interview later on with Dr. Taussig:

Dr. Taussig mentioned that since she wished authentic information concerning the hazard of this drug to reach the practicing physician as rapidly as possible, she submitted a letter to the AMA for publication shortly after her return from Europe in the late winter. She was told that inasmuch as *Time Magazine* had already run an item on the drug, they would not be interested in publishing such a letter. They are however publishing an article but this inevitably entails a considerable delay.

Dr. Taussig's article in *JAMA* appeared on June 30, 1962, 7 months after the drug was removed from the market in West Germany.

* * *

In an effort to expedite the new drug application through FDA, the company had contacted the medical reviewer, Dr. Kelsey, in over 50 phone calls, visits, and letter requests.

The application had been submitted on September 12, 1960. In the weeks and months which followed, company representatives repeatedly remonstrated with Dr. Kelsey. They pointed to the fact that the drug had been in wide use in West Germany since 1957 and was well regarded there as a safe, useful medication.

* * *

The initial clue which aroused Dr. Kelsey's suspicion as to possible hazard from the pending drug came to her attention not through an organized information service, but through sheer happenstance. While looking for something else, she chanced on a letter to the editor in the *British Medical Journal*. The letter mentioned the possibility that thalidomide might be responsible for certain neurological symptoms in the feet and hands.

The *British Medical Journal* is, it may be noted, but 1 of over 5,000 medical serials in the world. Chance finding of an article in even the most prominent publications of the world's literature is like a lucky finding of the proverbial "needle in a haystack."

The chronology of events, as reconstructed by the subcommittee, shows that the original letter to the editor on peripheral neuritis appeared on December 31, 1960; a reply by the British company appeared on January 14, 1961. The first notation of the British discussion appeared in FDA's summary chronology as of a date a month later—February 23, 1961. At that time Dr. Kelsey requested additional information from the company.

In her request of February 23, 1961, Dr. Kelsey asked for "a complete list of investigators to whom the drug had been furnished," so as to check up on possible neurological effects. The company did not initially comply with FDA's request. It sent a list of only 56 investigators who had used the drug for a period of 4 months or longer.

* * *

On November 28, the West German Ministry of Health issued what Dr. Taussig characterized as "a firm but cautious statement that Contergan, the trade name for thalidomide, was suspected to be a major factor in the production of phocomelia. Women were warned not to take the drug. The announcement was carried on the front page of every newspaper, on the radio, and on television."

A week later, on December 5, 1961, the American company sent out a letter with only this modest warning:

DEAR DOCTOR: We have received information from abroad on the occurrence of congenital malformations in the offspring of a few mothers who had taken thalidomide (marketed in Canada as Kevadon) early in their pregnancies. It is impossible at this time to determine whether, in fact, there is any causal relationship.

However, until definitive information is available to us, as a precaution we are adding the following contraindication to the use of Kevadon:

Kevadon should not be administered to pregnant women nor to premenopausal women who may become pregnant.

We are actively following this matter and you will be advised when it is finally determined whether or not this precautionary step was necessary.

* * *

Although the drug never emerged out of investigational status in the United States, the company distributed such vast supplies as to raise serious doubt as to whether the company was "testing" or promoting the drug. The company sent 2½ million tablets to 1,267 investigators. This supply was so vast as to be capable of causing incalculable harm if the "investigational" drug turned out to be hazardous.

* * *

[T]he American company gave additional indications it was not too interested in "investigational" reports. A manual which it issued to its detail men who were to distribute the drug for "investigation" stated:

... the main purpose is to establish local studies whose results will be spread among hospital staff members. You can assure your doctors that they need not report results if they don't want to, but that we, naturally, would like to know of their results. Be sure to tell them that we may send them report forms or reminder letters but these are strictly reminders and they need not reply.

* * *

Hundreds of "investigators" failed, contrary to the traditions of science, to keep adequate records. They did not know which patient they had given the drug to, at what dosage or when.

One result was that later on, when the hazards became known, the investigators were unable to contact the patients.

Many doctors, however, did not contact the patients even though they did keep the patients' name and address. An FDA survey concluded that 259 of 1,258 M.D.'s interviewed took *inadequate* steps to contact patients who had been given the drug. Many of the 259 physicians felt that such action was unnecessary because of the length of time that had passed since the patient was given the drug; others had no records indicating which of their patients had received the drug.

The same FDA survey revealed that more than half of the physicians interviewed had *no record* of the quantities of the drug *returned* or *destroyed*, pursuant to the manufacturer's instructions.

* * *

[ii]

University of Miami
Procedure for Review of Research Projects
Involving Human Beings (1966)*

* * *

(9) After a committee has been assigned a project it will continue to maintain surveillance over it and to provide advice for the investigator in order to safeguard the rights and welfare of human subjects until the project is complete, discontinued, or assigned by the Executive Committee to a different committee either on its own motion or at the request of the committee which has been responsible. The extent and nature of the surveillance shall be determined by the committee upon the basis of giving primary attention to projects involving special risks or unusual conditions and shall be reflected in the minutes of the meeting at which the project is approved. In any event, there is to be a periodic review, which it is contemplated will be on a quarterly basis, of a sample of projects selected by the Executive Committee for review of procedures and conformity with policy. The progress of such review and surveillance shall be re-

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flected in minutes of the committee from time to time as action is taken.

(10) Each investigator is obligated to report to the committee which approved his project any unexpected developments so that they may be evaluated and the project reviewed by the committee.

(11) Each committee is expected to furnish to the investigator of any project assigned to the committee advice and consultation initially and from time to time during a project when appropriate to safeguard the rights and welfare of the individual.

(12) The Office of Assistant Dean for Research, School of Medicine shall maintain all files on projects and maintain a set of minutes of all committees, including the Executive Committee. Those files will be available for inspection and study by the panel and others having good reason to examine them.

* * *

NOTES

NOTE 1.

YALE REPORTS ETHICS AND MEDICINE—CONTROL OF HUMAN EXPERIMENTATION*

* * *

MR. CALABRESI: [D]oes the committee just review the project at the beginning, or do they keep an eye on it as it goes along and suggest times when the experiment ought to be terminated? Because it seems to me that that is as important a question, as data come in, especially in these complicated blind or double-blind experiments, to know at what point the same considerations which would make an experiment improper make it improper for an experiment to continue. Or for that matter to end an experiment too soon.

DR. KATZ: We have talked about it [but] we haven't done anything about this [problem]. It raises even more complicated issues because if you begin to supervise ongoing experiments and how they are being conducted—for example,

whether what the experimenter tells us he will communicate to the patient, he actually does communicate—then one will have to institutionalize an extensive watchdog structure. . . .

MR. CALABRESI: But that's a rather different thing. . . . It is one thing to see whether the experimenter is telling you the truth, in terms of what he has communicated to the patient, and that may be hard and an unpleasant thing to police. The other thing is to say that either at given time intervals a report on the project is given to the committee or, if certain events occur, like serious harm to a certain number of patients involved in the experiment, that any of these things automatically should trigger a review of the experiment by people who are not involved in it and so who do not necessarily break the code or break the experiment by doing this.

DR. KLIGERMAN: I agree. Not only do I feel that there should be some lay persons aboard, but that the investigator should at some regular time, even once a year, send the results, a progress report, one page is all it takes, to the committee. I think that this would at least make him stop and think about what has happened. It would make him assess what he has done, and perhaps at an earlier time than he would have, had he not had to prepare such a report to the committee for review.

DR. KATZ: [S]ince I have been on the committee, I have not seen such progress reports. At least what we could do is to ask the experimenter that if anything happens which was not anticipated by the protocol, he should bring this to our attention immediately. . . . We could learn a great deal from such a procedure which would also aid us in reviewing future studies.

* * *

NOTE 2.

BERNARD BARBER, JOHN LALLY, JULIA MAKARUSHKA, AND DANIEL SULLIVAN THE STRUCTURE AND PROCESSES OF PEER GROUP REVIEW*

* * *

The Public Health Service Regulation,
"Protection of the Individual as a Research Sub-

* A weekly broadcast review presented by Yale University and WTIC, March 3, 1968. Participating were Guido Calabresi, Professor of Law; Morton Kligerman, Chairman, Department of Radiology, (Yale Medical School); and Jay Katz, Professor (Adjunct) of Law and Psychiatry. Reprinted by permission.

* A preliminary version (1970) of *Experimenting with Humans: Problems and Processes of Social Control in the Bio-Medical Research Community*. New York; Russell Sage Foundation (forthcoming). Printed by permission of the authors who retain all rights.

ject," requires not only an initial review of all research protocols but continuing review. The regulation states that "the committee shall carry out interim review of all research in such a manner and at appropriate intervals in the light of apparent risks, existing administrative and supervisory organization, and other factors as to assure itself that its advice is being followed." . . . 24 per cent of the responding institutions report no continuing review at all. 36 per cent claim continuing formal review. 33 per cent report wholly or partly informal review. 6 per cent report that continuing review is given not by the peer review committee but by some institutional officials, such as department heads. The lack of wholly satisfactory continuing review is further evident in the fact that some of the institutions claiming continuing review, formal or informal, indicated in their responses to our question to be specific about what this continuing review consisted in that it was fairly perfunctory or operated only in some cases, not all. For example, a few respondents indicated that continuing review consisted in "informal discussion at lunch," or "through personal contact with researchers," or "as concern arises on the part of investigator, administrator, or senior faculty member." It is evident that procedures and practices for continuing review will have to be strengthened in many bio-medical research institutions using human subjects.

* * *

NOTE 3.

LIZ ROMAN GALLESE
MEDICAL-ETHICS PANELS ARE SET UP TO
RESOLVE DILEMMAS ON RESEARCH*

* * *

In rare cases an ethics committee may have a physician-advocate peering over a researcher's shoulder to make sure all is well. In one big hospital, for example, a brain surgeon is seeking to use electrodes to stimulate the brains of patients undergoing surgery for various reasons.

The surgeon's project is based on discoveries that short bursts of electricity into certain parts of the brain can cause persons to "see" things, raising hopes that an artificial seeing device might someday be devised for the blind. As preliminary research, the surgeon intends to ask

the patients, under local anesthesia, what they "see" as he stimulates their brains.

The hospital's ethics committee recently approved the project when the researcher clarified his intention that the electrodes be placed only on the surface of the brain. But the committee was deeply worried lest an electrode be pushed into the brain itself, a move that might cause permanent brain damage.

The project is approved, the committee stated, only so long as the physician-advocate in the case is present in the operating room to make sure an electrode doesn't penetrate into the patient's brain.

f.

Should Harm Be Assessed?

[f]

Wolf Wolfensberger

*Ethical Issues in Research with Human Subjects**

* * *

Since the very question of experimental risk . . . appears so apt to arouse emotions that can becloud reason, conceptualization of the relation between certain types of research and experimental risks may be helpful. I propose that there are roughly three levels of research, and even though there is an underlying continuum most experiments with human subjects can probably be assigned to one of these levels.

In level-1 research, experimental activities and procedures are employed but are not consciously recognized or formally labeled as research. A considerable amount of the clinical management of human beings falls into this category. Many techniques of diagnosis and treatment, widely practiced in medicine, psychiatry, clinical psychology, social work, education, rehabilitation, and other human-management professions, lack adequate empirical validation and must be considered tentative and experimental. . . .

There appear to be three reasons why such activities are not recognized or labeled as research: (i) a certain hyperclinical type of practitioner finds it difficult to think of himself as being a researcher, and may even attach negative values to research activities; (ii) some experimentation loses its research identification be-

* *The Wall Street Journal* 1, col. 6, 17, col. 4 (April 14, 1971).

* 155 *Science* 47, 49-50 (1967). Copyright 1967 by the American Association for the Advancement of Science. Reprinted by permission.

cause of its sloppiness; and (iii) some experimental and ultimately nonvalidated procedures have been adopted so universally that they have lost their research identification.

There is no doubt that level-1 research can be risky to the subject. An invalidated medical treatment, like bloodletting as practiced in the 18th century, can be worse than no treatment at all. Is it really so inconceivable that some widely current but insufficiently validated human-management practices (psychotherapy, for example) may constitute the bloodletting of the 20th century?

Research at level 1 may also consist of the utilization of impersonal and grouped data collected in the course of routine and accepted operations of agencies. Thus school-enrollment, traffic-accident, and armed forces selection and rejection studies use information pertaining to individuals, group such information, and make it the substance of research. Such data are often collected without the knowledge or consent of the subjects and may or may not affect them.

Research at level 2 is clearly identified and conceptualized as research. Usually, but not necessarily, a distinct manipulation of subjects, individually or in groups, is entailed; at times it may be identified as research more by its "unnaturalness" than by anything else. A situation in which for several hours a subject has to push a button whenever a light appears on a screen (in a vigilance experiment, for instance is perceived quite differently from assignment to a dishwashing task as perhaps in a study of vocational-training practices. Regardless of the oddity of the task, a crucial characteristic of level-2 research is that it stays close to the mainstream of knowledge; the procedures employed are well tried, tend to be familiar at least to specialists, and are known to be harmless; the new knowledge sought is usually modest; and possible outcomes of the research can be fairly well described in advance. Most importantly, risk to the subject is very small, perhaps even smaller than in the often poorly conceptualized and planned and chaotically conducted level-1 research.

It is research at level 3 that tends to give rise to most of the ethical concern. Level-3 research is risky to the subject; either previous work has shown it to be risky or the procedures are novel and untried, and outcomes are less predictable. The fact that this kind of research may occasionally promise more substantial in-

crements in knowledge is likely to lead to dilemmas.

Risk to the subject may exist at any level of research, but there is a very useful distinction between risk that is *intrinsic* to the experimental task and risk *extrinsic* to it. Intrinsic risk arises from the very nature of the task. For instance, a drug may trigger convulsions or allergic reactions; a spinal tap carries a low but definite risk of damage to the central nervous system; and sensory deprivation can result in disturbed behavior.

Extrinsic risk might be viewed as being little or not at all under the control of the experimenter, and not being ordinarily foreseeable; it might be subdivided into types *a* and *b*. Thus type-*a* extrinsic risk may refer to consequences for which the experimenter or his agency is legally liable, even though they comply most meticulously with ethical demands. For example, a subject may slip on the waxed floor of the experimental room, break his leg, and sue for compensation. Type-*b* extrinsic risk may refer to consequences for which the experimenter or his agency is not legally liable: a subject may be struck by a car as he leaves home on his way to the experiment.

Some extrinsic risks are difficult to classify, especially those arising from psychic processes within the subject, of which the experimenter has little or no knowledge. For instance, even the most innocuous research task may seem threatening to some subject; such a perceived threat can cause psychological stress, which in turn can result in physical harm. It is unlikely but conceivable that the mere request to serve as a subject in an "experiment" might lead to heart failure. I have in fact witnessed a breakdown in functioning in a mildly retarded teenager who was asked to leave class and spend a few minutes on an undemanding, simple, and utterly harmless task; it appeared that a "friend" had told him something to the effect that the psychologist was going to cut his head open.

Except in instances in which research involves only record data, the researcher can never state with certainty that a subject will not experience some kind of trauma. At best, he can estimate the level of probability of trauma if intrinsic research risks exist, or state that, if trauma occurs, it will occur because of the extrinsic risks.

* * *

[ii]

Robert J. Bazell

*Food and Drug Administration—
Is Protecting Lives the Priority?**

In January officials of the Food and Drug Administration (FDA) knew that the use of bottled intravenous feeding solutions manufactured by Abbott Laboratories had somehow led to an outbreak of blood poisoning and several deaths. Yet they took no action. In early March, the FDA found out that a large percentage of the Abbott solutions were contaminated with the infectious bacteria responsible for the blood poisoning. Yet they did not ban the products. They only recommended that certain precautions be taken when the solutions were given to patients. Not until 22 March did FDA recommend that hospitals stop using the Abbott products and then only after consumer-advocate Ralph Nader appeared on national television denouncing the agency for its failure to act.

The intravenous (I.V.) solutions (mostly combinations of dextrose and salts in water) are used in virtually every hospital to feed nutrients to critically ill patients. Until the ban Abbott Laboratories supplied 45 percent of the 250,000 bottles of I.V. solutions administered daily to patients in the United States.

* * *

A decision by FDA officials to ban any product involves complex consideration, many of them subjective. And from the vantage point of hindsight, the FDA can make an easy target for critics. Nevertheless, the case of Abbott's I.V. solutions involved enough irregularities and a sufficient number of deaths to warrant close scrutiny. . . .

* * *

The decision to remove a product from use rests . . . with the FDA. All through the investigation, George Blatt of FDA's Office of Compliance kept tabs on the CDC [Center for Disease Control] findings. Blatt does not believe that the relation discovered in January between the disease and the Abbott products warranted any action by the FDA and, indeed, FDA did nothing at the time.

"You don't take legal action against a

firm," Blatt told *Science*, "until you have evidence that can stand up in court. You have to define where the problem is. And all you had at the time was an association of the disease with the product." He emphasized, however, that the decisions regarding action against Abbott were made not by him, but by the Commissioner of Food and Drugs, Charles E. Edwards.

But, in spite of the illnesses and deaths resulting from the products, Edwards says he knew nothing of the problem. In an interview with *Science*, both Edwards and his associate commissioner for compliance, Sam Fine, insisted that the first they heard of the difficulties, other than what had been published in the *New England Journal of Medicine*, was 11 March. That was after the discovery of the contaminated bottle caps.

* * *

On 11 March representatives of Abbott, FDA, and CDC met in Atlanta. The next morning David Sensor, the director of CDC, Edward J. Ledder, the president of Abbott Laboratories, Surgeon General Jesse Steinfeld, and Commissioner Edwards met in Washington to discuss the problem. That afternoon Edwards and Sensor announced at a press conference that a ban was not feasible and that "special precautions must be taken . . . to reduce the risk of septicemia from the use of Abbott Laboratories' intravenous infusion products." The precautions included gentle removal of the bottle caps, changing of the I.V. apparatus every 24 hours, and watching for the first signs of blood poisoning.

* * *

In explaining his decision on 13 March not to ban the use of the contaminated solutions, Edwards told *Science*, "You've got to understand that all we had at that time was very preliminary data. We believed that the precautions could allow the solutions to be used safely." Edwards also emphasized that FDA didn't have accurate information about the availability of replacement products from Abbott's competitors. And since Abbott was supplying 45 percent of the critical solutions, he could not simply order hospitals to stop using the Abbott products. "We might have killed more people by banning the Abbott solutions than by allowing their use," added Fine.

Yet FDA officials acknowledge that they did not even check on the availability of solu-

* 172 *Science* 41-43 (1971). Copyright 1971 by the American Association for the Advancement of Science. Reprinted by permission.

tions from other manufacturers until after the 13 March announcement. Thus while FDA met with Abbott on 12 and 13 March, Abbott's three competitors, Baxter Laboratories, Cutter Laboratories, and American Hospital Supply, heard from FDA a few days later. When on 19 March government specialists did complete a survey of the competitors, they concluded that, for the most part, hospitals' stocks of Abbott solutions could be replaced. "The reason for the delay," said Edwards, "was that we didn't know of the problem until 11 March. After that we acted as fast as possible."

Although the FDA had declared that the Abbott solutions could be used safely, the Army disagreed. On 15 March, the Army Surgeon General issued a worldwide notice ordering all Army medical facilities "to suspend from immediate use and issue all Abbott intravenous solutions." The Army and the FDA differed in their actions, according to one medical officer, because the Army wasn't depending solely on Abbott products. And "because in the military services we never take a chance with a product that might be faulty."

* * *

NOTE

M. B. VISSCHER

PUBLIC STAKE IN THE WISE CONTROL OF
CLINICAL INVESTIGATION*

* * *

... A drug which had been used in another country on some 300,000 human subjects for management of hypertension was found to have impressive anti-fibrillatory effects on the dog heart. The investigator carried out extensive toxicity studies in dogs at the dose levels required for the anti-fibrillatory effect and found no observable adverse effects. Lethal doses were many times the proposed therapeutic dosages. Application for permission to begin clinical studies was made, but numerous requirements for additional studies were laid down, including such stipulations as that possible local tissue injury at the site of intramuscular injection be fully investigated. Since the drug was intended to be used only in life-threatening situations, and

since the dogs employed in general toxicity studies had had intramuscular injections without gross evidence of local tissue damage, it seemed absurd to make these further studies as a prerequisite to clinical trial. If the drug were to be found to be clinically useful, it would actually be employed even if there were some damage to muscle at the site of injection because no satisfactory anti-fibrillatory drug is available today. After six months of delay, the Food and Drug Administration did grant permission to test the drug on humans, but months of time were lost, and the possible life-saving virtues of a drug which markedly raises the threshold for ventricular fibrillation have been denied to the whole human race for those six months. A considerable amount of humans do die every day because of uncontrollable ventricular arrhythmias. Excessive caution has probably cost the lives of thousands of persons, simply by postponing the time at which a drug may become generally available.

* * *

g. Should Societal Interests Be Considered?

[i]

Walsh McDermott

Comment on "Law as a System of Control"*

* * *

... While the public seems quite willing to accept that there are times in human experimentation when the interest of the individual cannot be paramount, it would probably not support the actual codification of that principle in either an administrative regulation or a statute. And these are the two forms of the law that have emerged to the forefront in this field of human experimentation. Attempts to create extralegal devices such as local committee review are likewise unsatisfactory. My objection to the committees is not that they perform no useful services, because they do provide such services of a limited sort; specifically, they serve to air the issue. But, as they are in effect self-appointed, they lack the authority to represent the interests of either the individual or society when these interests are in conflict in a particular case. For this reason they cannot be regarded as a

* V. Fattorusso, ed.: *Biomedical Science and the Dilemma of Human Experimentation*. Paris: Council for International Organizations of Medical Sciences 46, 49 (1968). Reprinted by permission.

* Paul A. Freund, ed.: *Experimentation with Human Subjects*. New York: George Braziller 218, 219-220 (1970). Reprinted by permission of the American Academy of Arts and Sciences.

major institutional form that meets the need; yet, they represent just about the only formal extra-legal structure that exists.

* * *

. . . I came to the conclusion that in medical research the problem of attempting to institutionalize the making of a judgment between the individual and society was basically unsolvable. Perhaps some day there might come to be a reasonably widespread, publicly voiced attitude on the individual vs. society issue that would permit appropriately flexible laws or administrative regulations. But until that presumably far-off day, as I saw it, we would simply have to live with the problem and handle it as best we could, by what must ultimately be arbitrary decisions. To ensure that these arbitrary decisions not be capricious, I could suggest only that we rely on the cultivated conscience of the experimenter, continuously reinforced by an organized effort to increase the local visibility surrounding each decision. Indeed, this seemed to me to be the chief role served by the local committees.

* * *

[ii]

Guido Calabresi

*Reflections on Medical Experimentation
in Humans**

* * *

[P]erhaps the best general system of control would be the oft-suggested establishment of groups (hospital committees, say) that are sufficiently broadly based so that their judgment can reflect society's unspoken choice between present and future risks, and yet unofficial enough so that they do not seem to represent the government choosing to sacrifice the individual for the good of the collective. Society, in the form of the government, could retain its position as the protector of individual lives and step in mainly to establish stricter rules in areas where the unofficial groups had erred and allowed lives to be taken too blatantly or in a way that undermined our commitment to human dignity.

If hospital committees are to bear the main burden of overseeing experiments and experi-

mental plans, if they are to be the principal instruments for balancing risks to present lives against future benefits, ways must be found of increasing the information that is available to these committees. It is not enough that they be made up of people of good will; their members must also be people who have available to them some sense of the balance that society desires between present and future lives. The difficulty here, of course, is that this sense cannot be given by government decrees, since that would involve society too clearly in the process of choosing against individuals. The sense of society's wishes must, instead, be brought to the committees through as many varied inputs as possible. In effect, the more the inputs of information and value judgments to the committees are broadened, the more the committees will seem to be doing no more than ratifying broad judgments inherent in the social system. In this way, the directness—the playing God by any single group—is reduced. This would be especially true if, in addition to the committees, there was not only some kind of market test (of the type I described) to be met, but also government intervention from time to time to protect individual lives by requiring more care than either the market or the committees deemed necessary.

The most obvious—but probably least important—method of broadening the input to the committees is by broadening the committees themselves. Many of these are now made up primarily of scientists from the very medical center where the research to be approved is to take place. The presence of scientists from other research centers and the presence of non-scientific members would certainly give the committees a greater sense of where the crucial balance is to be struck. My own guess is that while scientists from other medical centers would on occasion be stricter than local scientists in approving particular experiments, non-scientists on the committees would tend, on the whole, to approve some experiments that would not now be passed. This is especially true where the potential gains from an experiment are great, but the risks involved are also great. In such areas, I suggest, doctors are perhaps unduly hampered by fear of lawsuits (incidentally, the reduction of fear of such suits might be a side benefit of the kind of market compensation system I have described) and by the worthy tradition that, after all, the individual patient is in their care. Laymen, I believe, are less likely to be so emotion-

* 98 *Daedalus* 387, 399–400 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

ally concerned with either of these two factors and, hence, are more likely to give greater weight to society's long-run interest.

* * *

3.

In Reviewing Decisions and Consequences

a.

Through Public Scrutiny?

[i]

Guido Calabresi

*Reflections on Medical Experimentation
in Humans**

* * *

... The best way of testing lay reaction to particular experiments—indeed, the best way of broadening the inputs to the committees—lies in ... publication of the cases decided by the committees. Such cases could well be anonymous (at least at first). They could be collected and published in much the same way that decisions of courts are collected. The reports on any case could include, first, a factual part describing, among other things, the experience of the experimenter, the antecedent tests in non-human subjects, the major risks perceived, the scientific gains perceived possible, the availability of subsequent controls to limit the risks, the origin and life expectancy of the subjects, and the nature of the consent and the manner in which it was obtained; and, second, a jurisprudential section containing the decision of the committee (whether favorable or unfavorable), together with the principal arguments made for and against the decision reached.

Such published cases would soon become the subject of intense study both inside and outside the medical profession. Analyses in learned journals by lawyers, doctors, and historians of science would inevitably follow. These would undoubtedly re-argue the more important or path-breaking cases. If law cases are any guide, the analyses would sometimes conclude that the cases were wrongly decided, but frequently that they were rightly decided, and per-

haps more frequently that they were rightly decided but for the wrong reasons. To the extent that Law Reviews consider themselves courts of last appeal beyond the highest courts in the land, so would the learned journals in which this *giurisprudenza* would be dissected. From all this, a sense of what society at large deems proper in medical experiments might well arise. This sense would, in turn, guide the committees and make their decisions more sophisticated. The result would not only be better thought out decisions, but also a more complex system of controls, which, in effect, took into account much broader sources of information as to societal values. In addition, the very existence of open criticism through published cases would reduce the finality of the judgment of any given committee. They might decide one case improperly, but the community would have the feeling that over time its judgments as to the proper balance of present risks against future gains would make itself felt. Moreover, this method of introducing community views would, at least in part, avoid the dangers of governmental rule-making, for at no given time would the community as such seem to be choosing to take an individual life for the general good. (Of course, the presence of published cases—even if anonymous—might make information available that could lead to lawsuits: one advantage of the compensation fund described earlier is that, since compensation would already be given to the injured subject, no lawsuits and hence no attribution of fault would occur.)

Three practical objections can be made to the publication of hospital committee decisions. The first is that such publication would destroy the confidentiality of research and might result in the pirating of good ideas. The second is that hospital committees do not now ask for any very definite indication of the possible scientific benefits perceived in an experiment, but concentrate only on the risks to the subjects and the experience and reputation of the experimenter. As a result, it is argued, publication would be of little use in establishing the balance between risks and benefits that the public at large desires. The third objection is that published hospital committee decisions would not reflect the actual facts before the committee. Committees, to protect themselves, would so emphasize those facts that favored their decision that the results reached would seem to be obvious in every case.

The first objection, if valid, can easily be met by providing for delay in publication until

* 98 *Daedalus* 387, 400-403 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

after the experiment itself is completed and published. Since the aim of publication is not to pass judgment on the particular experiment, but to encourage debate (for the guidance of future committees) on which experiments are desirable and which are not, delay in publication causes no particular problems. The important point is that real cases be examined; whether the examination takes place immediately or two years after an experiment is approved or forbidden matters relatively little.

The second objection is, I believe, misplaced. It may well be that most experiments involve sufficiently small risks so that, given the reputation of the experimenter and the type of consent obtained, no specific indication of benefits foreseen is needed to justify approving the experiment. In every case where this was so, the published opinion of the committee should indicate that. And I would expect that such judgments based on low risk and high reputation would find support among most commentators. If, however, a very high-risk experiment were either approved or turned down without an attempt to learn why the experiment seemed to the investigator to be worth doing, I would expect that there would be substantial criticism. Such criticism might well bring about a change in current practice and enable some experiments that would now be turned down, absent consideration of the possible benefits of the experiment, to take place. Conversely, other experiments that involved substantial risks might not be deemed worthwhile given their small possible benefits. Either response to societal desires made known through publication and criticism would be more desirable than blind approval or rejection of a dangerous experiment.

The final objection—that written committee decisions would not represent the true facts on which the decisions were based—would seem more damaging if a similar criticism could not be made of many court decisions; yet the usefulness of publishing legal opinions remains enormous. Commentators would soon become as adept at divining the issues involved in a hospital committee decision as are legal commentators at analyzing a judicial opinion. The informed criticism of both negative and positive decisions that would follow would, I venture to predict, lose no more from the fact that the opinions would, to some extent, be artificial and stylized than does the analogous legal criticism lose from the same defect in court opinions. Thus, publication, even if the opinions were to

some extent artificial, would remain a highly significant device for broadening hospital committee deliberations and thereby increasing and diversifying societal control of medical experiments.

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[ii]

Louis L. Jaffe

*Law as a System of Control**

* * *

How should the institutions of the law figure in furthering and protecting the interests implicated in human experimentation? The law as we know it is a system of decisional organs and their formal and informal products: the legislature (statutes), the executive-administrative (regulations and adjudication), and the courts (adjudication). Any of these in varying combinations can make law governing the conduct of the experimenter and the rights of the subject. There is not as yet much law explicitly dealing with human experimentation but the common law (by which we mean the law devised and administered by the courts) has developed and continues to develop doctrines that are applicable. . . .

The advantage of common law judicial control is its flexibility—a characteristic consonant with the presently fluid condition of ethical attitudes toward experimentation. *Ad hoc* judicial decisions, it is true, may mean a stiff judgment for damages against an individual who learns only after the event the precise application of the rules governing his conduct. . . .

* * *

The committee system is today part of a system of self-regulation, but it could and probably should become part of the legal system of control either generally or on a selective basis. This change could come about by statute, by administrative fiat, or by judicial decision. It would be going too far to require that there be a committee procedure in every experiment. Every medical intervention is to some degree experimental, and the physician in his practice is constantly faced with the challenge to use new drugs or new procedures. If he is a specialist, his interest in these will not be limited to their effect

* 98 *Daedalus* 406, 407-408, 412-416 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

in the particular case: He will be looking for guidance in the future. A general statutory requirement requiring institutional committees in any "experiment" would raise monstrous problems of interpretation, would unduly complicate medical practice, and would add unnecessary steps to experiments where the risks to the subject or patient are trivial. But as has been the practice with grants from the NIH, a governmental authority or a foundation might in specified instances require committee procedure for experiments funded by the grant.

Finally, a court exercising its common-law jurisdiction in a suit for damages could condemn experiments of high risk if there had been no committee approval of the protocol. To reach this result, the most likely recourse would be to the concept of negligence, which subjects the injury-producing action of an individual or corporate body to the test of "due care." It is particularly relevant that "due care" is a continually evolving concept. What was "due care" yesterday may not suffice today. In the famous case of the *T. J. Hooper*, 60 F.2d 737 (1932), Judge Learned Hand held that a vessel had violated the standard of due care because it was not equipped with a radio that would have given warning of approaching storms. It was no answer, said the judge, that radios had not been generally adopted. "Courts must in the end say what is required; there are precautions so imperative that even their universal disregard will not excuse their omission." Absorbed into the law in this way the committees and the procedures that they develop become a functioning part of the legal system of control.

* * *

Upon what principles will the experimenter govern his conscience, the committees exercise their sanctioning function, the administrative authorities establish the conditions of experimentation, and finally the courts test the validity of experimental intervention? We need not assume that the principles will be the same at all four levels, though they will rest on a common base. In fashioning the common law, the judges will ordinarily allow a considerable latitude for the exercise of conscience and skill. A committee may demand safeguards that the law does not require. It may, for example, require experiments to be performed by a group or demand that the therapeutic and experimental functions be kept separate and be performed by different

personnel. A court, on the other hand, would probably not impose such conditions even though it believed them to be wise. A committee might veto a project on the ground that it did not hold sufficient promise of fruitful results. It is unlikely that a court would feel qualified to make such a judgment, and, if the experimental subject had been fairly treated, it would not condemn the experiment. Thus, there is a significant area of discretion within which conscience and technical judgment are to be exercised.

Though there is almost no judge-made law dealing specifically with experimentation in the modern sense, it is nevertheless justifiable, indeed necessary, to extrapolate a common law based on the application of relevant legal concepts. There have been few lawsuits directly raising questions of the legality of experimentation and even now, with the vast amount of experimentation, resort to the courts is spasmodic. Thus, we cannot look to the common law judges for detailed prescriptions and proscriptions. Nevertheless, we must posit a common law as the ultimate legal guardian of the interests involved in experimentation. Where there is serious debate concerning the propriety or the necessity of certain procedures, where there is a real conflict of interests, an appeal to putatively relevant concepts of the common law provides authoritative standards for judgment.

* * *

Judges are sensitive to the ethos of the times. Our society places a high premium on scientific experimentation and the pursuit of knowledge. To a greater extent than was formerly true, judges will be conscious of the conflict of interests and will seek to give due weight to each of them in any case involving experimentation carried on pursuant to current standards of propriety. The courts, for example, have been willing to take account of the conditions of modern surgery in permitting a further operation without consent where unexpected and serious pathology turns up in the course of an operation performed under anesthesia. We should proceed on the hypothesis, therefore, that in framing our ethical principles the common law will be hospitable to procedures that recognize the social value of human experimentation without sacrificing the interests of patients and subjects.

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NOTES

NOTE 1.

WALSH McDERMOTT
COMMENT ON "LAW AS A SYSTEM
OF CONTROL"*

* * *

What are the weaknesses of this approach of looking to the common law as our instrument for decision? Or, to put it differently, assuming the common law, fortified through extrapolation, is functioning with full effectiveness, how much of the problem remains unsolved? Several points have already been mentioned: human error or malperformance; no prospective decision in a particular case; and failure to remove the ultimate ethical responsibility from the investigator. As the last-named could not be accomplished by any institution presently conceivable, and as it by no means necessarily represents a desirable goal, its absence here is hardly an institutional failure.

One area in which the common-law approach might have a weakness as our sought-for institution would be that its advocacy of the interests of society in a particular experiment might not be specific, that is, framed in terms of that experiment, but would tend to be quite general.

For example, to what extent could the common law serve as a vigorous advocate of the best interests of society in a situation in which a powerful case for the social interest exists, yet to meet it demands the placing of an individual at an appreciable risk? One might argue that the common-law mechanism would perforce be doing this in every case, and in one sense this would be true. But in the personalized form of a lawsuit, the interest of society in the experiment itself is handled indirectly and might tend to become a side issue. By this I mean that a favorable decision based on "due care" might be very crudely paraphrased, "the physician meant well, he intended no injury, and he took due care to attempt to ensure that no injury occurred." This is clearly not quite the same as saying: "It was clearly in the best interests of society that this particular experiment be done because . . . this individual, through the hand of fate, was one of the few who would serve as a satisfactory subject; he gave his

informed consent; and due care was taken to minimize the possibility of his suffering harm." I suppose that such an all-embracing decision is neither to be expected nor desired, because it would tend to get the judge into technical areas beyond his competence. Yet, its absence does mean that the common-law approach will not meet the whole need.

Another possible weakness is that extreme interpretations of due care itself could lead us into the same built-in contradictions that are present, say, in the Helsinki Declaration. . . . [W]hile the physician is trained to weigh the probabilities of danger from off-setting risks, he is also trained to refuse to place his patient at any known risk *no matter how small the probability of danger* in the absence of a positive reason for doing so. Expressed differently, the fact that the probability of the occurrence of a known danger is extremely low is not in itself an ethical justification for placing the patient at risk. In an adversary proceeding involving the concept of due care, this "any known risk" principle might be invoked to establish a failure of due care.

The extent to which either of these two possible weaknesses will constitute problems cannot really be foreseen, because this approach through the common law has such a considerable degree of flexibility.

* * *

NOTE 2.

ALEXANDER M. BICKEL
COMMENT*

* * *

Because we know a little bit about medical experimentation at this time, I must raise a caution about collecting cases. The common law and other processes of adjudication out of which modes of behavior grow involve the resolution of manifest clashing interests. If we gathered information on how researchers have been behaving, we would be subject to the dangers of drawing from a process of adjudication in which we are self-interested. After all, committees passing on the research proposals are interested in furthering research. Mr. Jaffe says that

* Paul A. Freund, ed.: *Experimentation with Human Subjects*. New York: George Braziller 218, 222-223 (1970). Reprinted by permission of the American Academy of Arts and Sciences.

* *Proceedings of the Daedalus-NIH Conference on the Ethical Aspects of Experimentation on Human Subjects*. Boston: American Academy of Arts and Sciences 22 (1967). Reprinted by permission of the American Academy of Arts and Sciences.

the dynamic in favor of research is terrific. At no point in the process of quasi-adjudication is the interest of the individual, the subject, represented. Consequently, we might be misled and put that other interest aside. If we then attempted to look at the practice and perhaps formalize it, we would have minimized, if not excluded, the interest which we are here to analyze and assert.

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[iii]

James Turner
*The Chemical Feast**

The 1969 Ralph Nader Summer Study of the Food and Drug Administration's food protection activities was based on the conclusions of a preliminary report prepared during the summer and fall of 1968. . . . Based on interviews with present and former agency personnel, the preliminary report highlighted major problem areas in the FDA structure, including the control of cyclamates and other food additives, the failure of decision-makers to use scientific information effectively, and the misuse of food standards. In 1969 sixteen students or recent graduates (some of the 110 students who worked on the Nader Summer Studies that year) were divided into teams of two and assigned to research in depth each of ten identified problem areas, with two groups researching two related areas. . . .

The procedure of the Nader Summer Study Project was unique for a research effort. While the students spent many hours in the traditional library search for academic explanations of the problems they had discovered, the real heart of the project was the interviews with responsible agency officials and the collecting of official documents from them. In their four months of activity the sixteen members of the Nader team conducted over five hundred separate interviews, collected over ten thousand documents, and became regular fixtures in FDA libraries, reading rooms, and offices. Because of their daily presence at the agency, the students had an almost immediate impact upon FDA activities. The agency itself was eager to help. Commissioner Herbert L. Ley, Jr., and C. C. Johnson, his immediate superior in the Department of Health, Education, and Welfare, directed all employees to aid the investigation, and the Commissioner

and his staff made themselves available whenever possible to discuss information as it became available. They were glad to co-operate for their own reasons as well as simply to be helpful. In June, 1968, Theodore Cron, then Assistant FDA Commissioner for Information and Education and key adviser to Commissioner James Goddard, said in an interview that he welcomed the Nader investigation because he felt that several divisions of the agency were functioning badly and either intentionally or out of incompetence were providing the agency leadership with inaccurate or incomplete information. Many officials of the FDA who served under Dr. Ley seemed to share this view. The facts uncovered by the students supported it as well.

For the most part, the students who worked on the FDA investigation, both in 1968 and in 1969, began with faith in the quality of the American food supply but also with some skepticism, inspired primarily by (1) Ralph Nader's revelations in 1967 and 1968 that meat and poultry quality was not as high as had been widely assumed and (2) the realization that the FDA was a regulatory agency and therefore probably afflicted with the same bureaucratic density, inefficiency, and self-justification uncovered in other regulatory agencies brought under close scrutiny. It is fair to say that none of the students expected to find in the FDA the shocking disarray and appalling failure of responsibility that their investigations revealed almost daily. As the number of altered documents, misrepresented facts, and suppressed studies began to mount, the students' initial skepticism changed to a deep doubt about all the agency's activities and finally ended in the conviction that most agency efforts were a failure. The fact that most of the distortion and failure related directly to the safety or quality of food served to heighten their concern.

The first specific study the group completed concerned the Coca-Cola-Dr. Pepper fight to obtain a regulation that allowed the addition of caffeine to cola drinks and the Dr. Pepper drink without announcing the addition on the label. Agency documents showed that the overwhelming sentiment of the FDA officials involved in the decision was to require labeling. The record also showed strong reasons for following such a policy. But the first act of Commissioner James Goddard, taken four days after assuming office, was to sign a regulation that allowed the addition of caffeine without requiring that it be listed on the label. After spending ten days going over all the agency documents concerned with the decision,

* New York: Grossman Publishers 247-254 (1970). Copyright © 1970 by The Center for Study of Responsive Law. Reprinted by permission of Grossman Publishers.

the student investigator involved spent the next days conducting interviews with all the responsible individuals, after which he said, "I will never be able to trust another government official again. Every one of these men lied about their involvement in the decision to one degree or another. If I hadn't had the records, I would have never known there had been any disagreement with the final regulation." The experience of many other students was similar if less dramatic.

Two students discovered that in a January, 1969 memo from Dr. Marvin Legator to Commissioner Ley a recommendation that the marketing of cyclamates be stopped had been deleted from the original memorandum by an intermediary without informing either the sender or the receiver of the memorandum. This discovery was immediately communicated to all parties concerned and was largely responsible for Dr. Ley's acknowledgment on October 18, 1969, that he had a communication problem in his Bureau of Science. Similarly, after Dr. Ley testified to a Congressional committee that his agency had conducted a number of studies, all of which showed that MSG was safe, a student contacted the FDA researchers mentioned and found that two of the four studies cited had not been undertaken and that two others had not been completed. These discoveries were then relayed orally to the individuals responsible. Six weeks later, after no effort had been made by the FDA to correct the erroneous testimony, a report of the incident was prepared for Ralph Nader to send to the Congressional committee involved, calling attention to the errors.

In December, 1968, the preliminary investigators discovered that FDA studies showed that a very high proportion of deformed chicken embryos came from eggs injected with cyclamates and cyclohexylamine, tending to confirm dangers suggested by studies showing genetic deformities in rats injected with cyclamates. For the next nine months scientists both inside and outside the FDA as well as the study team members tried to get the FDA to conduct some kind of official evaluation of these studies. At the end of September, 1969, Paul Friedman, an NBC news reporter from Washington, specifically asked a member of the study team about the state of cyclamate research at FDA and was informed of the chick embryo study along with other studies. He then arranged to interview the FDA personnel responsible for the studies and broadcast the results on the local Washington news and the Huntley-Brinkley network report. The result was nation-

wide concern, which eventually led to the banning of cyclamates.

In various ways the results of the Nader group study were constantly communicated to the responsible officials within HEW. The purpose of the study was and is to contribute the effort of a group of concerned individuals to the solution of a major American problem—how to provide the highest quality, safest food at the most reasonable price to the American people. For this reason the students attempted at every opportunity to point out problems in need of attention and work toward solutions with agency personnel. In the course of this effort they discovered a kind of defeatist attitude which permeates every level of the FDA bureaucracy. There is little belief among the agency personnel that the FDA can really make any difference. Comments of various people associated with the FDA during the past ten years suggest how much frustration and despair grip the agency. . . .

* * *

Once the FDA's regulatory failures are seen as part of a general failure of protection for the public, reform of the FDA becomes only part of a more general problem. The public-interest activities of professionals supported by the activities of large groups of people are examples of actions to be taken as part of an overall campaign designed to make government more responsive to the real needs of the public. Legislative and regulatory actions will have to be undertaken in conjunction with the private activities of concerned citizens. One of the major failures of previous reforms was the belief that passing laws solved problems; this is rarely the case. However, it is often necessary to pass new laws as part of a more general attempt to solve a given problem. The same is true of the reorganization of all regulatory agencies. There will have to be new legislation passed to define more accurately the role to be played by the government in the food regulations area. The FDA will have to be reorganized so that it represents the public interest. The most important lesson learned during the Nader Summer Study of the FDA was the futility of trying to treat the FDA as an isolated organization. . . .

A spirit of concern about the future of America lives among a large segment of American youth. Many are trying in numerous and diverse ways to harness this spirit to the practical tools of change so that life for all Americans can be better. They have great hope, great energy,

and with support from others a good chance of success.

* * *

However, none of it will succeed without the support and participation of the consuming public. Each individual consumer and every organization of consumers must make their dissatisfaction known from the local shop level to the national level of corporate managers and government officials. So little is now known about the particular abuses to which American people are subjected daily that it is often impossible to take corrective action. The Consumer Federation of America is organizing consumer chapters for the express purpose of finding abuses and planning action to correct them. Any group of local citizens, effectively organized, can provide a great deal of defense for themselves against the abuses of corporate insensitivity. Cities across the country are beginning to establish consumer-protection agencies which can be a focal point of effort on behalf of the public. Public action must be the primary part of the campaign to restore concern for the public interest in major American power centers, or the campaign will fail.

NOTE

CHRISTOPHER LYDON
NADER AND F.C.C. MEMBER CRITICIZE
KENNEDY CONSUMER AID PLAN*

Senator Edward M. Kennedy wants Congress to charter a new Public Counsel Corporation to represent the peoples' interest before Federal agencies.

But Ralph Nader, the consumer advocate, and Nicholas Johnson, a Federal communications commissioner, told the Senator today that a new organization might only compound the frustration of consumers.

All three men agreed this morning that the public commissions that were designed to represent the public interest had become some of the biggest obstacles to effective citizen participation in Government.

* * *

The Public Counsel Corporation Senator Kennedy has proposed would have a bipartisan board of 15 men and women, appointed by the

* *The New York Times* 24, col. 1 (July 22, 1970). © 1970 by The New York Times Company. Reprinted by permission.

President and funded by Congress. It would have authority to intervene in specific cases or to propose fundamental reforms.

"Given the corporate domination of our national politics and government," Mr. Johnson commented on the Kennedy bill, "the question is whether any political appointee to an agency funded by the Government can do anything effective on behalf of people who are oppressed and manipulated by the large corporations. I think what you've done here is about as well as Government can do, but I don't know if it's good enough."

Mr. Nader, who has supervised a number of critical studies of the regulatory process and enlisted a corps of young "public interest" lawyers to challenge it, said it was important to get public funding for such efforts but that a new public counsel's office would be at best a beginning.

Mr. Nader said that the Nixon Administration's record in the consumer field was "woefully inadequate" and that it would be important to keep any new Public Counsel Corporation free of the Justice Department, which, he said, has become "anticonsumer" under Attorney General John N. Mitchell.

"The strongest case can be made," Mr. Nader proposed, "for actually requiring that the 300 top lawyers in Washington—already rich beyond the dreams of avarice—spend all their time representing the public interest. This is on the same level as telling people to stop what they are doing and put out fires, or stop what they are doing and fight an epidemic, or stop what they are doing and save the country."

b.

Through Professional Evaluation?

*CIOMS Roundtable Discussion
Comments on Editorial Censorship**

* * *

SIR JOHN ECCLES: In the problem of how you can educate or inform the whole of the medical community and other investigating human beings on these problems of ethics, there is another side to it that occurs to me, illustrated by certain journals now with regard to animal ex-

* V. Fattorusso, ed.: *Biomedical Science and the Dilemma of Human Experimentation*. Paris: Council for International Organizations of Medical Sciences 94-95 (1968). Reprinted by permission.

perimentation. For example, *The Journal of Physiology* has certain strict regulations to the effect that experiments not conforming to certain standards governing the treatment of animals—avoiding unnecessary pain, for example—will not be published. This is true of experimental brain research also. I wonder whether a recommendation should not be made that scientific and medical journals should take action to prevent the publication of experimental investigations on human subjects which transgress the ethical principles that have been developed to safeguard the subject as a person. Such principles could be broadly interpreted, but at least they would alert the whole of the scientific medical community to the reality of the problem.

* * *

PROFESSOR FLORKIN: It means that research workers would not carry out a physiological experiment on animals when they could not publish the results, for the knowledge they gain thereby would be private to them and they want to make it available to the scientific public. In the present state of affairs, it is obviously impossible to find out whether people carry out experiments not conforming to ethical standards, but certainly it would be useful to recommend that research work should not be published when it offends against generally accepted rules. What is proposed is an initial cleaning-up operation.

PROFESSOR HALPERN: Since we are making publication dependent on something that seems to be a rule—the ethical rule—can we, as far as experiments on man are concerned, define such a rule in a way that will enable the editorial board to accept or reject the manuscript? The fact that we have no criteria would place an arbitrary weapon in the hands of the editorial board; would it not say that such and such work is ethically all right, such and such work not? How would you defend yourself if you submit a paper and it is refused? I state this problem, which Sir John Eccles will perhaps be able to elaborate on and give assurances about.

SIR JOHN ECCLES: It is quite clear from the discussion of today that no one can define the situation sharply. We have to go through a process of progressive education and we have to be alerted to the problem. The editorial boards of different journals will handle it in different ways, but this is all right too. Let them handle it. We want to alert them to the problem and gradually, I think, a degree of what might be called moral obloquy may descend upon the people

who are doing unethical experiments. You cannot prevent these experiments being done, but gradually you can develop a conscience in investigators and in editorial boards, and this is at least one way to approach the problem. It is a process of what I should call “moral education.”

* * *

MR. SABA: Since, as Professor Halpern has stressed, no ethical rules have been established, a prohibition of an absolute kind might have the effect of preventing knowledge from being spread. I wonder to what extent we should not differentiate between scientific information, which is an essential means of progress, and a recommendation. We should not recommend that experiments should be carried out in violation of professional ethical standards or what are generally considered as commonly accepted moral standards. But if scientific information has been obtained by an experiment carried out in-advicably, would you prevent it from being disseminated?

* * *

NOTES

NOTE 1.

THE MASSACHUSETTS GENERAL HOSPITAL HUMAN STUDIES—GUIDING PRINCIPLES AND PROCEDURES*

Ordinarily data which have been unethically obtained will not be published. While the specific loss to medicine might be great, it is never as great in any reasonably conceivable circumstances as the moral loss sustained by medicine when unethically obtained data are published. Suppression of unethically obtained data will do much to curb the enthusiasm of the careless or the occasional unscrupulous investigator to carry on unacceptable practices. A parallel case can be seen in the Mapp decision of the United States Supreme Court, where it was recently ruled that evidence unconstitutionally obtained is never admissible in a court, however valuable the data might be in the pursuit of justice.

In the publication of experimental results it must be made unmistakably clear that the proprieties have been observed in the study. One of these proprieties is adequate disguise of the identity of the subject.

* Boston: The Massachusetts General Hospital 10 (2d ed., 1970). Reprinted by permission.

NOTE 2.

BRITISH MEDICAL RESEARCH COUNCIL
MEMORANDUM ON CLINICAL
INVESTIGATION*

* * *

A further matter to which the Council would draw attention is that of propriety in publication. It cannot be assumed that it will be evident to every reader that the investigations being described were unobjectionable. Unless such is made unmistakably clear misconceptions can arise. In this connection a special responsibility devolves upon the editors, and editorial boards, of scientific journals. In the Council's opinion, it is desirable that editors and editorial boards, before accepting any communication, should not only satisfy themselves that the appropriate requirements have been fulfilled, but may properly insist that the reader is left in no doubt that such indeed is the case.

* * *

NOTE 3.

T. F. FOX
THE ETHICS OF CLINICAL TRIALS†

* * *

Speaking for one journal [*The Lancet*], I can say that, though we may not seem to be directly concerned in research, we too have our point of view. We do not want to publish information which, according to professional ethics, has been wrongly obtained; in fact we go so far as to believe that no use should ever be made of such information. To protect ourselves from publishing something we do not want to publish, we feel entitled to ask questions which must sometimes be more than a little irritating. Moreover, in line with the Medical Research Council, we think it advisable that, where criticism may arise, an author should avert it by explaining in his paper that the people on whom he experimented were true volunteers, or that valid consent was given on their behalf; and we reserve the right to refuse a paper unless such assurance is given. Finally, if we publish the paper, and one of our readers regards the assurance as inadequate, we will usually print his protest; for we think it professionally healthy that investigators should have to meet occasionally the public chal-

lenges of those who are troubled by their accounts of what they are doing.

* * *

NOTE 4.

JAY KATZ
HUMAN EXPERIMENTATION*

[I]t would be unfortunate if data "improperly obtained" were not published. Such an editorial policy would maintain the low visibility of "unethical experimentation" and preclude not only review but also careful and constant appraisal of the conflicting values inherent in experimentation. Indeed, to make these problems even more visible and subject to our collective scrutiny, all clinical research papers submitted for publication should include in the section on *methods* a clear statement of how consent was obtained. . . .

C.

Through Governmental Action?

[i]

Statement of Edwin I. Goldenthal—
Acting Deputy Director, Office of New Drugs,
Bureau of Medicine,
Food and Drug Administration†

* * *

The New Drug Application for MER/29 was submitted by the William S. Merrell Company on July 21, 1959. I did not make the initial review of the application but was involved, in a supervisory capacity, with pharmacological application reviews of all New Drug Applications. Based on the pharmacology review of the application, FDA notified the drug's sponsor, in a letter dated September 14, 1959, that the application was incomplete because of a questionable margin of safety. We suggested a one-year oral study in rats and a three-month oral study in dogs, with one dosage level in each of these experiments selected with production of specific evidence of toxicity as a goal. Dr. F. Joseph Murray, Executive Assistant to the Director of Re-

* 275 *New England Journal of Medicine* 790 (1966). Reprinted by permission.

† Materials in this section are reprinted from *Competitive Problems in the Drug Industry—Hearings on the Present Status of Competition in the Pharmaceutical Industry before the Subcommittee on Monopoly of the Senate Select Committee on Small Business*, Part 10, Appendix V, 91st Congress, 1st Session (1969).

* Memorandum MRC 53/649 (October 16, 1953). Reprinted by permission. See p. 847 *supra*.

† 28 *Medico-Legal Journal* 132, 139 (1960). Reprinted by permission.

search of the William S. Merrell Company, by letter of September 24, 1959, to Dr. Jerome Epstein, the medical officer assigned this application, indicated his firm's disagreement with our conclusions. Dr. Murray maintained that the submitted animal data, particularly the results of the monkey study, showed MER/29 to have an "exceptionally good" margin of safety.

On October 6, 1959, Dr. Murray and another Merrell representative, Dr. William King, met with several members of the Division of Pharmacology to discuss the New Drug Application. I was present at that meeting. They advised us that they had some additional animal studies underway; specifically, a six-month dog study and a six-month rat study. They indicated that these tests were not mentioned in the initial NDA submission because no results had been obtained. We recommended that they administer the drug to one group of dogs for a minimum of three months, at the highest dose the dogs could tolerate, in an attempt to produce some evidence of toxicity.

We also recommended that they start an additional two groups of rats at dosage levels higher than those used in previous studies, and that treatment be continued for a period of one year.

In a letter to Dr. Epstein of October 13, 1959, Dr. Murray again asserted that the animal studies had demonstrated safety of MER/29, and stated: "We feel that the significance of the studies carried out in monkeys has been entirely overlooked."

On October 16, 1959, representatives of the William S. Merrell Company met with members of the Administration to discuss further the toxicological studies which we felt were necessary to support the safety of MER/29. They indicated they were planning to initiate a six-month dog study at dosage levels expected to produce toxicity and a rat study of twelve months' duration. In a letter dated November 6, 1959, the Administration acknowledged the firm's correspondence of September 24 and October 13, and said the results of the additional toxicity studies agreed upon would be reviewed when submitted.

On February 12, 1960, the firm submitted additional toxicity data on MER/29 consisting of results of three-month and nine-month studies in rats and a three- to six-month study in dogs. . . . I was concerned about the inherent toxic potential of the drug and the possible long term effects of elevated blood desmosterol. MER/29 was believed to reduce cholesterol levels by block-

ing the metabolic conversion of desmosterol to cholesterol. My recommendation was that the application should not be approved in the absence of satisfactory results from extensive, well-controlled clinical studies in which individuals received the drug for a period of several years. This was based on the high potential toxicity of the drug shown in the animal studies. By letter of February 29, 1960, Dr. Murray referred me to our telephone conversation in which adverse effects of MER/29 on the eyes of rats were discussed. He alleged that "the corneal changes have now been found in the control animals" and stated that the firm's consulting pathologist "feels that the changes are inflammatory," and not caused by the drug.

* * *

On March 31, 1960, FDA received personally from Dr. Murray, a tabulation of liver function tests. The firm continued to emphasize that an earlier toxicity study in monkeys, had likewise shown a total absence of toxicity from MER/29, and that monkeys being primates, were phylogenetically closer to man than either rats or dogs. Thus, he argued, the drug was safe under the conditions of use set forth in the New Drug Application. On April 19, 1960, FDA notified the William S. Merrell Company that the application was made conditionally effective and that the action allowing the application to become effective was based solely on the evidence of the safety of the drug. On May 12, 1960, FDA acknowledged receipt of the final printed labels and labeling and made NDA 12-066 fully effective, subject only to the terms set forth in the FDA letter of April 19, 1960.

My next involvement with this application was on November 7, 1961. I sent a memorandum to Dr. John Nestor, the medical officer then handling the application, in which additional data were reviewed. In light of reports of adverse reactions in humans, particularly the eye changes, the question had been raised as to whether or not the application should be suspended. While I agreed that the application should be suspended, I was not convinced that the new data submitted by the firm would be sufficient to support a revocation of the application. On November 13, 1961, various personnel within the Administration met to evaluate the situation and to decide on a course of action. The decision reached was that the drug should be removed from the market and the application suspended. In the absence of new clinical evidence that the drug was unsafe,

however, this could not be done under the provisions of the Federal Food, Drug, and Cosmetic Act at that time. This question was reviewed with FDA scientists and the conclusion was reached that the available evidence would not support suspension action. On November 27, 1961, a drug warning letter was agreed upon by the William S. Merrell Company and FDA. This letter informed physicians of the incidence of cataracts and the necessity of early detection by slit lamp examination. It also advised that they be on the look out for hair changes, ichthyosis and other skin changes, depression of adrenocortical function, and other side effects associated with MER/29 therapy.

In March 1962, FDA was informed by a former employee of the firm that some parts of the chronic monkey data on MER/29 submitted to the Food and Drug Administration had been falsified. We were advised that one of the drug-treated monkeys had become ill and lost considerable weight during the latter part of the study and that a normal, untreated, healthy animal had been substituted. She stated that the report submitted to the FDA by the William S. Merrell Company, as part of the New Drug Application, had been modified to include data on this untreated monkey instead of the monkey receiving MER/29. There was also some question as to whether or not this sick monkey had been subject to autopsy.

It was decided that members of the Administration should visit the William S. Merrell Company to investigate this alleged falsification. On April 9, 1962, Dr. John Nestor of the Bureau of Medicine, Supervisory Inspector Thomas M. Rice, and I visited the firm's Cincinnati facilities and met with representatives of the firm. During the morning, a discussion was held regarding clinical experience with MER/29, particularly reports of the adverse effects. In the course of our discussion, we asked to see the raw data from the monkey studies. Pertinent laboratory records were made available to us. Our search for specific data was difficult because of the confusing manner in which these records had been kept. Upon reviewing some of their laboratory notebooks and weight charts, however, it became evident that the data were somewhat different from those submitted in the New Drug Application.

Discrepancies such as the following were uncovered: Notebooks and weight charts indicated that a marked loss of weight occurred in one monkey during the last five weeks of the

reported study; the data submitted in the New Drug Application indicated that there was a weight increase of this monkey during that period. We could not find the record of autopsy for another monkey in this study. According to the NDA, a third monkey had received MER/29 for 16 months, whereas the firm's notebook and charts indicated that this monkey had received MER/29 for only 8 months. The laboratory records on three of the monkeys showed three different dates for the autopsy of these animals. Moreover, the autopsy dates given in the New Drug Application did not correspond to those found on the charts and notebooks. Delving further into the records, I discovered reports on another monkey which had been treated with MER/29, apparently as part of a second toxicity study in this species. Only one monkey study had been mentioned in the New Drug Application. The officials of the firm responsible for these studies were asked if they could explain the discrepancies. They had no immediate explanation.

Before leaving the firm that day, we were asked if we were satisfied with the results of our visit. We replied that while we had received the utmost cooperation, we had discovered some discrepancies in the monkey studies which had not been explained to our satisfaction. The senior officials of the firm indicated that they would discuss our findings with their personnel in an attempt to clarify the matter. We indicated that we would return on the following day.

On the morning of April 10, 1962, we again visited the firm. A conference was held with company representatives. An official told us that, although they had worked late into the evening, they were still unable to find any explanation for the discrepancies which we had noticed on the previous day. We met further with the officials of the firm who were directly involved with these studies and they, too, indicated they had been unable to explain the discrepancies.

On April 11, 1962, a memorandum summarizing our findings was sent to our Division of Regulatory Management. I indicated that we had found certain discrepancies between the chronic monkey studies submitted in Merrell's New Drug Application and those found in their laboratory records. We felt that these discrepancies did not represent an oversight on the part of the William S. Merrell Company, but constituted evidence of the submission of fraudulent and misleading data to the FDA. I indicated that the net effect of these misleading data was to make the drug appear less toxic to monkeys than was actually the

case. These data were of particular significance at the time of our consideration of the NDA, when representatives of the William S. Merrell Company had vigorously maintained that evidence of safety obtained in these monkey studies outweighed any questionable findings in lower species, i.e., rats and dogs. It was apparent that the discrepancies uncovered in our visit supported the allegation by the former Merrell employee that fraudulent monkey data had been submitted to the Food and Drug Administration.

On the basis of these findings, I recommended that the NDA be suspended. Moreover, I felt that sufficient evidence had been obtained to support prosecution of the William S. Merrell Company and the individuals involved and recommended such action.

On April 12, 1962, representatives of the firm met with FDA and advised us that they were immediately withdrawing MER/29 from the market. They requested that we suspend the New Drug Application. On May 22, 1962, a formal order suspending the New Drug Application for MER/29 was signed by the Commissioner of Food and Drugs.

Subsequently, as our investigation continued, we found that two of the reports of rat toxicity studies submitted in the New Drug Application contained falsified data. Regarding a six-week, two-dosage level study, the William S. Merrell Company reported in the NDA that four of the eight females at the high dosage (75 mg/kg) had died during the course of the experiment. Examination of Merrell's notebooks revealed that no females at that dosage level were alive at the end of six weeks. Seven of the female rats had died, and the eighth had been sacrificed. The firm's failure to report truthfully the results of this experiment resulted in further complications. Final organ weights and hematological values were reported in the NDA for these animals at the six-week period. In checking the firm's laboratory records, no organ weights or hematological values were found for these animals. This is not surprising since the animals did not survive for these determinations. The values which were reported were identical to those reported for rats in another study on MER/29—at a different dosage level and for a different duration.

In a second rat study, according to the New Drug Application, 20 rats per dosage group received MER/29 for three months. The NDA states that "In the rats receiving 40/mg/kg/day of MER/29, 8 out of 20 had grossly visible

opacity of the cornea. [T]here was also an associated conjunctivitis." The firm held that this was not a drug-induced phenomenon since it was also observed in control rats. When we checked their laboratory records, however, we found that actually 60 rats per dosage level had been administered MER/29. At the time of our review of the New Drug Application, we had no knowledge of these further studies.

These additional data, which were withheld by the William S. Merrell Company, established conclusively that MER/29 was capable of inducing cataract formation. After the three-month sacrifice, there were approximately 40 rats per dosage level still receiving MER/29. On March 28, 1960, approximately four months after the start of the experiment, and *before the New Drug Application was approved*, the eyes of the remaining rats were examined. The firm's notebooks state that the eyes of many of the rats receiving MER/29 "did not react to light or motion, therefore giving the appearance of being blind." At the highest dose level, 25 out of the 36 rats showed this blinding effect. Only 1 of the 38 control rats showed this effect. None of these data were submitted for inclusion in the New Drug Application. This omission is extremely serious since knowledge that MER/29 was causing cataracts in rats certainly would have caused the FDA to delay, and probably to withhold, permission to market the drug. As it developed, cataracts were one of the most disturbing features of toxicity which occurred in patients after the drug was released.

As early as November 1960, the William S. Merrell Company had been notified by another pharmaceutical firm, Merck, Sharp and Dohme, that MER/29 had shown extremely serious adverse effects in their experiments with rats and dogs; the drug had produced cataracts and other eye changes. Moreover, Merrell representatives had actually visited Merck, Sharp and Dohme during January 1961, to examine the affected animals. No mention of these findings to the Food and Drug Administration was made by the William S. Merrell Company until January 2, 1962, when FDA and the William S. Merrell Company had received reports that this drug caused cataracts in human beings.

* * *

In this statement I have described my part in the MER/29 investigation and outlined the major aspects of those investigations insofar as my involvement was concerned. I feel that it can

be concluded, from the evidence available, that the William S. Merrell Company withheld some important information and misrepresented other important information with the result that an unsafe drug was allowed to go on the market.

* * *

NOTES

NOTE 1.

E. F. VAN MAANEN
THE WILLIAM S. MERRELL CO.
INTER-DEPARTMENT MEMO—MAY 5, 1959

* * *

I would like to request the respective Department Heads to go over their sections in the MER/29 brochure and to weed out extraneous material, such as windy descriptions of methods and results which were negative and are not contributing anything to clinical investigators. At the same time, add new material, particularly those experiments which indicate the safety of the compound as well as its mechanism of action.

In the toxicity section, I would like to request Dr. King to delete all material on the funny lymphocytes. I wonder also whether the reticulocyte change in the rat experiment needs the emphasis it has. Naturally, we should include our new chronic toxicity studies in monkeys.

* * *

NOTE 2.

THE WILLIAM S. MERRELL CO.
CAMPAIGN STRATEGY—JANUARY 9—
FEBRUARY 17, 1961

* * *

Objective: To persuade "wait and see" G.P.'s and internists to prescribe MER/29 now for at least three patients.

Materials: MER/29 patient trial kit (10 per man); new case history brochure (150 per man); supplementary materials: *Archives of Internal Medicine* journal (Ruskin paper); direct mail and journal ad tear sheets.

It is no longer possible for you to "wait out" undecided doctors. The time for very definite forceful action is now. Such action is far and away your major responsibility this campaign.

By now you can identify the doctors not using MER/29. Yet, you know they should be. Very often, you know most of their reasons for not using it—cholesterol may not be atherogenic; desmosterol is a question mark; possible liver

toxicity; doesn't work; doesn't do anything fast enough; costs too much. Doctor "X" hasn't started using it yet. Are any of these legitimate? No! From our viewpoint: we know they aren't true, we know what MER/29 can do for a person who needs it, and we know they have not stopped top MER/29 salesmen. There is no point in trying to overcome each of these objections. That's the long way around.

The quick way to get the non-prescriber using MER/29 is to use every resource you have at your command to show him that he will be benefiting himself and his sick patients in a giant way just as soon as he uses MER/29. That's any doctor's hot button . . . and you must come down on it harder than ever before.

Yes, MER/29 works by lowering cholesterol—doctors know this. Now, show them what they don't understand well enough yet—just how much MER/29 can benefit their patients!

And, you can show any given doctor five benefits of MER/29 therapy in 5 minutes.

Here are two powerful tools placed at your disposal for this important job:

1. A field-tested structured presentation (with new selling aid).
2. The MER/29 patient trial program.

MER/29 Structured Detail

Doctor, when you are considering a course of therapy for a patient you must have good reasons for your selection. This is true in the case of MER/29. Knowing this and guessing that you have yet to decide in favor of MER/29, I would like to summarize today the important reasons why MER/29 should be a routine part of your treatment for patients with any manifestation of hypercholesterolemia.

First, MER/29 is a proven drug. It has been administered under controlled conditions to more than 2000 patients for periods up to three years. There is no longer any valid question as to its safety or lack of significant side effects. There is no longer any doubt about its ability to lower significantly the total sterol content of the human body.

But, here is what is most important. Here is the fact that recommends MER/29 for your routine use. You want to help sick people feel better while they are getting better—that is what is important to you. Mounting evidence makes it increasingly clear that MER/29, in some but certainly not all cases, affects for the better such manifestations of hypercholesterolemia as inter-

mittent claudication, angina pectoris, myocardial infarction or ischemic ECG patterns.

As evidence of concurrent benefits obtained by lowering cholesterol in some patients, let me illustrate what I mean with some case histories which might parallel cases you see in your practice. . . .

(Insert at least two case histories—local if you can and as many as you can—until he gets restless in his chair!!!)

These results are occurring not because of some temporary change, but, as the Wilkins' group at Massachusetts Memorial Hospitals and others have pointed out, because MER/29 by lowering cholesterol may actually improve the adequacy of circulation.

* * *

Here's one that seems like a red hot idea for MER/29—if it's your style. It's from Tim Bowen, Charlotte, N.C. Aimed particularly at the "wait and see" physician, Tim's close goes something like this (we got it third hand):

Doctor, I can appreciate and admire your caution about any new drug, but MER/29 has been on the market almost a year now and was studied in thousands of patients for years before that. Its rate of use indicates that acceptance is broadening rapidly. Perhaps these words of Alexander Pope have some bearing to your consideration of MER/29: "Be not the first by whom the new are tried, nor yet the last to lay the old aside."

Lots of power there—can your style be bent just a bit to fit?

* * *

NOTE 3.

R. H. McMASTER

THE WILLIAM S. MERRELL CO.

INTER-DEPARTMENT MEMO—APRIL 19, 1960

Dr. Engelberg has made a verbal request for \$500.00 to support his continued study of the effects of MER/29 on the lipoprotein fractions as assayed by the Codman technique using the ultracentrifuge. The results with the first two or three patients in whom this technique has been tried have been rather equivocal if not completely negative. Dr. Engelberg, however, is of the opinion that before any conclusions can be drawn, the experiment should be extended to include a larger group. He does not wish to subject these private patients to the expense of having these rather elaborate laboratory studies done and feels that The Wm. S. Merrell Company

should foot at least a part of the bill. He believes that \$500.00 will cover the costs for cholesterol determinations and the separation of the high and low density lipoprotein fractions by ultracentrifuge in another ten to twelve patients.

Although it begins to appear that any report from this study may be a negative one, we may find that we are money ahead to keep Dr. Engelberg busy at it for a while longer rather than to take a chance on his reporting negatively on so few patients. As you are aware, the Codman technique is in some disfavor and certainly has never been generally accepted as providing for a true "atherogenic index" as claimed.

My personal recommendation is that the grant-in-aid be approved only to keep Dr. Engelberg occupied for a while longer.

NOTE 4.

FRANK N. GETMAN

THE WILLIAM S. MERRELL CO.

INTER-DEPARTMENT MEMO—

OCTOBER 24, 1961

* * *

Sherry Silliman and Fred Lamb have both advised me that a New Drug Application may not be suspended or revoked without a hearing—such hearings are not public. Apparently, however, the fact that a hearing is being called does become publicized.

. . . Silliman, of Norwich, said that the notice of hearing came after failure to reach agreement following a number of discussions with the FDA. According to him, news of the hearing was first published in Werble's "Pink Sheet," and he says Werble appears to have a good "pipeline" into the FDA. He added that the FDA does publish notices of hearings to be held. . . .

Going on with the Norwich case, the hearing technically is still in progress. All testimony on both sides was completed before the Examiner months ago. Briefs were filed in April, with no decision yet. Anticipating an adverse decision, Norwich plans an appeal to the courts. The product is still on the market and available to the physician. It has not been promoted in any way since the notice of hearing, and this was an agreement which Norwich made with the FDA. Naturally, sales have dropped drastically, but the product is still being prescribed by those physicians who have found it a very valuable drug. Norwich made its own publicity release to the public and to the stockholders after the notice of hearing had been received.

In the McNeil case, I know nothing more than what I have read in the "Pink Sheet," which stated McNeil sent out letters to MD's and drug wholesalers, setting in motion a "voluntary" recall program because of jaundice, hepatitis, and liver damage reports. As far as we can tell, McNeil, after conferences with Food and Drug in which a hearing was probably threatened, took this action rather than go through a hearing.

In the White Laboratories' Entecqual case, the Government seized the drug on the basis that representations in promotional material for MD's differed materially from the labeling claims permitted by the effective New Drug Application—in other words, false and misleading labeling. Apparently this followed a failure to agree with the FDA on appropriate disclosure of side effects and also an appropriate dosage exclusion limitation for children—these negotiations going on while the NDA was in effect. Other actions such as multiple seizures or a suspension of the NDA were being considered by the FDA before White withdrew the drug from the market.

This background is furnished in view of the request that I provide, in advance, a company statement in the event of government action. I told Art Boschen this morning that in view of our lawyers' advice on advance release it didn't seem necessary, but after tying the above factors together I am making the following suggestions:

In the event of rumor that the FDA is about to suspend the NDA:

"We have not received notice of any such hearing, as provided in the law. We are not in a position to comment until we do—if we do."

In the event of receipt of notice of hearing:

"The Wm. S. Merrell Company, Division of Richardson-Merrell Inc., has today received a notice of a hearing from the Federal Food and Drug Administration to determine whether its effective New Drug Application on MER/29 should be suspended. In our opinion such suspension would be unwarranted and unnecessary, and we believe that evidence presented at the hearing will sustain this position," stated H. R. Marschall, president of Richardson-Merrell (or Frank Getman, president of The Wm. S. Merrell Company Division).

Let me know your final preference on who makes the announcement.

Admittedly, the letter announcement is extremely brief, but I am proposing it in this form for two reasons—the first is that the less said, the better, as long as it adequately covers our

position—and secondly, it is hard to give added reasons until we get the notice of hearing, which is similar to a complaint and outlines the reasons why the NDA should be suspended. If it should be a claim we withheld evidence, that would call for one type of statement, whereas if it were based on certain kinds of toxicity, it would call for another.

* * *

NOTE 5.

FOOD AND DRUG ADMINISTRATION SUSPENSION ORDER—MAY 22, 1962

Wm. S. Merrell Company, Cincinnati, Ohio, the applicant for and the holder of effective New Drug Application No. 12-066 applying to MER/29 (triparanol) capsules, having requested the suspension of the effectiveness of said application, on the ground that clinical experience shows the drug is unsafe for use under the conditions of use upon the basis of which the application became effective, and thereby having waived Notice of Hearing as provided by Section 505(e) of the Federal Food, Drug, and Cosmetic Act, prior to such suspension;

The Commissioner of Food and Drugs, by virtue of the authority vested in the Secretary by the provisions of the Federal Food, Drug, and Cosmetic Act [Section 505(e); 52 Stat. 1052; 21 U.S.C. 355(e)] and delegated to the Commissioner by the Secretary (20 FR 1996) finds that clinical experience shows that MER/29 (triparanol) capsules are unsafe for use under the conditions of use upon the basis of which the application became effective;

Wherefore, on the foregoing finding of fact and the request of the applicant, the effectiveness of New Drug Application No. 12-066 applying to MER/29 (triparanol) capsules is suspended, effective May 22nd, 1962.

[ii]

Morton Mintz
*The Therapeutic Nightmare**

* * *

In March 1964, no-contest pleas were entered by the William S. Merrell firm to six of the nine counts in which it was named. Richardson-Merrell, named in the three remaining counts of the twelve-count indictment, pleaded nolo con-

* Boston: Houghton Mifflin Company 243-247 (1965). Copyright © 1965 by Morton Mintz. Reprinted by permission.

tendere to two. The same plea was entered by each of the scientists. Van Maanen had been named in nine counts, King in seven, and Werner in five. The pleas were consented to by the Department of Justice.

The count that Werner and Van Maanen did not contest, the fourth, was also one of the six to which the William Merrell firm pleaded no contest. . . .

Count two in the indictment was not contested by the third scientist, King, nor, again, by the William S. Merrell Company. The charges here were that the defendants "knowingly and willfully concealed and covered up, and caused to be concealed and covered up, by trick and scheme, material facts" in what purported to be "full reports of all investigations which were made by The William S. Merrell Company to show whether" MER/29 was safe. The true bill went on to specify that between mid-February and the end of March 1960 Werner and the Merrell firm withheld from FDA reports that certain investigations had been made, reports of results in some cases, and reports of adverse effects. Six investigations were described. In the first, all three of the female monkeys receiving daily 10 milligrams per kilogram of body weight (10 mg/kg) developed blood disorders, and one experienced ovarian changes. In the second, no evidence of recent ovulation was found in four female monkeys on 5 mg/kg per day. In the third, eight out of ten rats were dead seventeen days after being put on a dosage of 50 mg/kg per day, and the remaining two, whose dosage was cut in half, were dead a week later. In the fourth, female rats developed blood disorders. In the fifth, male and female rats that received 15 mg/kg of triparanol before and during cohabitation over a four-month period produced fewer offspring. In the sixth, pregnant rats dosed with 25 mg/kg per day had smaller litters; and among the newborn there was an increase in the death rate in the first twenty-four hours after birth.

Three months later, on June 4, the defendants appeared in United States District Court in Washington for sentencing. In behalf of Richardson-Merrell, Lawrence E. Walsh told the court:

All I can say is there certainly was no intention by this company or any of its employees to put on the market a dangerous drug. Whatever errors of judgment there were, this was not the intent.

I would say one further thing: That whatever these individuals did, they did what they thought they were doing on behalf of the company and, if there

must be punishment, we ask that it fall on the company and not on them.

Chief Judge Matthew F. McGuire agreed with Walsh, who is, incidentally, himself a former federal judge and deputy attorney general from 1957 to 1960. "That is the view I have taken," McGuire said. Speaking only of failure to comply with the law's requirements for full reporting on drug testing, he imposed the maximum fines allowed on the corporate defendants—\$60,000 on William Merrell, and \$20,000 on Richardson-Merrell, which in the fiscal year that ended a few weeks later had a consolidated net income of \$17,790,000 on sales of \$180 million, compared to \$17,514,000 on sales of \$170 million in the year ended June 30, 1963.

"I have taken the view," Judge McGuire said from the bench, "that responsibility in the background of this case is a failure, for want of a better term, of proper executive, managerial and supervisory control and that the responsibility of what happened falls on the company and its executive management. . . ." As vice president for research, Werner was presumably part of management. The Judge said, however, "I do not think, in this particular defendant's case, there was any willful violation of the statute." He placed Werner and his colleagues King and Van Maanen on probation for six months. Each had faced a maximum sentence of \$10,000 and five years in prison.

Judge McGuire did not characterize the acts of withholding and falsifying data about a drug that was prescribed for hundreds of thousands of persons. Those who had expected him to express a sense of shock were disappointed. The sentences imposed on the scientists were unquestionably compassionate. What deterrent and educational impact they may have on others remains to be seen.

The pleas of *nolo contendere*, which the judge said were "tantamount to a plea of guilty," not only averted the publicity that would have accompanied a trial, but also precluded use of a trial record to civil litigants, who generally could not use the indictment or the pleas as evidence.

MER/29 was prescribed to an estimated 418,000 persons. According to Richardson-Merrell, "substantially less than 1 percent"—fewer than 4180, that is—were injured. The "classical triad" of injuries was usually operable cataracts in both eyes, loss or thinning of hair, and severe skin reactions. Among those who have claimed these and other injuries were between 400 and 500 persons whose approximately 175 lawyers

pooled their resources, in a "MER/29 Group," to an extent believed without precedent in a product-liability case. The "Group," whose trustee is Paul D. Rheingold of New York, one of the lawyers who took Mrs. Jordan's deposition, has filed damage suits in 36 states and the District of Columbia.⁶

In the address made by Dr. Walter Modell in 1962 at the convention of the American Association for the Advancement of Science, he described "the pattern for disaster with new drugs: a short-sighted view of all effects; faulty experiments; premature publication; too-vigorous promotion; exaggerated claims; and careless use—in brief, a break in the scientific approach somewhere along the line." Perhaps this pattern was not cut to fit the MER/29 case precisely, but it comes close enough for a drug that physicians, in polls reported by the *Medical Research Digest*, had rated the most significant medical advance in medical therapy of 1960 and 1961.

d.

By Action of Subject?

[7]

Roginsky v. Richardson-Merrell, Inc.
378 F.2d 832 (2d Cir. 1967)

FRIENDLY, CIRCUIT JUDGE:

In this diversity action Sidney Roginsky sought to recover compensatory and punitive damages for personal injuries, primarily cataracts, from taking at his home in Pennsylvania a drug,

⁶In a letter to Senator Humphrey, Rheingold said that in addition to the "classical triad" of injuries there has been "a large number" of other reactions attributed to MER/29, even if less often involved. "These include," he wrote, "liver damage, spleen damage, personality change, diminished libido, impotence, damage to fingernails, sweat glands affected, vomiting and nausea, kidney damage, headaches, loss of normal circulation, pains in various parts of the body, anemia, gastrointestinal upset, ulcerative colitis, diminished adrenocortical function, and fatigue. Some of these, of course, may have only coincidentally occurred with the true reactions to MER/29."

Through April 1965 the outcome of civil damage suits brought by persons claiming to have been injured by MER/29 has been varied. Some have been won, some lost, and some settled. On April 27 in San Francisco, a man who had suffered cataracts was awarded, after a seven-week jury trial, \$175,000 in actual and \$500,000 in punitive damages. The judgment, which was expected to be appealed, was reportedly the largest in a product-liability case in California history.

MER/29, developed by Richardson-Merrell Company for lowering blood cholesterol levels. Roginsky's was the first to be tried of some 75 similar cases now pending in the District Court for the Southern District of New York. Several hundred actions have been filed elsewhere, see Rheingold, "Products Liability—The Ethical Drug Manufacturer's Liability," 18 *Rutgers L. Rev.* 947—48 n. 4 (1964), in at least three of which trial courts have rendered large judgments for the plaintiffs.³

Although other theories of liability for compensatory damages had been advanced in the complaint, plaintiff withdrew all except negligence and fraud upon the Food and Drug Administration (FDA). Defendant moved for a directed verdict on all claims for injury by cataract as unsupported by sufficient proof of causation and on the fraud and punitive damage claims as unsupported by the evidence; the motions were denied. The judge instructed the jury it must first determine the issue of causation; if it found for the plaintiff on that, it should then pass upon the other issues, which he explained in a charge to which defendant took no exception. He helpfully submitted six separate questions: (1) causation, (2) negligence, (3) fraud upon the FDA, (4) amount of compensatory damages, (5) liability for exemplary damages, and (6) the amount thereof. The jury gave

³In *Toole v. Richardson-Merrell, Inc.*, No. 524722, Superior Court, San Francisco County, Calif., the jury awarded \$175,000 in compensatory and \$500,000 in punitive damages, the latter of which the trial court reduced to \$250,000 in the light of the other pending cases and the California rule requiring a reasonable relationship between compensatory and punitive damages. In *Ostopowitz v. Wm. S. Merrell Co.*, Supreme Court, Westchester County, N.Y., Jan. 4, 1967, the jury awarded \$350,000 in compensatory and \$850,000 in punitive damages to the injured party, and \$5,000 to her husband for loss of services. The trial judge sustained the award of compensatory damages although plaintiff's cataracts had been successfully removed, but ordered a new trial unless she consented to a reduction of punitive damages to \$100,000, the figure previously awarded in this case. See N.Y.L.J., Jan. 11, 1967, p. 21. In *Golden v. Richardson-Merrell, Inc.*, Civ. No. 5992, W.D.Wash., Apr. 7, 1966, appeal dismissed on stipulation of counsel, judgment on a verdict of \$150,000 was rendered for a plaintiff who claimed the same injuries from taking MER/29 as does Roginsky. In two cases juries have returned verdicts for the defendant. See *Cudmore v. Richardson-Merrell, Inc.*, 398 S.W.2d 640 (Tex. Civ. App. 1965); *Lewis v. Baker*, 413 P.2d 400 (Or. 1966).

affirmative answers to all the questions relating to liability and fixed compensatory damages at \$17,500 and punitive damages at \$100,000, which the judge later declined to eliminate or reduce, 254 F.Supp. 430 (1966). . . . We affirm the award of compensatory damages but find that the evidence was not sufficient to warrant submission of the punitive damage issue to the jury.

* * *

We thus come to the issue of punitive damages, an issue of extreme significance not only in monetary terms to this defendant in view of the hundreds of pending MER/29 actions and to the plaintiff as well, but, from a longer range, to the entire pharmaceutical industry and to all present and potential users of drugs. Plaintiff, of course, does not claim that defendant intended to harm him; his contention is that defendant's negligence rose to such a level of irresponsibility or worse as to invite this extraordinary sanction.

* * *

The legal difficulties engendered by claims for punitive damages on the part of hundreds of plaintiffs are staggering. If all recovered punitive damages in the amount here awarded these would run into tens of millions, as contrasted with the maximum criminal penalty of "imprisonment for not more than three years, or a fine of not more than \$10,000, or both such imprisonment and fine", 21 U.S.C. § 333 (b), for each violation of the Food, Drug, and Cosmetic Act with intent to defraud or mislead. We have the gravest difficulty in perceiving how claims for punitive damages in such a multiplicity of actions throughout the nation can be so administered as to avoid overkill. Judge Croake did all that he could here, instructing the jury that it "may consider the potentially wide effect of the actions of the corporation and, on the other hand. . . . the potential number of actions similar to this one to which that wide effect may render the defendant subject." Yet it is hard to see what even the most intelligent jury would do with this, being inherently unable to know what punitive damages, if any, other juries in other states may award other plaintiffs in actions yet untried. We know of no principle whereby the first punitive award exhausts all claims for punitive damages and would thus preclude future judgments: if there is, Toole's judgment in California, which plaintiff's brief tells us came earlier, would bar Roginsky's. Neither does it seem either fair or

practicable to limit punitive recoveries to an indeterminate number of first-comers, leaving it to some unascertained court to cry, "Hold, enough," in the hope that others would follow. While jurists might comprehend why Toole in California should walk off with \$250,000 more than a compensatory recovery and Roginsky in the Southern District of New York and Mrs. Ostopowicz in Westchester County with \$100,000, most laymen and some judges would have some difficulty in understanding why presumably equally worthy plaintiffs in the other 75 cases before Judge Croake or elsewhere in the country should get less or none. And, whatever the right result may be in strict theory, we think it somewhat unrealistic to expect a judge, say in New Mexico, to tell a jury that their fellow townsman should get very little by way of punitive damages because Toole in California and Roginsky and Mrs. Ostopowicz in New York had stripped that cupboard bare, even assuming the defendant would want such a charge, and still more unrealistic to expect that the jury would follow such an instruction or that, if they didn't, the judge would reduce the award below what had become the going rate. There is more to be said for drastic judicial control of the amount of punitive awards so as to keep the prospective total within some manageable bounds. This would require; for example, a reduction of the instant \$100,000 award to something in the \$5000-\$10,000 range, still leaving defendant exposed to several million dollars of exemplary damages. We perceive nothing in the New York decisions that would prevent our reducing a punitive damage award because of the large number of suits arising out of the same conduct by the defendant. But there is equally nothing to indicate that New York would follow such a course, and a state otherwise willing to impose such self-denying limits might be disinclined to do so until assured that others would follow suit.

Although multiple punitive awards running into the hundreds may not add up to a denial of due process, nevertheless if we were sitting as the highest court of New York we would wish to consider very seriously whether awarding punitive damages with respect to the negligent—even highly negligent—manufacture and sale of a drug governed by federal food and drug requirements, especially in the light of the strengthening of these by the 1962 amendments, 76 Stat. 780 (1962), and the present vigorous attitude toward enforcement, would not do more harm than good. A manufacturer distributing a drug to

many thousands of users under government regulation scarcely requires this additional measure for manifesting social disapproval and assuring deterrence. Criminal penalties and heavy compensatory damages, recoverable under some circumstances even without proof of negligence, should sufficiently meet these objectives, see Note, *supra* note 6, 41 N.Y.U.L. Rev. at 1171, and the other factors cited as justifying punitive awards are lacking. Many awards of compensatory damages doubtless contain something of a punitive element, and more would do so if a separate award for exemplary damages were eliminated. Even though products liability insurance blunts the deterrent effect of compensatory awards to a considerable extent, the total coverage under such policies is often limited, had experience is usually reflected in future rates, and insurance affords no protection to the damage to reputation among physicians and pharmacists which an instance like the present must inevitably produce. On the other hand, the apparent impracticability of imposing an effective ceiling on punitive awards in hundreds of suits in different courts may result in an aggregate which, when piled on large compensatory damages, could reach catastrophic amounts. If liability policies can protect against this risk as several courts have held, the cost of providing this probably needless deterrence, not only to the few manufacturers from whom punitive damages for highly negligent conduct are sought but to the thousands from whom it never will be, is passed on to the consuming public; if they cannot, as is held by other courts and recommended by most commentators, a sufficiently egregious error as to one product can end the business life of a concern that has wrought much good in the past and might otherwise have continued to do so in the future, with many innocent stockholders suffering extinction of their investments for a single management sin.

However, the New York cases afford no basis for our predicting that the Court of Appeals would adopt a rule disallowing punitive damages in a case such as this, and the *Erie* doctrine wisely prevents our engaging in such extensive law-making on local tort liability, a subject which the people of New York have entrusted to their legislature and, within appropriate limits, to their own courts, not to us. Our task is the more modest one of assessing the sufficiency of the evidence within the framework of New York decisions on the award of punitive damages for recklessness. As to this, we are con-

vinced that the consequences of imposing punitive damages in a case like the present are so serious that the New York Court of Appeals would subject the proof to particularly careful scrutiny.

* * *

... New York demands, as it might have to before punishing a defendant with fines similar to those imposed on a criminal charge, that the quality of conduct necessary to justify punitive damages must be "clearly established." *Cleghorn v. New York Cent. & H.R.R.R.*, 56 N.Y. 44, 48 (1874). Cf. *Hedrick v. Jebiley*, 198 N.Y.S. 2d 346 (N.Y. City 1960). As the Supreme Court has recently reminded us, the standard of proof "by clear, unequivocal and convincing evidence . . . is no stranger to the civil law." *Woodby v. I.N.S.*, 385 U.S. 276, 285, 87 S.Ct. 483, 17 L.Ed.2d 362 (1966), citing 9 *Wigmore*, Evidence § 2498 (3d ed. 1940). It would be hard to think of a situation more appropriate for invoking that standard than where the manufacturer of a new drug honestly believed to assist in prolonging human life is faced with claims for penalties by hundreds of plaintiffs running into millions of dollars, in addition to many millions more for damages sustained. We have little doubt that in such a case the New York Court of Appeals would require a judge to scrutinize the evidence in far closer detail before submitting punitive damages to a jury than it would on an issue of compensatory damages for negligence or breach of contract. If that prophecy should prove to be wrong, we would then be obliged to decide in future cases whether we nevertheless have power to impose a higher standard of proof for the award of punitive damages in a federal trial, cf. *San Antonio v. Timko*, 368 F.2d 983, 985 & n. 1 (2 Cir. 1966), as we surely would if we do.

The judgment as to compensatory damages is affirmed; the judgment as to punitive damages is reversed. No costs.

NOTES

NOTE 1.

TOOLE V. RICHARDSON-MERRELL, INC.
251 CAL. APP. 2D 689, 702-704,
60 CAL. RPTR. 398, 408-409 (1967)

SALSMAN, ASSOCIATE JUSTICE:

* * *

Section 355(b) of the Federal Food, Drug, and Cosmetic Act requires an applicant to submit "... full reports of investigations which have

been made to show whether or not such drug is safe for use. . . ." As we have related in the statement of facts, reports submitted to the FDA by appellant in support of its application were in some respects false, and in other respects entirely failed to reveal the cataractogenic character of its drug as shown by its effect on rats and dogs. The trial court instructed the jury that if a party to this action violated section 355(b) ". . . a presumption arises that he was negligent," and at the same time called the jury's attention to the fact that the presumption, if found applicable, was not conclusive but could be overcome by a showing that, under all the circumstances, the violation was excusable or justifiable. (See *Alarid v. Vanier*, 50 Cal. 2d 617, 621, 327 P. 2d 897, and cases cited.)

Appellant contends the court's instruction was error in that no private cause of action arises because of a violation of section 355(b). (See *United States v. Gilliland*, 312 U.S. 86, 93, 61 S.Ct. 518, 85 1.Ed 598). In support of this contention appellant cites a 1933 proposal to include in the Federal Food, Drug, and Cosmetic Act a provision for a private right of action for damages for injury or death caused by violation of the act, and notes that this proposal was never adopted by the Congress. Appellant views this as a demonstration of congressional intent that no such private right of action exists. Respondent, however, did not attempt to state a cause of action for damages for breach of the federal statute. He stated a cause of action based upon alleged negligent conduct on the part of appellant which negligent conduct he asserted was the proximate cause of his injuries. In support of this cause of action, as well as others stated, he introduced a great deal of evidence by which he hoped to convince the jury that appellant had falsely stated the results of its tests of MER/29 on rats and dogs and hence had violated section 355(b). This was done, not to support a cause of action based upon the statute, but for the purpose of showing that appellant had violated statutory standards, thus raising a presumption of negligence on its part because of such conduct. This was entirely proper.

* * *

Appellant concedes that violation of the labeling and marketing provisions of the act may be shown to establish negligence, but argues there is a difference between violation of the labelling and marketing provisions and violation of the reporting provisions, because the label-

ing provisions of the statute are designed to protect the public, whereas the reporting provisions are concerned merely with raw data comprehensible only to scientists in the FDA. We find this argument unconvincing. The act is designed to protect the public as a whole and to keep dangerous and deleterious products from reaching the uninformed consumer. We see no logical distinction between the labelling provisions of the act on the one hand and the reporting provisions on the other, with respect to the class of persons to be protected or the harm to be prevented. Permission to market a drug depends in part at least upon an evaluation of test data submitted by an applicant. The submission of false and misleading reports of tests can only subvert the administrative decision, defeat the purposes of the act, and make the legend on the label a useless guide so far as protection of the public is concerned.

* * *

NOTE 2.

GOTTSCHALKER V. CUTLER LABORATORIES
182 CAL. APP. 2D 602, 611-612,
6 CAL. RPT. 320, 326 (1960)

DRAPER, J.:

* * *

Defendant strongly argues that public policy will best be served by denying recovery in warranty for "new" drugs. The argument is that development of medicines will be retarded if manufacturers are held to strict liability for their defects. While this argument might have merit if the warranty involved had to do with the mere failure of a medicine to cure or of a vaccine to prevent, it seems to be of but little weight where, as here, the warranty is limited to an assurance that the product will not actively cause the very disease it was designed to prevent. In any case, defendant's own argument is that the Legislature has indicated a full awareness of the problem by the statute (Health & Saf. Code, § 1623) providing that the distribution of blood and blood plasma is not a sale. If a sound public policy requires extension of this exception to biologics generally, or to polio vaccine specifically, the argument properly is one for the Legislature. For the courts to extend the legislative exemption would, in view of the statutory recognition of the problem, amount to judicial legislation.

* * *

[ii]

Irving Ladimer

Clinical Research Insurance*

* * *

Accepting the concept of participation in obligation in return for benefit deriving from bio-medical research, i.e. social responsibility, argues for accepting a *modus operandi* for removing the adversary attitude and proceeding whenever actual or potential injury develops. The magnitude and importance of the issues gravely affect the public interest. Scientific evaluation requires, at the clinical stage, the deliberate exposure of human beings, selected and available as test subjects. Although it is universally agreed that human volunteers—volunteers who have expressly or by implication consented to take part—may not be used unless every reasonable means has been taken to assure their safety, there is always the possibility of an untoward occurrence.

Assurance techniques for handling injury should be comprehensive, covering all aspects of participation for the patient or subject. They should also relieve the investigator of personal and economic jeopardy. Otherwise, there can be no proper expectation that volunteers or investigators will take part in such projects. This is not a vague threat or theoretical view.

In California, a fully equipped exposure chamber, specialized instrumentation and a team of investigators remained idle for years (1959–61) because the State found no legal basis for indemnifying or insuring the research hazards in a project requiring exposure to known air pollutants, thus placing liability on the investigator, and relegating the volunteers to legal action to recover. There was, moreover, no assurance that the investigator's personal malpractice policy would apply since such research did not clearly come within regular or standard medical practice. Even though the public authorities recognized the necessity for such research, there was no legislation or case law which, with certainty, provided direct protection to the volunteers or, in turn, supported the investigator or the public hospital if they chose to bear that responsibility. Thus, an injured volunteer would have no recourse but to sue for damages. Depending on the relationships, he might proceed against the

investigator and his staff; the hospital, agency or laboratory conducting the studies; the governmental department and perhaps the grantor or sponsor supplying the funds or approving the plan. The suit, following general practice and principle, would be based on demonstration of negligence or some other defect on the part of the investigator or sponsor. If the plaintiff won, payment might be due from any or all of the defendants.

It is submitted that this posture is both insufficient and unsuited to the nature and character of research. Studies on human beings, because they involve some intervention, exposure, manipulation or deprivation, are not intentional assaults and batteries which, in other contexts, properly call for recompense to account for the tort. It is equally inappropriate that a volunteer should have to face this prospect to be "made whole" to the extent that money and perhaps medical care can provide. Public interest programs, whether large or small, and human progress through medical science deserve comparable progressive methods to meet social responsibilities.

It is noteworthy that, within recent years, Federal agencies have, in appropriate cases, included funds as part of the research grant to defray liability costs. These are generally used to pay for liability insurance premiums. The National Institutes of Health has made such allowance. Under the 1957 Price-Anderson amendments to the Atomic Energy Act, the Commission may provide such insurance within its licensed or contract activities to cover catastrophic accidents, but Congress has made no similar provision for other hazardous programs. . . .

. . . The customary approach, however, has been to assume that some liability or malpractice policy is the answer. But, . . . the pay-off generally depends on proof of fault, whereas the likelihood of harm comes not so much from negligence of commission or omission but from the inherent nature of research. Chance factors, unknown elements, unanticipated actions and reactions and idiosyncratic responses are all too familiar gremlins that penetrate the fabric of the most closely knit research designs in clinical research. . . .

* * *

. . . It may be some time before the National Institutes of Health, to which this issue has been informally referred, will develop an answer.

* 16 *Journal of Chronic Diseases* 1229, 1230–1234 (1963). Reprinted by permission of Pergamon Press. Copyright 1963.

When it does, that answer may understandably be limited to the specific type of Federal sponsorship it offers. The problem, however, is not essentially different for the non-Federal institution or research hospital, the foundation, the voluntary health association and, of course, for the private pharmaceutical firms which support much of the drug testing. For them, particularly, in the aftermath of thalidomide and under the Drug Amendments of 1962 which require disclosure and patient consent in investigational drug trials, the necessity of sensible, fair and understandable protection is painfully obvious and menacingly present. The traditional umbrella-type of liability insurance, even if multiplied, does not meet the need.

Social cost. [S]ince the benefits of research redound to society, society should accept the responsibility for assuring that the investigator who proceeds with care and caution should not be inhibited in his research because of any inherent hazard. Likewise, the partner-subject—"clinical material" for the investigator—should not be placed at disadvantage, if injury should result directly from his participation. The cost of protection should therefore be considered a proper charge to the business of doing research, to be assumed by the sponsor, in much the same way as other administrative costs are borne by government or industry in production and service operations.

Entitlement based on relationship. Entitlement to recompense by the injured person should reasonably depend, in view of the current American research system and its implications, on the relationship of the parties and on the relationship or causal connection of the harm or loss to the clinical study. Simply put, an application of the workmen's compensation concept, rather than employer liability or malpractice, would seem feasible. Under this approach, the patient-subject, solely by being a recognized participant, would be eligible. Compensation would accrue upon establishing a cause-effect relationship between the clinical activity and the injury, harm or disability.

It would not be necessary to show fault, negligence or lack of caution, that is, to establish specific culpability. Several casualty insurance companies have recommended that claims for auto accidents, now so frequent and so difficult to attribute to one of the parties, be settled without attempting to judge fault.

Another solution, also avoiding the determination of culpability, is that of limited health

and accident insurance written on each patient-volunteer. The occurrences of an accident or disability would then automatically invoke the stipulated benefits. The workmen's compensation form, however, is to be preferred since a sponsor or "employer" could carry such coverage for the entire research enterprise, effectively insuring all projects and participants with minimum administration.

Risks and contingencies. Assuming the conduct of studies under competent guidance and by qualified staff in approved research units (criteria could be established in cooperation with insurance carriers: this step could lead to an immeasurably useful secondary advantage in raising standards to achieve insurability) the contingencies could arise from (1) inherent risk or hazard of substances or procedures employed; (2) incidental or accidental events associated with, but not directly related to, the studies; and (3) peculiarities of the participants. It is essential, however, to cover all of these types, so as to avoid the need for distinguishing among them to establish maximum good faith and broad responsibility for any proximate occurrence. There is no great likelihood of self-inflicted injury or contributory negligence such as might rule out a plaintiff suing under a liability policy.

Consequences. The related consequences of an untoward event might include all or any of the following:

1. Illness or disability: direct or immediate; chronic; subsequent—physical, mental or social.
2. Death: immediate or subsequent.
3. Income loss: immediate or subsequent or potential.

These contingencies may arise at, during or following a study. Accordingly, the compensation, including medical service in broad aspect and cash payment, may be due at once or later and to the individual or dependent. An appropriate plan would therefore have to recognize that termination of a project or study would not necessarily terminate the need for protection. This consideration argues for use of some insurance system based on payment of premiums rather than on self-insurance, although the latter may well be feasible for a large, permanent research institution.

Service benefit. On the principle that the protection be commensurate with the need and character of such endeavor, appropriate insurance would seem to require *first*, immediate and sustained high quality medical care (physician's

services, medication, hospitalization, after-care, if required, and rehabilitation when suitable) and *second*, cash compensation. Under this philosophy, there can be no "damages" of a windfall or exemplary nature or questionable payments for speculative costs and losses. The program should be such as fairly to encourage patient cooperation and volunteering by healthy subjects, for example, and not serve to demean medical research or to promise exorbitant returns.

In essence, protection as here considered is indeed the protection required—care and costs—not the gamble of win-or-lose all, which rarely gives the victim what he necessarily requires, even if he "wins," and certainly not if he loses.

Experience. There is no known actuarial experience which would indicate the costs of such a program. It can be reasoned, however, that absolutely and proportionately (that is, relative to the total cost of a clinical program) the cost will be small, not great.

First, there are actually very few compensable occurrences within the sphere of responsible research. Second, the sponsor's assumption of medical care to meet primary needs, often at the research premises, will tend to lessen out-of-pocket costs. Researchers will, in practice, want to follow such cases as part of their studies. Third, the adoption of such programs will tend to improve controls and designs. Fourth, and finally, the spirit and philosophy of such protection, which should be fully explained in advance as part of the consensual relationship, should serve to diminish rather than induce any questionable claims.

* * *

[iii]

Guido Calabresi
*Reflections on Medical
Experimentation in Humans**

* * *

The basic [market device to supplement other systems of controlling experimentation] would be a compensation fund for subjects injured in unsuccessful experiments. A separate fund would exist at each medical center where experiments on humans were being undertaken. Moneys for the fund could come from two sources—income from successful results of pre-

vious experiments, such as new marketable drugs, and grants from government or foundations based on the expectation that the researches undertaken would be more than worth the moneys used to compensate those subjects who were injured. The effect of such a fund—apart from compensating the victims, which may be desirable in itself—would be to stimulate greater analysis within each medical center of the possible benefits and risks a given experiment entails.

There are five principal difficulties with using such a fund in helping to control medical experiments. First, any compensation system is bound to be unacceptable if it directly or indirectly suggests that a doctor is at "fault" when a properly structured experiment fails. Second, often experiments may in a sense be successful, and yet the subject will nonetheless die or fail to recover completely. (He may have lived longer or as long as he would have had he been in the control group, and yet it may be difficult to show that his death was not due to the experiment.) Third, it may be hard to distinguish a subject in a medical experiment from the ordinary patient who, presumably, would not be compensated simply because the treatment chosen for him failed. Fourth, the institutions in which medical experiments are undertaken are typically charitable and, hence, not subject to market pressures in the usual sense. Fifth, the system may unduly hamper research in new or small medical centers. All of these difficulties are serious, but none is insurmountable.

The first three are best treated together since they all pertain to the fact-finding and administration needed to award compensation. A judicial system for deciding the issues seems totally inappropriate. It smacks too much of finding mistakes or wrongdoing and, as such, would be unacceptable. Accordingly, the best way of handling the issues would be for medical centers to institute such funds voluntarily and establish administrative boards to resolve questions of fact arising under the fund. It is to be hoped that the boards would be regional (so that no center could chisel on its own unlucky experiments) and staffed primarily by scientists. Since payments would, at least initially, be a matter of practice rather than contract, the findings of such panels would come to be regarded as final. (Ultimately, this practice would be likely to change as subjects came to expect payment, but by then the tradition and function of the panels would have been established and judicial review would

* 98 *Daedalus* 387, 395-398 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

probably not be harmful.) The boards would determine, first, whether the injured party was, in fact, a subject in an experiment or a member of a control group for such an experiment; and, second, whether he had suffered damage as a result of being a subject; and, finally, what the appropriate compensation would be under established schedules of damages.

Determination of whether the injured party was a "subject" could be made on the basis of something like the following criterion: Would the "subject's" own personal physician (responsible only for his patient's welfare and not for the advancement of knowledge) have recommended such a course of treatment—not only at the start, but throughout the course of the "experiment"—if he had available to him the information that the experimenters had (or would have had but for use of a double-blind experimental format)? It may be readily seen that this criterion may provide compensation for members of control groups as well as actual subjects. It also considers that a person may become a "subject"—that is, be treated in a fashion based on society's best interest rather than his own—not just at the beginning of an experiment, but anywhere along its course. For this reason, and to protect the possibility of double-blind experiments, the criterion deems relevant any knowledge that the experimenters would have had, but for the experimental format chosen.

Determination of damages would be difficult for the boards. But the issues are, in fact, no harder than those faced in establishing damages before non-expert groups, as is done throughout accident law. As such, there is no reason to discuss them here.

The problem of avoiding the stigma of fault or wrongdoing also does not come up in the hypothetical system described. I do not suggest that such funds be used in place of other controls over medical experiments on humans, but only as additional controls. It follows that all the experiments I am considering will have successfully gone through whatever procedures are established for examining and approving, in plan and design, any experiment involving human beings. Failure to carry out the experiment in accordance with the approved plan and negligence in carrying out the plan would not be issues to be decided by the panels set up to administer the compensation fund. The first would be subject to whatever sanctions were made part of the pre-experiment approval procedures. The second would remain, as it is now, a part of the law of

malpractice. In neither case would such determinations be needed or even useful in deciding the issue of compensation from the fund.

The fourth difficulty in using a compensation fund as an added control on medical experiments in humans arises because such experiments are usually carried out in charitable institutions. Accordingly, it may be questioned whether financial pressures have the same effect on such institutions as they are said to have in competitive industries. Would the need to pay compensation for experiments that fail cause greater care within each institution in selecting experiments and experimenters, or would it simply put pressure on the institution to try only those experiments that have the greatest potential market payoff, regardless of the scientific importance of the results? There is no doubt that some pressure for marketable results would come from such a system. But the market is not the primary or even the secondary source of funds for such institutions. These sources are the government and charitable contributions, which would continue to give according to their judgment of the reputation of the institution and researcher involved. And reputations are based largely on past successful researches—quite apart from whether the past research got financial recognition in the market or only acclaim in the scientific community. It seems unlikely, therefore, that basic research of real promise would suffer from the existence of a compensation fund.

In fact, if one views research institutions as industries that have two possible markets for their products (one the industrial market, the other the scientific community), both of which reward successes handsomely in straight financial terms, the analogy to normal market control situations becomes quite striking. In each case, the payoff for success is notable, and the point of market control is to bring the real costs involved in trying something new to the attention of those who will decide whether the attempt is worth the risks.

The fifth problem with employing a compensation fund is the danger that research in new or small medical centers will be hampered. There is no doubt that it will. A new or small medical center must find an angel. It must convince someone that what it proposes to try is important enough to justify the potential compensation-liability as well as the cost of doing the experiment itself. But, I would suggest, this is precisely the point of the market control system. Not all medical research that involves risks to humans

can be justified. One way of determining if it is justified is by seeing whether there is enough confidence in the proposed experiment or in the research center where the experiment would be carried out to fund payment not only for the test tubes and animals used, but also for the human beings who may suffer injury in the experiment. If there is not, it is a fair sign that the particular experiment is too risky (in relation to its possible beneficial results) to be tried by the particular research team or center. Professor Everett Mendelsohn of Harvard has suggested on various occasions that most significant pioneering research is, in fact, carried out by a very few people in a very few places. If this is so, requiring research centers to meet the full cost of experiments (including the cost of injuries to subjects) may be one of the least invidious ways of concentrating risky research among those who can do it best.

One may summarize the use of a compensation fund in the following way. Requiring compensation of injured subjects causes the full cost of research in humans to be placed on the research center. Accordingly, approval by the center of a particular experiment will require conscious consideration not only of the possible payoff (either in market or scientific terms), but also of the risks, converted to money, that the project entails. This may not deter many experiments, but it may cause those involved in the most risky or least useful ones to consider carefully whether the experiment is worth it, whether it is best done by those who propose to do it, and whether there is an alternative, and safer, way of obtaining approximately the same results. It may well be that all these considerations are already firmly in the minds of the experimenters. If so, nothing is changed by requiring compensation. But if researchers—like auto makers, coal-mine owners, and the rest of mankind—tend to consider costs and benefits a bit more carefully when money is involved, a useful added control device will have been imposed.

* * *

e.

By Action of Investigator?

The King v. Bourne
[1939] 1 K.B. 687

* * *

MACNAUGHTEN, J., in summing up the case to the jury, said: Members of the jury, now that you have heard all the evidence and the speeches of counsel, it becomes my duty to sum up the

case to you and to give you the necessary directions in law, and then it will be for you to consider the facts in relation to the law as laid down by me, and, after consideration, to deliver your verdict. In a trial by jury it is for the judge to give directions to the jury upon matters of law, and it is for the jury to determine the facts; the jury, and the jury alone, are the judges of the facts in the case.

The charge against Mr. Bourne is made under § 58 of the Offenses Against the Person Act, 1861, that he unlawfully procured the miscarriage of the girl who was the first witness in the case. It is a very grave crime, and judging by the cases that come before the Court it is a crime by no means uncommon. This is the second case at the present session of this Court where a charge has been preferred of an offense against this section, and I only mention the other case to show you how different the case now before you is from the type of case which usually comes before a criminal court. In that other case a woman without any medical skill or medical qualifications did what is alleged against Mr. Bourne here; she unlawfully used an instrument for the purpose of procuring the miscarriage of a pregnant girl; she did it for money; 2£5s. was her fee; a pound was paid on making the appointment, and she came from a distance to a place in London to perform the operation. She used her instrument, and, within an interval of time measured not by minutes but by seconds, the victim of her malpractice was dead on the floor. That is the class of case which usually comes before the Court.

The case here is very different. A man of the highest skill, openly, in one of our great hospitals, performs the operation. Whether it was legal or illegal you will have to determine, but he performs the operation as an act of charity, without fee or reward, and unquestionably believing that he was doing the right thing, and that he ought, in the performance of his duty as a member of a profession devoted to the alleviation of human suffering, to do it. That is the case you have to try today.

It is, I think, a case, of first instance, first impression. The matter has never, so far as I know, arisen before a jury to determine in circumstances such as these, and there was, even amongst learned counsel, some doubt as to the proper direction to the jury in such a case as this.

The defendant is charged with an offense against § 58 of the Offenses Against the Person Act, 1861. That section is a re-enactment of ear-

lier statutes, the first of which was passed at the beginning of the last century in the reign of George III. (43 Geo. 3, c. 58, s. 1.) But long before then, before even Parliament came into existence, the killing of an unborn child was by the common law of England a grave crime: see Bracton, Book III. (*De Corona*), fol. 121. The protection which the common law afforded to human life extended to the unborn child in the womb of its mother. But, as in the case of homicide, so also in the case where an unborn child is killed, there may be justification for the act.

Nine years ago Parliament passed an Act called the Infant Life (Preservation) Act, 1929 (19 and 20 Geo. 5, c. 34). Sect. I, sub-s. I, of that Act provides that "any person who, with intent to destroy the life of a child capable of being born alive, by any wilful act causes a child to die before it has an existence independent of its mother, shall be guilty of felony, to wit, of child destruction, and shall be liable on conviction thereof on indictment to penal servitude for life: Provided that no person shall be found guilty of an offense under this section unless it is proved that the act which caused the death of the child was not done in good faith for the purpose only of preserving the life of the mother." It is true, as Mr. Oliver has said, that this enactment provides for the case where a child is killed by a wilful act at the time when it is being delivered in the ordinary course of nature; but in my view the proviso that it is necessary for the Crown to prove that the act was not done in good faith for the purpose only of preserving the life of the mother is in accordance with what has always been the common law of England with regard to the killing of an unborn child. No such proviso is in fact set out in § 58 of the Offences Against the Person Act, 1861; but the words of that section are that any person who "unlawfully" uses an instrument with intent to procure miscarriage shall be guilty of felony. In my opinion the word "unlawfully" is not, in that section, a meaningless word. I think it imports the meaning expressed by the proviso in § I, sub-s. I, of the Infant Life (Preservation) Act, 1929, and that § 58 of the Offences Against the Person Act, 1861, must be read as if the words making it an offense to use an instrument with intent to procure a miscarriage were qualified by a similar proviso.

In this case, therefore, my direction to you in law is this—that the burden rest on the Crown to satisfy you beyond reasonable doubt that the defendant did not procure the miscarriage of the

girl in good faith for the purpose only of preserving her life. If the Crown fails to satisfy you of that, the defendant is entitled by the law of this land to a verdict of acquittal. If, on the other hand, you are satisfied that what the defendant did was not done by him in good faith for the purpose only of preserving the life of the girl, it is your duty to find him guilty. It is said, and I think said rightly, that this is a case of great importance to the public and, more especially, to the medical profession; but you will observe that it has nothing to do with the ordinary case of procuring abortion to which I have already referred. In those cases the operation is performed by a person of no skill, with no medical qualifications, and there is no pretense that it is done for the preservation of the mother's life. Cases of that sort are in no way affected by the consideration of the question which is put before you today.

* * *

I do not think it is necessary for me to recapitulate the evidence that has been given before you as to the reasons why Mr. Bourne in this case thought it right to perform the operation. You remember his evidence. The learned Attorney-General accepts his evidence as a frank statement of what actually passed through his mind. In view of the age and character of the girl and the fact that she had been raped with great violence, he thought that the operation ought to be performed. As I told you yesterday, and I tell you today, the question that you have got to determine is not are you satisfied that he performed the operation in good faith for the purpose of preserving the life of the girl. The question is, has the Crown proved the negative of that? If the Crown has satisfied you beyond reasonable doubt—if there is a doubt, by our law the accused person is always entitled to be acquitted—if the Crown has satisfied you beyond reasonable doubt that he did not do this act in good faith for the purpose of preserving the life of the girl, then he is guilty of the offence with which he is charged. If the Crown has failed to satisfy you of that, then by the law of England he is entitled to a verdict of acquittal. The case is a grave case, and no doubt raises matters of grave concern both to the medical profession and to the public. As I said at the beginning of my summing-up, it does not touch the case of the professional abortionist. As far as the members of the medical profession themselves are concerned—and they alone could properly perform such an operation—we may hope and expect that none of them

would ever lend themselves to the malpractices of professional abortionists, and in cases of this sort, as Mr. Bourne said, no doctor would venture to operate except after consulting some other member of the profession of high standing.

You will give the matter your careful consideration, and if you come to the conclusion that

the Crown has discharged the burden that rests upon it, your verdict should be guilty. If you are not satisfied of that, then your verdict should be not guilty.

* * *

Verdict Not Guilty.

CHAPTER TWELVE

Experimentation with Uncomprehending Subjects

The incapacity of uncomprehending subjects to participate in research decisions highlights two fundamental questions: When, if ever, should subjects be used for research without their own consent? What persons or institutions should be authorized to formulate, administer, and review rules about the participation of non-consenting subjects?

Investigators have strongly advocated the use of uncomprehending subjects, such as children, for some experiments in order to advance knowledge about the beginnings of life in general or childhood diseases in particular. Yet they have neither sought nor been given sufficient guidance on the permissible limits of such research.

The question of “permissible” experimentation emerges in this context for a number of reasons. First, unlike research with competent subjects in which the decision to conduct experiments has at least until recently rested with the investigator alone, the use of uncomprehending subjects requires the legal permission of the state which has assumed, though often failed to exercise, the role of *parens patriae* for the incompetent in society. However, the circumstances under which the state’s permission must be obtained has never been well defined. This ambiguity has obscured the fact that the decision to experiment with uncomprehending subjects raises questions of public policy as well as scientific merit. Second, the dependent position of uncomprehending subjects has burdened the conscience of many inves-

tigators and led them to question the extent to which they should engage in such research. Since this topic is freighted with great anxiety, it is understandable that the participants have been unwilling or unable to consider carefully who should accept responsibility for the decision to experiment with uncomprehending subjects.

Although the cases presented in this chapter focus on children, the problems raised extend also to adults deemed intellectually or psychologically incapable of making understanding decisions about their own welfare. In studying these materials consider the following questions:

1. What characteristics define the group (or groups) of uncomprehending patient-subjects?
2. Should the use of uncomprehending patient-subjects, if permitted at all, be restricted to research which aims to cure their disease, seeks to aid in diagnosing their condition, or attempts to learn more about the disease from which they are suffering?
3. Must these prospective benefits be intended for the individual subject or can they accrue to the group of which he is a part? If so, how and by whom should the group be defined?
4. Should research be conducted with healthy uncomprehending subjects to supply more information about the "norms" for this group or to provide "controls" for an experiment?
5. Who should be authorized to give permission for research on uncomprehending "volunteers" and patient-subjects? What general principles should guide such delegation of authority?
6. Should "incompetent" patient-subjects who are institutionalized be included in, or be the primary source for, experiments?
 - a. Does consent by relatives, the superintendent of the institution, or court-appointed guardians make a difference?
 - b. Does participation by such subjects depend on whether non-institutionalized patient-subjects are available as an alternative?
7. Under what circumstances should research not be permitted even with the consent of relatives or others acting on behalf of non-consenting patient-subjects?
8. In the case of children, at what age or by what other criteria should they be considered "comprehending" patient-subjects?
9. Should distinctions be made between research with subjects who do not consent and those who cannot consent?

A.

Case Studies of Children as Patient-Subjects

1.

**Arthur J. Moss, Edward R. Duffie, Jr., and
George Emmanouilides
Blood Pressure and Vasomotor
Reflexes in the Newborn Infant***

The present investigation was undertaken to determine the intra-arterial pressure in normal full-term and premature infants during the early days of life. The effects of crying, of exposure to cold, and of postural tilting also were studied in order to appraise vasomotor reactivity.

* * *

Catheterization of the umbilical arteries was attempted in 113 normal newborn infants and was successfully accomplished in 100. In each case the procedure was discussed in detail with one or both parents followed by a written consent. Of the infants studied, 74 were full-term and 26 were prematurely born. The age at the time of study ranged from 1 to 77 hours. . . .

One of the umbilical arteries was isolated and a No. 5F nasogastric feeding tube was inserted and advanced into the aorta. This caused little discomfort and, with few exceptions, the infants appeared to be completely content. . . .

* * *

Cold pressor tests were made in 46 infants (29 full-term and 17 premature). This procedure was conducted as follows: 1 foot was immersed to the ankle in ice water at 4°C to 5°C for a period of 1 minute. The aortic pressure was recorded continuously during the immersion and at 30-second intervals thereafter for 2 to 5 minutes. Since the infant invariably cried when exposed to cold, 1 to 3 pretest immersions at 1-minute intervals were made until all signs of discomfort disappeared. This eliminated the complicating effects of crying and straining. . . .

The effect of posture (70° head-up tilt) on the arterial pressure was studied in 50 infants (27 full-term and 23 premature). The subjects were secured to a circumcision board with the upper extremities restrained in flexion and the lower extremities in extension. The board was

tilted over the edge of the table with the catheter tip at the estimated level of the right atrium. Great care was taken to fix the fulcrum at this level. Tilting was accomplished within a second and usually did not cause any signs of discomfort. When it did, the test was repeated until a satisfactory pressure recording was obtained.

* * *

The results of this study indicate that newborn infants, whether premature or full-term, react to postural tilting in the same manner as do adults. This is submitted as further evidence that the vasomotor regulatory mechanisms are present and functional at birth and are independent of maturity.

* * *

NOTES

NOTE 1.

CLAUDE J. MIGEON, JEAN BERTRAND, AND
PATRICIA E. WALL

PHYSIOLOGICAL DISPOSITION OF
4-C¹⁴-CORTISOL DURING LATE PREGNANCY*

* * *

The present work is an attempt to elucidate further the metabolism of corticosteroids during pregnancy. It was thought that radioactive cortisol might be useful since it would permit a dynamic study without interfering with the endogenous production of steroid.

If, following the injection of radioactive material to a mother, a large part of the dose were to cross the placenta, we had to be assured that the newborn would dispose of the compound as rapidly as do normal adults. Therefore, in a first step of the present study, we measured the urinary excretion of radioactivity during the 48-hour period following the administration of a minimal dose of 4-C¹⁴-cortisol (1.5×10^2 microcurie) to two newborns, 15 and 20 hours of age. Since . . . the 48-hour excretion of radioactivity was within normal limits, it was considered safe to proceed with the injection of mothers shortly before delivery.

The other subjects of the study were nine pregnant females, 20 to 38 years of age. An

* 32 *Pediatrics* 175-178 (1963). Reprinted by permission.

* 36 *Journal of Clinical Investigation* 1350 (1967). Reprinted by permission.

"elective, repeat caesarean section" was performed approximately at term and before onset of labor in all cases. . . .

* * *

NOTE 2.

A. M. RUDOLPH, J. E. DRORBAUGH,
P.A.M. AULD, A. J. RUDOLPH, A. S. NADAS,
C. A. SMITH, AND J. P. HUBBELL
STUDIES ON THE CIRCULATION IN THE
NEONATAL PERIOD—THE CIRCULATION IN THE
RESPIRATORY DISTRESS SYNDROME*

* * *

The purpose of the present study is to further delineate the changes in the circulation of infants with normal cardiovascular and pulmonary function and to determine whether a circulatory disturbance may be responsible for production of the syndrome of respiratory distress in certain newborn infants.

Studies of the circulation were conducted by means of cardiac catheterization in 28 newborn infants. These infants were carefully observed for evidence of respiratory distress, and were separated into three groups on the basis of the severity and duration of respiratory signs. Group I comprised 19 infants either with no signs of respiratory distress or with mild evanescent symptoms. Four of these babies showed unquestionable evidence of mongolism, and one was microcephalic. Eight of the 19 were infants of diabetic mothers. Their ages at the time of cardiac catheterization ranged from 2 to 34 hours. . . .

* * *

Group II consisted of nine infants with mild respiratory distress. All these were infants of diabetic mothers. Four infants were males and five, females. The ages at time of study varied from 2 to 11 hours. . . . Group III included 10 infants with severe respiratory distress. Seven of these infants were males and three, females. Five of this group were infants of diabetic mothers. Their ages at the time of catheterization were 3 to 21 hours. . . .

The decisions to perform studies on the infants were made only after careful clinical observation. Radiologic and electrocardiographic studies were carried out for all the infants with

respiratory symptoms and for the majority of those with no respiratory distress. The procedure was performed after full discussion with and consent of at least one of the parents. . . .

In 15 newborn infants cardiac catheterization was attempted by inserting the catheter into the umbilical vein, with the aim of manipulating it through the ductus venosus into the inferior vena cava and then into the heart. In view of the tendency for the catheter to enter portal veins, with difficulty in maneuvering beyond the ductus venosus, the attempt was abandoned in five instances. In 10 infants, included in this report, the catheter could be manipulated into the heart, but in only 2 of these was it possible to pass the catheter into the pulmonary artery. In the remaining 28 infants, the catheter was inserted through the right saphenous vein in the groin. Under local procaine anesthesia, a small incision was made just below the groin and the saphenous vein was readily isolated. . . .

After the catheter was passed into the right atrium from the inferior vena cava, an immediate attempt was made to enter the superior vena cava. The catheter was then again withdrawn and manipulated into the right ventricle. A very careful continuous monitoring of the electrocardiogram was then conducted with the aid of an oscilloscope, and attempts were made to pass the catheter into the pulmonary artery. The catheter was rapidly withdrawn if ventricular ectopic beats were induced; consequently in only 22 instances was the pulmonary artery catheterized. In the other 16 instances the attempts to enter the pulmonary artery were abandoned in view of the induction of numerous ectopic beats during these manipulations.

* * *

2.

**Horst Bickel, John Gerrard, and
Evelyn M. Hickmans
Influence of Phenylalanine Intake
on Phenylketonuria***

In phenylketonuria phenylalanine accumulates in the blood and cerebrospinal fluid, probably because phenylalanine is not converted to a normal extent into tyrosine. On the assumption that this excessive concentration of phenyla-

* 27 *Pediatrics* 551-552 (1961). Reprinted by permission.

* 2 *The Lancet* 812-813 (1953). Reprinted by permission.

lanine (or perhaps of some breakdown product) is responsible for the mental retardation found in this condition we decided to keep a girl, aged 2 years, with phenylketonuria on a diet low in phenylalanine. She was an idiot and unable to stand, walk, or talk; she showed no interest in her food or surroundings, and spent her time groaning, crying, and banging her head. . . .

* * *

[A] gradual improvement in the child's mental state took place within the next few months: she learnt to crawl, to stand, and to climb on chairs; her eyes became brighter; her hair grew darker; and she no longer banged her head or cried continuously.

* * *

In view of the importance of establishing whether the clinical improvement noted (which depended at first largely on the observation of the mother) was real and due to the diet rather than to natural development, we decided to add L-phenylalanine 5 g. daily to the diet. This was added to the hydrolysate without the mother's knowledge, so that any change should be noted without bias.

A definite deterioration in the child's condition ensued, the mother reporting with distress that her daughter had lost in a few days all the ground gained in the previous ten months; that within six hours of starting the fresh supply of "food" the child had begun to cry and to bang her head as in the past, and within twenty-four hours could no longer stand and could scarcely crawl.

In view of the importance of obtaining adequate proof of the value of the special diet, at present very expensive, the mother agreed to a further similar trial in hospital, which permitted close correlation of clinical and biochemical findings and cinematographic records. After a period of observation on a low-phenylalanine diet, L-phenylalanine 4 g. daily was again added to the diet. Within twenty-four hours the patient became irritable and drowsy, lost interest in her food and surroundings, developed facial eczema, and salivated profusely. She also became ataxic and vomited repeatedly. By the sixth day she could no longer stand or crawl. The additional phenylalanine was then discontinued, and within three weeks she had almost completely recovered.

* * *

3.

Robert M. Zollinger, Jr., Martin C. Lindem, Jr., Robert M. Filler, Joseph M. Corson, and Richard E. Wilson Effect of Thymectomy on Skin-Homograft Survival in Children*

Recent investigations have indicated that the thymus gland has an important role in the initiation of immune potential in animals. Specifically, thymectomy in the neonatal period and thymectomy combined with total-body irradiation in adult animals have permitted prolonged survival of skin homografts. The latter principle has been utilized in an effort to prolong survival of human adult renal autografts. . . . There is no information available regarding neonatal thymectomy in man, but a study of the effect of thymectomy on skin homografts in immunologically competent children appeared practical from the point of view of clinical transplantation.

This is a report of data obtained from children, beyond the neonatal stage, undergoing major corrective heart surgery, in which the thymus is frequently dissected and partially removed for aortic-arch exposure. When desired, a complete thymectomy could be accomplished without increasing the hazards of surgery. Thus, an opportunity for the study of skin-homograft survival in patients having a carefully performed thymectomy was available for the first time.

Eighteen children of both sexes from three and a half months to eighteen years of age were chosen from among those operated upon at the Children's Hospital Medical Center for congenital heart disease. Eleven of these patients were randomly selected to have a total thymectomy whereas the remaining 7 had only a biopsy of the thymus and served as controls. At the conclusion of each heart operation a full-thickness skin homograft, approximately 1 cm. in diameter and obtained from an unrelated adult donor, was sutured in place on the chest wall.

The grafts were biopsied when initial gross evidence of rejection, such as edema, loss of pink color or failure to blanch with pressure, was apparent. When indicated serial biopsies were taken. . . .

. . . The mean rejection time of skin homografts in the totally thymectomized children was

* 270 *New England Journal of Medicine* 707-709 (1964). Reprinted by permission.

nine and four-tenths days, with a range of eight to thirteen days. The mean rejection time in the control group was ten and nine-tenths days, with a similar range. All rejections were fairly prompt, and the microscopical findings confirmed and closely correlated with the clinical observations. . . . No major complications occurred in the recovery periods. There was no gross infection delay in healing or prolongation of hospital stay in these patients.

* * *

In the neonatal animal the thymus has been linked to the production of small lymphocytes and to the development of lymphatic tissue. . . . Metcalf demonstrated a humoral "lymphocytosis stimulating factor" that originates in the thymus but has its effect on the cells in the peripheral lymphatic tissues. . . . Other investigators, however, believe that immunologically competent cells or their progenitors may originate in the thymus and migrate to the peripheral sites.

Thymectomy in laboratory animals, both neonates and adults, has resulted in lymphopenia, with a decreased number of small lymphocytes. In the adult the lymphopenia develops slowly over several months. In this study the total white-cell counts, the differentials and the total lymphocyte counts showed no consistent alteration. The period of elapsed time, however, was only ten to fourteen days.

* * *

Of interest has been the finding of cachexia in small animals thymectomized in the perinatal period. Many young children have undergone this procedure in the past during intrathoracic surgery, and no reports of a similar postoperative syndrome have appeared to date. It is true that some residual thymus has often been left behind, and the exact documentation of the amount of thymus removed is not available. This study was undertaken, therefore, with some historical reassurance as well as the plan to observe closely the growth and development of these children over the years. Since many young patients will continue to have at least partial thymectomy for vascular rings, tracheal compression and open-heart exposure it is doubly important that a known group of completely thymectomized persons be analyzed carefully. It is our specific plan to repeat the elements of this study after an interval of six to twelve months.

. . . No apparent difference in skin-homograft survival was noted between the two groups.

* * *

NOTES

NOTE 1.

BYRON H. WAKSMAN
THYMUS EXPERIMENTATION*

. . . A series of papers over the last two years has shown that the thymus has a key role in the development and maintenance of several types of immune function. . . . The clear-cut possibility that thymectomy, perhaps in combination with irradiation or "immunosuppressive" medication, can be used to prevent the rejection of homografts or the manifestations of diseases having an immunologic basis has created an atmosphere of optimism regarding the treatment of many surgical or medical conditions previously regarded as hopeless.

The proposal to use thymectomy as a therapeutic tool, however, must be tempered by the consideration that suppression of immune mechanisms, sufficient, for example, to prevent homograft rejection, must at the same time remove important defenses against infection. The unhappy consequences of immunologic deficiency have been vividly illustrated by many recent papers. It would hardly be appropriate to produce in the patient a condition analogous to agammaglobulinemia or perhaps to agammaglobulinemia with alymphocytosis to achieve a prophylactic or therapeutic result at any level less than lifesaving. It remains to be demonstrated whether it is possible to achieve a controlled intermediate degree of immunologic deficiency, sufficient to permit homograft survival but insufficient to lead to recurrent infection. Indeed, this question has not yet been satisfactorily answered at the level of experimentation in the laboratory animal.

One may properly question the philosophy underlying the use of agents or techniques that affect immune responses in general to reduce the response to a specific antigen. Recent studies on specific acquired tolerance hold out the hope that it may soon be possible, by suitable treatment of adult subjects, to suppress permanently immunologic reactivity to specific antigens while immunologic responsiveness to unrelated anti-

* 270 *New England Journal of Medicine* 1018-1019 (1964). Reprinted by permission.

gens remains unimpaired. There is also a clear-cut possibility that, by manipulation of the thymus itself, it will be possible to achieve specific tolerance. This approach seems, on many grounds, preferable to what one may designate as the "nonspecific" approach.

With these facts in mind, one may well question the value and propriety of studies like that by Zollinger and his associates . . . in which total thymectomy was carried out as a purely experimental measure in subjects not having a disease to which this procedure is relevant. One may criticize the publication of data obtained at a time (immediately after thymectomy) when no positive finding could be anticipated, as noted in the authors' own discussion. One wonders whether the usual hazards, notably the possible transmission of serum hepatitis from graft donors and the unnecessary immunization against isoantigens, were sufficiently offset by the usefulness of the data obtained to be worth risking in these subjects. One may also ask if the long-term hazards, unknown at present, were duly noted and called to the subjects' attention. It seems pertinent to raise these questions at a time when the literature, especially in the field of transplantation, is being flooded with reports of human experimentation based in many cases on inadequate laboratory data and with insufficient attention to the long-term hazards.

NOTE 2.

R. M. ZOLLINGER, JR., M. C. LINDEM, JR.,
R. M. FILLER, J. M. CORSON, AND R. E. WILSON
ETHICS OF THYMUS EXPERIMENTATION*

The questions raised by Dr. Waksman . . . were considered by us and by our advisers. If one can set aside the scientific or moral rationalizations for performing thymectomies in human beings at the present state of knowledge the fact remains that thymectomies were and are being performed during various thoracic procedures. It was from this group that the patients of the study were chosen. The article unfortunately implied the creation of thymectomized patients whereas the patients were merely chosen from among the many who have total thymectomy as a necessary part of aortic exposure during cardiac surgery.

The skin-homograft donors were chosen carefully, and to date no case of hepatitis has

appeared in similar studies by several local investigators. In addition we believe the homografts introduced few new isoantigens beyond those received in the multiple transfusions required in open-heart surgery. In this setting the added hazards in this investigation were believed to be reasonable—not only because of the application of this study to transplantation but also because of its need in all cardiac and thoracic patients in whom thymectomy has been or may yet be done.

NOTE 3.

MELVIN LEWIS, AUDREY T. MCCOLLUM,
A. HERBERT SCHWARTZ, AND JEROME A. GRUNT
INFORMED CONSENT IN PEDIATRIC RESEARCH*

* * *

Charles, a blind 7-year-old boy, was expected to die within the year from an inoperable brain tumor. Charles' mother gave consent for the boy to be hospitalized and subjected to endocrine studies that could not benefit him in any way. The justification for the studies was the possibility of their leading to earlier identification of brain tumors in other children.

The mother's motives in giving her consent for the studies were complex. She told the staff that she felt Charles' life would have been worthwhile if, through the studies, it led to knowledge that would benefit other children. This statement implied that her consent was partly a way of dealing with Charles' impending death (although Charles would die, the knowledge gained through him would live on) and partly a way of compensating for his loss (Charles would die so that other children might live). However, the statement also implied the existence of unconscious anger toward Charles, since it disregarded the severe stress to which the child would be subjected.

The psychological stress proved to be particularly severe since the medical procedure heightened the fears commonly experienced by a child at Charles' developmental stage—concern about body intactness and manipulation. Frequent venipunctures, necessary for the research, led to acute panic states in the child. Moreover, the usual means of dealing with such stress through play, visual, auditory and tactile experiences, and motor activity were denied to

* 270 *New England Journal of Medicine* 1314 (1964). Reprinted by permission.

* 16 *Children* 143, 147-148 (1969). Reprinted by permission.

Charles by his blindness and the imposed restraint necessary to the procedures.

When Charles was threatened with further restraint because reaching his difficult veins satisfactorily would require cutting through his skin, the investigator terminated the research.

* * *

4.

Howard E. Ticktin and Hyman J. Zimmerman Hepatic Dysfunction and Jaundice in Patients Receiving Triacetyloleandomycin*

Triacetyloleandomycin (TriA), a drug that has been introduced for the treatment of infection caused by staphylococci and other gram-positive organisms, has been widely used, minimal toxicity being reported. Several isolated cases of jaundice in children receiving the drug have been observed. Robinson, however, has recently reported that in 5 of 48 patients who received TriA for fourteen days or longer elevated serum glutamic pyruvic transaminase values developed. These observations seem at variance with the previous reports of lack of side effects in patients receiving the drug for periods of sixty days or more.

The present study was undertaken in the attempt to determine the incidence and type of hepatic dysfunction relatable to the administration of TriA. This study demonstrates impaired hepatic function in over half and jaundice in 4 per cent of a group of patients receiving the drug for two weeks or longer.

The 50 patients studied included mental defectives or juvenile delinquents who had been inmates of Laurel Children's Center for two months or longer. There was no recognizable organic disease other than the mildly to moderately severe acne for which the drug was given. In none were there any systemic evidences of pyoderma. There were 38 males and 12 females, with ages ranging from thirteen to thirty-nine years. . . .

* * *

Eight patients, who had marked hepatic dysfunction, were transferred to the hospital for more intensive study. These included 6 in whom symptoms also developed. Two of the 6 patients

with symptoms (abdominal aching and anorexia) became jaundiced.

Liver biopsy was performed at the height of the dysfunction or jaundice, or both, in these 8 patients by the intercostal route with the use of the Menghini needle. In 4 of these patients it was repeated later.

A "challenge" dose of 1 gm., as four divided doses, was given on one day to 4 of the hospitalized patients, after their liver-function tests had returned to normal limits. . . .

. . . In all but 8 patients the tests of liver function yielded normal results at the beginning of the study. In 6 of these patients slightly abnormal bromsulphalein excretion was observed. . . .

Tests performed two weeks after the beginning of TriA administration revealed that in 54 per cent of the patients abnormal bromsulphalein excretion developed. . . .

In all these patients the abnormality was present, and in most cases greater, on retesting at three or four weeks after the beginning of therapy. Sixty-one per cent had abnormal bromsulphalein excretion. . . .

* * *

In 44 of the 50 patients there were no clinical evidences of reaction to the drug. Symptoms developed in only 6 patients, consisting of anorexia and mild aching in the epigastrium or right upper quadrant. In the 2 patients with overt jaundice dark urine and light stools were noted.

* * *

In the 4 patients in whom liver biopsies were obtained twice, the second specimens showed distinctly less abnormality than the first. In 2 the biopsy appeared almost normal. In the other 2 there was still distinct evidence of hepatocellular abnormality although cholestasis had disappeared.

Four patients were challenged with a 1 gm. dose of the drug after liver function had returned to normal. Within one or two days, hepatic dysfunction again developed in 3 of the 4. . . . Hepatic function returned to normal in all 3 patients within seven days after the challenging dose. . . .

The development of hepatic dysfunction in more than half the patients who received TriA for a period of two or more weeks seems reasonably ascribable to the administration of the drug. The sequence of normal hepatic function before administration of TriA, development of progressively worsening dysfunction as the drug was

* 267 *New England Journal of Medicine* 964-968 (1962). Reprinted by permission.

administered and the return to normal after its withdrawal strongly suggests that its administration was responsible for the development of the hepatic abnormality. This impression seems confirmed by the effect of a "challenge" dose, which, in 3 of 4 patients tested, again led to the development of abnormal hepatic function.

* * *

NOTES

NOTE 1.

MORE HUMAN GUINEA-PIGS*

Triacetyloleandomycin (TriA) is a derivative of the antibiotic oleandomycin and has a similar spectrum of action against staphylococci and other Gram-positive organisms. It has not been marketed in the United Kingdom as yet, but has been widely used in the U.S.A. as an alternative to penicillin or erythromycin. Until recently it was said to have few side-effects.

However, several isolated cases of jaundice have now been reported, and two enterprising physicians (H. E. Ticktin and H. J. Zimmerman) have published a study of 50 patients in whom the effects of this drug on the liver have been intensively examined. The patients concerned included "mental defectives or juvenile delinquents who had been inmates of Laurel Children's Center for two months or longer. . . ."

Ages of the patients ranged from 13 to 39 years and it is not stated to what extent they volunteered for the experiment or, in the case of the mental defectives, understood its purpose. There seems to be one or two lessons to be learnt from this study. The first is that liver toxicity from drugs may be like the iceberg, in which seven-eighths of the danger lies below the surface. The occasional case of jaundice may in fact indicate that large numbers of patients are suffering liver dysfunction which is only demonstrable by laboratory tests. The second is that it seems very questionable what value TriA has which would justify its use in view of this present information and the alternatives available. The third is that juvenile delinquency in the United States obviously carries hazards which many of us had not previously suspected. The pimpled gangster of today may find himself the bilious guinea-pig of tomorrow. It seems a little hard, perhaps, for a boy who has spent his formative years learning how to dodge flick-knives to

fall victim to intercostal perforation by the Menghini needle.

* * *

NOTE 2.

ROSS G. MITCHELL

THE CHILD AND EXPERIMENTAL MEDICINE*

* * *

[Throughout the nineteenth century very] few articles refer to parental permission for . . . studies, and there is seldom any expression of doubt about the morality of the work. Children from orphanages and "foundlings" were commonly used as subjects for these investigations. It is perhaps not surprising that this type of research was accepted unquestioningly, for infant and child mortality was still very high and methods of therapy were often drastic. Moreover, medicine had but recently emerged from an era in which children were little regarded, a world where foundlings were bought and sold and child labor was the rule. It is salutary to recall that a hundred years ago the American Society for Prevention of Cruelty to Animals was empowered by the courts to act in a case of cruelty to a child on the grounds that a child is an animal. A society for the prevention of cruelty to children was not founded until 1875—nearly ten years later. Against such a background, the use of orphans and foundlings for experiments would hardly have seemed to require permission or indeed justification.

With the advance of technology, research methods began to be more sophisticated. Techniques advanced from the mere withdrawal of blood to the injection of substances for experimental purposes. The first documented instance of this is probably the experiment by Oliver, who in 1894 injected crude extract of endocrine glands into his own son. After 1900, studies on the newborn infant began to increase, and these often involved the injection of chemicals such as fluorescein or experimental nutrients such as fat infusions. Fortunately at the same time there appears to have been some quickening of medical conscience, and the references to orphans and foundlings gradually diminished. Despite this, reports seldom referred to the obtaining of permission except curiously enough, from medical staff. Thus there were frequent acknowledgments in the early paediatric journals of the kindness

* 2 *British Medical Journal* 1536-1537 (1962). Reprinted by permission.

* 1 *British Medical Journal* 722, 725-726 (1964). Reprinted by permission.

of obstetric staffs in giving permission for experiments "on their cases"—a possessiveness which still exists to some extent to-day among doctors, as though the undertaking of medical care somehow conferred ownership of the patient on the physician.

* * *

5.

Office of Science and Technology Privacy and Behavioral Research*

Our society places a high value on the rights of the individual, among them the right to privacy. When the techniques and research methods of the behavioral scientist impinge on these rights, they pose a crucial question for the scientist and for society.

* * *

Some examples of research procedures that may harm the participant through a violation of his rights . . . may help to define the area of our concern:

1. In a study designed to discover the causes of personality qualities in children it was necessary to secure measures of the children's personalities. One device that has been widely used is the so-called sociometric measure which assesses certain personality characteristics of a child on the basis of judgments about him by his classmates. A set of statements about the child's behavior was prepared. Examples are: "He usually suggests a good idea for a new game." "He always gets mad when we don't do what he wants." "He can read better than anyone else in the class." The children were instructed to fill in the name of the child best described by each of these statements. By tabulating the answers given by all children in a class, it was possible to find out the peer judgment about various qualities of personality.

The problem of confidentiality did not enter this situation because the results were never seen by the children, their parents, or the teacher. However, the "sociometric method" invades privacy in the sense that it forces children to think about certain qualities of behavior shown by one another and to reach firm conclusions about what is "best" or "worst." The normal processes by which reputation develops were replaced by an artificial intervention:

2. In a series of experiments designed to discover the effects of a student's feelings of success or of failure at a particular task, the experimenter artificially induced feelings of success and failure in different groups of subjects. In the failure experiment, a subject was asked to learn a rather complex motor task and the experimenter expressed surprise at how slowly the subject learned, compared his performance unfavorably with that of other students, and expressed sympathy with him for his clumsiness. The net result was to induce in the subject a feeling of inferiority and of self-derogation. By the end of the experimental session, some subjects were depressed, brooding, and angry, and had lost a measure of self-esteem.

It is routine for an experimenter to explain the state of affairs following such an experiment. The subject can normally recover his usual level of self-esteem, but it is the responsibility of the experimenter to make sure that this recovery occurs. It should be added that the body of research of which this example is a part has led to a substantial modification of educational policy in America. The research showed clearly that the lowering of self-esteem and failure reduce learning ability. Educationally, the principle has been applied to modify teachers' schoolroom behavior in such a way that unsatisfactory performance can be challenged by means that avoid injuring the student's self-esteem.

* * *

6.

Kidney Transplantation in Identical Twins*

a. **Letter to Charles B. Barnes, Jr., President,
Peter Bent Brigham Hospital
from the Hospital's Attorneys**

You have asked us on behalf of the Peter Bent Brigham Hospital [P.B.B.H.] for our opinion as to the civil and criminal liability of the hospital and its trustees, officers and employees upon the following assumed facts.

The parents of fourteen-year-old twins, one of whom has two diseased kidneys, enter into an agreement with a surgeon to perform a kidney transplant operation at the hospital. The operation contemplates the following acts: one surgeon

* Washington, D.C.: U.S. Government Printing Office 10-12 (1967).

* This study combines documents related to two kidney transplants performed in 1957; the names of the patients and their families have been changed.

removes one of the diseased kidneys from the ill twin while another surgeon removes a healthy kidney from the well twin. One of the surgeons then sews the healthy kidney into the ill twin. After a period of time, if all goes well with the ill twin, a second operation is performed to remove the second diseased kidney.

We understand that the twins must be identical and that the operation has, based on experience, a fair chance of preserving the life of the ill twin, whose disease would otherwise be fatal. It is also assumed that there is a danger that either or both of the twins may die on the operating table. The degree of danger can vary substantially. Moreover, removal of a healthy kidney from the well twin materially decreases his capacity to survive physical injury or disease involving the kidneys, since he no longer has a spare kidney upon which to rely if one should become injured or diseased.

We also assume that because of their age the twins do not understand the nature or consequences of the surgical procedure although a normal adult might be expected to do so. Further, we assume that it is difficult to explain the surgical procedures and that explanations may have the tendency to cause emotional strains which might prejudice the chances of a successful transplantation. Finally, we assume that there is no negligence on the part of anyone connected with the operations.

It is our opinion that upon these facts:

1. As a charitable corporation, the Peter Bent Brigham Hospital is immune from liability in this as in other situations involving possible torts.

2. With respect to the liability of any trustees, officers or agents of the hospital who participate in authorizing the procedure:

- (a) The parents may give effective consent to the operation on the ill twin, i.e., a consent which is binding upon them and the ill twin.

- (b) The parents have no power to give effective consent to the operation on the well twin, except insofar as the rights of the parents are concerned.

- (c) The operation on the well twin may well be prohibited by the terms, if not the spirit, of the criminal statutes of this Commonwealth.

The Corporation's Freedom from Liability

Although there is no decision of the Massachusetts Supreme Judicial Court which deals

squarely with the question whether a charitable corporation's immunity from tort liability extends to injuries resulting from intentional acts, the Court has never made any distinction in its opinions between such injuries and those resulting from negligence. Moreover, the various theories upon which the immunity rests are equally applicable to intentional and to negligent acts, and courts in other jurisdictions which still maintain the immunity have rejected any distinction based upon the character of the allegedly tortious act. See Annotation, 25 A.L.R. 2d 29, 52. Accordingly, there is no reason to believe that the Peter Bent Brigham Hospital would itself be held liable for the performance of a kidney transplantation at the hospital even if one assumes that under some circumstances the operation may be improper. Furthermore, since it is a corporation, the hospital cannot be guilty of crimes against the person. See *Commonwealth v. Proprietors of New Bedford Bridge*, 2 Gray 339, 345.

The immunity of the corporation from liability does not, of course, extend to the individuals who, either as trustees, officers or agents of the hospital, authorize or participate in the surgical procedure. The remainder of this opinion deals with the nature and extent of their liability.

The Civil Liability of Trustees, Officers and Agents

The legal problems in the kidney transplantation procedure are hardly less novel than its medical aspects. Needless to say, therefore, there are no authorities, judicial or otherwise, which are squarely in point. However, there are certain principles which have been established in more or less analogous situations which are helpful, if not definitive.

An attempt to state the basic rule governing this and other situations involving acts affecting the person of a minor is set forth in Section 59 of the American Law Institute's *Restatement of the Law of Torts*. While this statement has never been cited by the Massachusetts Supreme Judicial Court, neither has it been rejected. Furthermore, there is nothing in the decisions or opinions of the Court which is inconsistent with the rule as expounded by the Institute.

Section 59 states that:

(1) If a person whose interest is invaded is at the time by reason of his youth or defective mental condition, whether permanent or temporary, incapable of understanding or appreciating the consequences

of the invasion, the assent of such a person to the invasion is not effective as a consent thereto.

(2) The assent of a parent, guardian or other person standing in like relation to one described in Subsection (1) has the same effect as though given by the person whose interest is invaded, if such parent, guardian or other person has the power to consent to the invasion.

It was long ago established that a surgical operation for the benefit of a child constitutes an invasion of his person to which his parent does have the power to consent. Accordingly, assuming that both the ill twin and his parents assent to the operation by which diseased kidneys are removed and replaced by a healthy one, no liability will result from its performance.

The kidney transplantation presents a different question as far as the well twin is concerned. The operation which involves the removal of one of his kidneys, leaving him less capable of withstanding disease or injury, is clearly not an operation for his benefit. Whether such an operation constitutes an invasion of his person to which his parent has the power to consent is a question which neither the American Law Institute nor the decisions of the courts have answered. The best that can be found in the way of authority are statements which have appeared by way of dicta in court opinions. Unfortunately, even these provide no clear answer.

In *Bonner v. Moran*, 126 F. 2d 121 (D.C. Cir. 1941), the Court was called upon to decide whether a surgeon was liable to a minor for performing an operation which involved removing skin from his body and grafting it on the body of another patient. The youth had consented to the operation but no consent of either parent had been obtained. The Court held that the surgeon was liable to the minor for performing the operation. In its opinion, the Court said that the rule that a parent's consent is not necessary in an emergency, or where the minor is close to majority rests upon an assumption that the operation is for the minor's benefit. The Court went on to say that if the parent's consent had been obtained in the case before it, the action by the minor for assault and battery could not have been maintained.

There is no reason to believe that the Massachusetts Supreme Judicial Court would not have held, as the Court of Appeals for the District of Columbia did, that a surgical operation upon a minor which is not for his benefit and as to the nature and consequences which he has no clear understanding renders the persons per-

forming it civilly liable in the absence of the consent of the parent. However, the question remains: Is the parent's consent sufficient if the minor, whether or not he expressed his assent, was incapable of understanding or appreciating the consequences of the operation? The dictum in the *Bonner* case would seem to indicate that the answer is "yes." However, that answer seems plainly inconsistent with statements of the Massachusetts Supreme Judicial Court. The cases in which the statements were made (*Banks v. Conant*, 14 Allan 497 and *Taylor v. Mechanics' Savings Bank*, 97 Mass. 345) were less closely analogous to the present situation on their facts. However they probably represent more reliable indicia of the attitude which our Court would take toward the problem presented than does the dictum in the *Bonner* case.

In each of the Massachusetts cases it was held that a parent could not recover money paid to an infant upon his voluntary enlistment in the Armed Forces. The court said by way of dictum in each instance that the parent could not require his son to enlist against the minor's wishes and that the money was paid to the son as an inducement "to undertake a service of an arduous and hazardous nature." In the American Law Institute's terms, the enlistment was an invasion of the minor's interest to which the parent had no power to consent.

If a parent has no power to make an effective decision regarding his child's enlistment because of the hazardous nature of the service, the conclusion seems inescapable that the parent likewise has no power to give effective consent to an operation which is both hazardous and personally detrimental to the child.

Criminal Liability of Trustees, Officers and Agents

The absence of effective consent is no less a matter of concern in attempting to weigh the possibility of criminal liability in connection with a kidney transplantation involving minor twins. Again, the problem is a novel one. Obviously, the minds of those concerned with the procedure would be free of the evil intention or moral turpitude usually associated with those acts which are defined and prohibited as crimes. In fact, the dominant motive for the procedure as a whole undoubtedly would be preservation of the life of the ill twin. Nevertheless, that purpose would be accomplished by inflicting upon the well twin a serious and permanent physical injury without benefit to himself and without his intelligent con-

sent. Accordingly, there is serious danger that the procedure would involve criminal liability.

In summary, it is our opinion that any trustees, officers, or agents of Peter Bent Brigham Hospital who authorize or participate in kidney transplantations involving minor twins will become civilly liable to the well twin and subject to the possibility of criminal prosecution.

b.

**Petition to Supreme Judicial Court of the
Commonwealth of Massachusetts,
Suffolk County**

RESPECTFULLY represents your Petitioners:

1. That the Petitioners and Respondents are all the parties having or claiming any interest which might be affected by any declaration of the Court under these proceedings.

2. That the Petitioner, Gail Williams, is a resident of Sioux City, Iowa, and brings this Petition as mother and guardian of her minor children, Charles Williams, and John Williams, hereinafter mentioned in the Petition; and in behalf of said minor children as their next friend.

3. That the Respondents, namely, J. Hartwell Harrison, M.D., Joseph E. Murray, M.D., John P. Merrill, M.D., and Warren R. Guild, M.D., are practicing physicians in the Commonwealth of Massachusetts attached to the staff of the Peter Bent Brigham Hospital.

4. That the Respondent, Peter Bent Brigham Hospital, is a Massachusetts charitable corporation located in Boston in the County of Suffolk.

5. That the Respondent, Victoria M. Cass, is a physician and acting director of the respondent hospital and as such is charged with responsibility for the direction of the operation of the charitable functions of said hospital and has authority to determine whether or not the facilities of said hospital may be utilized by the physicians and surgeons attached to its staff for the performance of any operation which they desire to do in the course of their practice of medicine and surgery carried on by them for care and cure of their several patients.

6. That your Petitioner, Gail Williams, is the mother of Charles Williams and John Williams, two minor children born on November 28, 1943; that said minors are identical twins, one of whom has two diseased kidneys, the other of whom has two healthy kidneys.

7. That both said children are patients in

respondent hospital in Boston, County of Suffolk, Commonwealth of Massachusetts, to undergo kidney transplantation operations to save the life of the sick twin, Charles Williams, who allegedly will die in the event that these operations are not performed.

8. That the said respondent physicians have successfully performed kidney transplantation operations on a number of identical twins, and are of the opinion that successful transplantation operations can be performed on Charles Williams and John Williams.

9. That your Petitioners, Gail Williams, Charles Williams and John Williams, have requested and urged the respondent physicians to perform said operations, which said Respondents agreed to perform on the conditions set forth in Paragraph 16, but now refuse to perform said operations because they have been advised by competent legal counsel that, as John Williams is a minor, he cannot consent to an invasion of his person which will deprive him of a well kidney, and that your Petitioner, Gail Williams, cannot legally consent to said operation because it is an invasion of the person of said John Williams which allegedly is not for his benefit.

10. That respondent physicians desire to utilize the facilities of respondent hospital to perform the kidney transplant operations described in Paragraph 7 and the Respondents, Victoria M. Cass and the Peter Bent Brigham Hospital, desire to permit said physicians to use said facilities and to allow them to have the assistance of nurses and others employed by said hospital for purposes of said kidney transplantation operations in the event that this Honorable Court shall determine that the Petitioner, Gail Williams, or a guardian of John Williams appointed by a Court with jurisdiction therefor, has the authority and power to grant formal consent which shall be binding upon the Petitioner, John Williams, and all persons claiming by, through, or under him and having any title whatsoever to claim damages for any loss or injury which they or said Petitioner, John Williams, may incur or suffer by reason of anything which may happen to the Petitioner, John Williams, in the course of said kidney transplantation operations and which consent shall absolve said Victoria M. Cass and said hospital and each of them, their agents, employees and servants and Respondents from any and all liability to them or to the Commonwealth or any public authority, whether by reason of common law or any statute of the Commonwealth.

11. That Respondents, Victoria M. Cass and the Peter Bent Brigham Hospital, therefore allege that all Petitioners are severally ready to grant consent as aforesaid, but unless and until this Honorable Court shall declare that consent may be legally given as aforesaid, said Respondents have been advised that they cannot conformably to law permit said operations to be performed on the premises of and with the use of the facilities of said hospital, all of which are subject to the direction of the Respondent, Victoria M. Cass. If this Honorable Court shall so declare, said Respondents will make such premises and facilities and employees whose assistance the respondent physicians desire available to them for purposes of said kidney transplantation operations upon the Petitioners, Charles Williams and John Williams.

12. That your Petitioners, Gail Williams, Charles Williams and John Williams, are capable of understanding and appreciating the consequences of these surgical operations.

13. That your Petitioner, John Williams, has been fully informed, and understands the nature of the operations and its possible consequences.

14. That there is risk of grave emotional impact upon your Petitioner, John Williams, if this operation is not performed and your Petitioner, Charles Williams, dies.

15. That the operation is necessary for the future well-being of your Petitioner, John Williams, and that in this respect performance of the operation will confer a benefit upon your Petitioner, John Williams, as well as your Petitioner, Charles Williams.

16. That the respondent physicians agreed with the Petitioner, Gail Williams, acting on behalf of her minor children, Charles Williams and John Williams, to perform said operations to save the life of said Charles Williams, but only in the event that consent to said operations could be given which would be legally binding upon said children.

17. That an actual controversy has arisen between the parties as to whether consent to said operations can be given by the Petitioner, Gail Williams, or by anyone else to said operations, which would be legally binding on said children.

WHEREFORE your Petitioners pray:

1. That the Court determine whether or not the Petitioner, Gail Williams, or anybody else can give consent to the operations mentioned

in Paragraph 8, which will be legally binding on said Charles Williams and John Williams.

2. That the Court determine that your Petitioner, Gail Williams, have the right and authority to consent legally to said operations, or in the alternative, to authorize the Petitioner, Gail Williams, to consent to said operations or to appoint a guardian ad litem for said minor children to consent to said operations.

3. That this Honorable Court enter a binding declaration stating whether or not a document signed and sealed by John Williams, or by Gail Williams, or by any legally appointed guardian of John Williams, or by any other identified person wherein it shall be provided that by reason of the performance by the respondent physician or any of them or by any other practicing physician or surgeon attached to the staff of the Peter Bent Brigham Hospital of kidney transplant operations upon Charles Williams and John Williams upon the premises of the Peter Bent Brigham Hospital with the use of its facilities and with the assistance of its employees neither the Peter Bent Brigham Hospital nor its acting director, Victoria M. Cass, nor any agent, officer, employee or servant of either, shall be or become under any liability whatsoever by reason of any provision of the law of Massachusetts, whether common law or by statute, to the Commonwealth, to John Williams, or to any other person whomsoever will be effective to accomplish the said purpose.

4. For such other and further relief as to this Honorable Court may seem meet and proper.

C.

Psychological Report on John Williams

Patient was very cooperative and highly motivated to do well. His attitudes were excellent so that we can accept the results as representative of his personal functioning. He gives a history of eighth grade education, which he would have completed this year, were it not for his having to leave school to come to this hospital. He reports that his grades were "all right" and that he was not flunking any courses. Following graduation he has plans to take up carpentry. He works in his spare time at various jobs, which include baby sitting and waiting on tables.

In terms of his intelligence, he shows adequate functioning. His I.Q. is in the dull normal range; that is, 83, which in terms of competence places him within the perfectly acceptable range

of understanding and judgment. If he were not competent to make decisions, 25 per cent of the general population would also be incompetent. This level of 83 is probably representative of his capacity, even though his education has undoubtedly been very poor. He shows great gaps in knowledge, for example, which are consistent with a poor educational background. In some mental functions he shows average ability, which suggests that he perhaps could have attained a higher score under an optimal educational setting.

I would say, therefore, that in terms of comprehension, judgment and intelligence, he is perfectly capable of making decisions. He has the capacity to grasp concepts consistent with his intelligence and should be treated as a competent, self-sufficient individual.

d.

Notes of Petitioners' Attorney on Court Hearing

John Williams took the stand and testified in substance that he is 14 years old. He knows that his brother Charles is ill with a kidney ailment. John stated he was willing to submit to the operation for the removal of a kidney from himself to be implanted in Charles.

Cross-examination was waived on behalf of the doctors but the attorney on behalf of P.B.B.H. asked John whether the doctors had said to him that they would take out one of his kidneys and put it into Charles, to which John said yes. The attorney asked John whether he knew the dangers. John said yes. He said he was willing to consent to the operation.

Dr. Warren Guild of Lexington, Massachusetts, was the next witness. . . . He is acting director of the Kidney Laboratory of P.B.B.H.

Dr. Guild has run tests on Charles and the well twin to determine the nature of the kidney problem, the heart condition and contents of blood vessels and the overall physical condition. He found that Charles' kidneys are two percent effective. As a result the heart action is not good. He also found that Charles is very anemic. In Dr. Guild's judgment Charles will die within a matter of weeks.

Dr. John Hartwell Harrison of Brookline took the stand. . . . He obtained his surgical training at P.B.B.H. and has been on the staff there and on the Harvard Medical School faculty for 21 years.

Dr. Harrison then testified as to the procedures that would be followed in the operations. At the time of the operation the well twin is in one operating room and the sick twin is in a contiguous operating room, with access between the rooms. The operations are done simultaneously and on a very rigid time control. Dr. Harrison takes out the kidney from the donor twin at the moment when Dr. Joseph Murray has prepared the blood vessels in the sick twin so that a grafting may be done. When the kidney is removed from the well twin, it is placed in a sterile basin and grafted as rapidly as possible so that the kidney may be without oxygen for as short a time as possible. Dr. Murray attaches the blood vessels to the kidney. Thereafter Dr. Harrison attaches the kidney to the urinary tract.

Removal of the sick kidneys from the ill twin depends upon the ill twin's condition. The doctors try to remove the kidneys as soon as possible but it all depends upon the ill twin's response and condition.

Dr. Harrison further stated that this operation has been done in three cases on adults. In no case so far has there been any problem experienced with the donor of the kidney. In the case of the donees two had no trouble, one had some troubles, but all are now well.

As to the seriousness of the operation, Dr. Harrison said it is a major operation and all major operations are serious. As a result, the donor would be going through a major operation.

On cross-examination Mr. Lyman [the attorney for Mrs. Williams] asked whether the operation is successful only on identical twins. Dr. Harrison stated that that was true. Mr. Lyman asked whether the subject matter of the operation had been explained to John, and Dr. Harrison said yes.

Mr. Wait [the attorney for the hospital] asked on cross-examination what John had been told. Dr. Harrison stated that John had been told that the kidney would be taken out and put into Charles. He was further asked what John's circumstances would be after the removal of the kidney. Dr. Harrison said that John's condition would be satisfactory but he would have only one kidney. He would have to be careful in the case of infection or traumatic troubles. In other words, if the kidney became infected or hurt as a result of an accident the consequences would be very serious. Mr. Wait summarized the testimony as: "It is like a car with one tire, without

a spare." Mr. Wait then asked Dr. Harrison whether the explanation to John had been spelled out in words of one syllable. Dr. Harrison answered that the situation had not gotten to that point but would be before the operation was done. Mr. Wait asked whether technicians and nurses in the employ of the hospital would have to assist at the operation and whether the operation would take place at P.B.B.H., and Dr. Harrison said yes to both portions of the question.

Dr. Joseph Murray of Wellesley took the stand. He stated that he is a surgeon . . . and had been on the staff of P.B.B.H. and is on the teaching staff of Harvard Medical School faculty. His specialty is plastic surgery. He said he had heard Dr. Harrison testify and agrees completely with his statement as to procedure. Dr. Murray was asked whether he had explained to John about the taking out of a kidney and putting it into Charles. Dr. Murray said he had explained the situation and had done so prior to the time of making the experimental skin graft. The skin graft has already been done. Cross-examination was waived on behalf of the doctors and P.B.B.H.

Dr. Christopher Standish, a psychiatrist, testified. . . . He is an assistant professor of psychiatry at the Harvard Medical School and formerly was in a teaching position at Boston University Medical School and on the staff at Massachusetts Memorial Hospital.

He examined John and tried in the beginning to get to know John, to understand his level of intelligence and John's understanding of what was said to him. He also examined John's processes of thought to see whether he understood about the risks of the operation, what he thought about leaving school to come to P.B.B.H., what his thoughts are as to his brother's illness. Dr. Standish testified that he is of the opinion that John appreciates the situation with respect to Charles and what can be done by a transplant operation. Dr. Standish has tried to estimate what John's feelings are in the sense of whether there was indecision as to the choice of permitting taking of a kidney or not or whether John looked upon it as a sort of childish game. Dr. Standish has concluded that John has a firm conviction that he should permit the kidney to be taken. This conviction does not arise with the intent to please either himself (John) or his mother or anyone else. Apparently John found no need to justify the decision. John said in effect: Charles is my twin and if Charles dies it will be very

rough. Dr. Standish said that at that point in the conversation John had begun to weep.

Dr. Standish said that he had ascertained from John that in March he (John) was first told of the possibility that Charles might be saved by John's giving a kidney. John gathered that his mother and the doctor had been discussing the subject. Dr. Standish said that John said that his mother had told him (John) that the choice lay with John. John's first reaction was: Why give Charles a kidney when Charles has a good one? (It was apparently explained to John that the second kidney would become ill also, but Dr. Standish did not so testify.)

Dr. Standish said he tried to ascertain what pressures there might be on John in connection with the making of the decision. John had told him that the only pressures had been against his giving a kidney. His mother had told him (John) that people said that John would have to be away from school and in the hospital for some time and that he might be ill. Others had said that the doctors were experimenting. John apparently gave Dr. Standish the understanding that none of these remarks had made any impression upon him (John).

Dr. Standish examined how John had made up his mind. It appeared that John visited Charles with his mother. Thereafter the doctor (in Iowa apparently) explained the function of the kidney and that the kidney was getting worse. It was at this time that John decided to give a kidney to his brother Charles. There apparently was no conflict in John's mind and the decision apparently came naturally. John's present state of mind is that he must give the kidney. His state of mind is calm on the subject of the giving of the kidney. John's only question is apparently why the court is worried and wishes that the decision would be made quickly. He cannot understand why it is any of the court's business and wants to get the operation over with so that he can go back to school and his girl friend.

Dr. Standish said that he examined the relationship between John and Charles and gave two illustrations of how they conducted themselves together in the course of everyday life. From time to time Charles would take a girl to the movies. John would go to the same movie show alone. Part way through the performance Charles would excuse himself and would say to the girl that when he came back he would give a password so that she would know it was Charles (presumably because the movie theater was dark). Charles would then go out and would

meet John. He would tell John the password. John would go back and give the password to the girl and spend the rest of the evening with the girl without her knowing that there had been a substitution. Another illustration: John would make a bet with some other boy. If John won the bet Charles would go and collect the bet and then John would turn up and say he had not been paid. A third illustration occurred in school. Charles and John sat side by side. At times Charles would be prepared in his lessons and John would not. On one occasion there was a poetry assignment. Charles had recited. Just before John was going to be called upon John asked permission to be excused from the room. While John was out of the room Charles would move into John's place. Then John would come back into the room and sit in Charles' place. The teacher would then call on Charles thinking that John was being called upon to recite. Charles being prepared, would recite on behalf of John and the teacher would be none the wiser.

In the light of the foregoing, Dr. Standish was asked what he thought the emotional effect would be on John if the operation could not be performed. Dr. Standish said he was of the opinion that John felt that the identity of the two twins had been destroyed because one had healthy kidneys and the other ill kidneys. Hence if John could give a healthy kidney to Charles, then each would have a healthy kidney. In other words, Dr. Standish felt that there would be a beneficial emotional result to John if he (John) was permitted to give the kidney to his brother.

I telephoned Dr. Harrison. He had not heard what the decree may contain. I told him what the Judge had indicated but that we could not count on it until the decree had been signed and the Judge had made his findings of fact. I further emphasized to Dr. Harrison that if the Judge did enter a decree permitting the operation, this decree would be in no way binding in any other case in which twins were involved and that we would have to go through precisely the same procedure.

e.

Findings, Rulings, and Order of the Supreme Judicial Court

This is a petition for a declaratory decree brought under G.L. (Ter. Ed.) c. 231A, inserted by St. 1945, c. 582, § 1 heard by me upon a statement of agreed facts and oral testimony.

Mrs. Gail Williams, and her husband Frank

Williams, are the parents of Charles Williams and John Williams, born November 28, 1943. They have their domicile in Sioux City, Iowa. Mrs. Williams is guardian or temporary guardian of her minor children appointed by Probate Court within this Commonwealth. She brings this petition as mother, guardian, and next friend. She is the only parent of the children who is in Massachusetts and presently available here to consent to the operation as parent. Her husband has appeared in the proceedings and adopted the allegations and prayers of the petition.

The defendant physicians are highly skilled physicians and surgeons on the staff of the defendant Peter Bent Brigham Hospital and have performed several successful kidney transplant operations. The petitioners have requested that the defendant physicians perform a transplant operation transferring a healthy kidney from John Williams, who has two healthy kidneys, to his brother Charles whose two kidneys are diseased. John appears to be in good health, and medical opinion is that no unusual risks are involved to John beyond the inevitable risk of a major surgical operation and the hazards incident to having only one kidney in the event of later injury to that one kidney.

For a period of several months, it has been apparent that Charles' kidneys were in a seriously deteriorating condition and the possibility of a transplant operation has been under medical consideration. John has been giving thought to his action in the matter during this period. Charles is now suffering from an advanced kidney ailment which will result in his death in a relatively short period unless a kidney from his identical twin brother is transplanted in him successfully. Such an operation is the only hope of saving Charles' life. Although the operation could be postponed for a time, it has greater chance of success in saving Charles if performed before Charles' condition reaches an emergency state. This type of operation has been successful in the experience of the defendant physicians, when performed on identical twins. Preliminary tests indicate that John and Charles are identical twins.

John testified before me. He is a boy of fourteen with good understanding and intelligence. He has been fully informed of and understands the nature of the operation and its possible risks and consequences. He has talked with a donor of a kidney in a similar operation. The mother of the boys has also been informed of the possible consequences and understands them. She consents to the operation. John and his mother

desire that the operation take place and John's consent to it is the result of his own decision, free from pressure or coercion, made with admirable courage, generosity, and appreciation of the factors involved.

I find the facts stated above. I also find upon the testimony of John and of a qualified psychiatrist, who has examined John at length, (1) that if this operation is not performed and Charles dies, there is danger of serious emotional impact upon John, (*Brown v. Board of Education*, 347 U.S. 483, 493-494), and (2) that, because the risk of emotional disturbance will be reduced and because of the probability that John will be enabled by the operation to have the continued companionship of his twin brother, John will receive a benefit from the operation, and (3) that the operation, if the doctors decide to perform it, is necessary to John's future welfare and happiness.

This petition presents a proper case for a declaratory decree. Section 9 of c. 231A provides that such a petition as this lies "to remove, and

to afford relief from, uncertainty and insecurity with respect to rights, duties, status and other legal relations. . . ." It further provides that c. 231A should be liberally construed. Because of the fact that the defendants have been advised that they may become liable to the well twin in tort or suffer criminal prosecution if they operate or be liable in contract if they fail to operate, they are unwilling to undertake it. I am of opinion that an actual controversy has arisen so that a justiciable question is presented.

. . . I rule, as a matter of law, that it is proper for the defendant surgeons with the assistance of the defendant, the Peter Bent Brigham Hospital, its agents, and servants, to perform the operation described in the petition and the agreed statement of facts with the consent of the petitioner, Gail Williams, and her husband Frank Williams, and of John, and of Charles, if he is able to give it, without incurring any civil liability to John or to Charles or any criminal prosecutions.

* * *

B. Appraising the Role of the Participants*

1.

In Formulating Policy

a. Deciding about Choice of Subjects?

[i]

Bonner v. Moran
126 F.2d 121 (D.C. Cir. 1941)

GRONER, C. J.: This is an action for damages for assault and battery. There was a verdict and judgment for the defendant (appellee). The facts are these: Appellant, a colored boy residing in Washington city, was at the time of the events about to be stated 15 years of age. His cousin, Clara Howard, who lived in North Carolina, had been so severely burned that she had become a hopeless cripple. She was brought to Washington by her aunt, who was also the aunt of appellant, and taken to the charity clinic in the Episcopal Hospital, where she was seen by appellee, a

physician specializing in plastic surgery. Appellee advised that a skin graft would help her, provided the blood of the donor matched. After a number of unsuccessful efforts to match her blood, the aunt persuaded appellant, then a student in junior high school, to go with her to the hospital for the purpose of having a blood test. His blood matched, and the aunt telephoned appellee, who came to the hospital and performed the first operation on appellant's side. His mother, with whom he lived, was ill at the time and knew nothing about the arrangement. After the operation, appellant returned home and while there advised his mother that he was going back to the hospital to have his side "fixed up." Instead, he remained and in the subsequent operations a tube of flesh was cut and formed from his arm pit to his waist line, and at the proper time one end of the tube was attached to his cousin in the effort to accomplish her relief. The result was unsatisfactory, because of improper circulation of the blood through the tube. Accordingly, the tube was severed, after appellant had lost a considerable amount of blood and himself required transfusions. The tube of flesh was later removed and appellant

* This appraisal section focuses on uncomprehending subjects. For a fuller exposition of the factors requiring appraisal, consult section D of Chapter Eleven, beginning at p. 818 *supra*.

was released from the hospital. From beginning to end, he was there nearly two months.

There was the usual amount of contradictory evidence as to what occurred prior to the first operation and during the period when appellant was in the hospital. We notice this only for the purpose of saying that there was sufficient evidence, if believed by the jury, to show that appellant's mother never knew the nature of the operations or consented to them. At the close of all the evidence, appellant's counsel asked the court to instruct the jury that, before appellee could have the right to perform the operation, he must first have obtained the consent of appellant and of appellant's parents. The court declined so to instruct, but on the contrary told the jury that if they believed that appellant himself was capable of appreciating and did appreciate the nature and consequences of the operation and actually consented, or by his conduct impliedly consented, their verdict must be for the defendant. The decisive question on the appeal is the correctness of this charge to the jury.

* * *

... Here, as we have already seen, the question is whether the consent of a boy 15 years of age dispenses with the necessity of consent by his parents. The trial court decided that it did. In this the court followed Section 59 of the Law Institute *Restatement of the Law of Torts*. There it is stated that, if the child is capable of appreciating the nature, extent, and consequences of the invasion, his assent prevents the invasion from creating liability, even though the assent of the parent is expressly refused. The institute rule is bottomed on the principle that the very nature of rights of personality is freedom to dispose of one's own person as one pleases. But even if this conclusion be granted, it overlooks the infancy exception to such a rule. In deference to common experience, there is general recognition of the fact that many persons by reason of their youth are incapable of intelligent decision, as the result of which public policy demands legal protection of their personal as well as their property rights. The universal law, therefore, is that a minor cannot be held liable on his personal contracts or contracts for the disposition of his property. . . . Hence it is not at all surprising that, generally speaking, the rule has been considered to be that a surgeon has no legal right to operate upon a child without the consent of his parents or guardian.

There are, of course, exceptions to the rule.

One of them is in cases of emergency, when obviously an operation is necessary; others perhaps in cases in which the child has been emancipated, or where the parents are so remote as to make impracticable the obtaining of their consent in time to accomplish proper results. And where the child is close to maturity, it has been held that the surgeon may be justified in accepting his consent. But in all such cases the basic consideration is whether the proposed operation is for the benefit of the child and is done with a purpose of saving his life or limb. The circumstances in the instant case are wholly without the compass of any of these exceptions. Here the operation was entirely for the benefit of another and involved sacrifice on the part of the infant of fully two months of schooling, in addition to serious physical pain and possible results affecting his future life. This immature colored boy was subjected several times to treatment involving anesthesia, blood letting, and the removal of skin from his body, with at least some permanent marks of disfigurement.

* * *

As we have already indicated, the question here is different from that in any of the cases to which our attention has been drawn, for here we have a case of a surgical operation not for the benefit of the person operated on but for another, and also so involved in its technique as to require a mature mind to understand precisely what the donor was offering to give. We are constrained, therefore, to feel that the court below should, in the circumstances we have outlined, have instructed that the consent of the parent was necessary. Undoubtedly, the case from the doctor's standpoint is a hard one. At all times he was rendering, without compensation, his skill and professional services to alleviate pain and suffering. Doubtless this fact weighed with the jury, who regarded his activities in the matter as impelled wholly by humane and charitable motives. But by his own testimony it clearly appears that he failed to explain, even to the infant, the nature or extent of the proposed first operation. As to those which followed, he claims, and we assume correctly, that the matter was fully explained. And there is evidence that during the ensuing progress of the experiment the mother, too, was apprised of her son's heroism and gloried in the newspaper notoriety which followed, and which, as nearly as we can gather, resulted in public contributions of money for the boy's future education. Whether this attitude of

the mother was a sufficient ratification, we have no need to decide, since that question is not now in the case. However, if on a new trial the evidence in this respect is substantially the same, the question whether there was consent by ratification should be submitted to the jury under appropriate instructions. And if, after the mother learned of the preliminary operation, she made no objection thereto but publicly expressed her pride in her son's courage and without remonstrance allowed him to return for the completion of the experiment, such action on her part would be tantamount to consent by implication; and that, in the circumstances, would be sufficient.

On the whole case, we are of opinion that there was error in giving the instruction objected to, and in refusing to instruct that the consent of the parent was necessary.

Reversed and remanded for a new trial.

NOTES

NOTE 1.

BRITISH MEDICAL RESEARCH COUNCIL
RESPONSIBILITY IN INVESTIGATIONS ON
HUMAN SUBJECTS*

* * *

The situation in respect to minors and mentally subnormal or mentally disordered persons is of particular difficulty. In the strict view of the [English] law parents and guardians of minors cannot give consent on their behalf to any procedures which are of no particular benefit to them and which may carry some risk of harm. Whilst English law does not fix any arbitrary age in this context, it may safely be assumed that the Courts will not regard a child of 12 years or under (or 14 years or under for boys in Scotland) as having the capacity to consent to any procedure which may involve him in an injury. Above this age the reality of any purported consent which may have been obtained is a question of fact and as with an adult the evidence would, if necessary, have to show that irrespective of age the person concerned fully understood the implications to himself of the procedures to which he was consenting.

In the case of those who are mentally subnormal or mentally disordered the reality of the consent given will fall to be judged by similar

criteria to those which apply to the making of a will, contracting a marriage or otherwise taking decisions which have legal force as well as moral and social implications. When true consent in this sense cannot be obtained, procedures which are of no direct benefit and which might carry risk of harm to the subject should not be undertaken.

Even when true consent has been given by a minor or a mentally subnormal or mentally disordered person, considerations of ethics and prudence still require that, if possible, the assent of parents or guardians or relatives, as the case may be, should be obtained.

Investigations that are of no direct benefit to the individual require, therefore, that his true consent to them shall be explicitly obtained. After adequate explanation, the consent of an adult of sound mind and understanding can be relied upon to be true consent. In the case of children and young persons the question whether purported consent was true consent would in each case depend upon facts such as the age, intelligence, situation and character of the subject and the nature of the investigation. When the subject is below the age of 12 years, information requiring the performance of any procedure involving his body would need to be obtained incidentally to and without altering the nature of a procedure intended for his individual benefit.

* * *

NOTE 2.

WILLIAM J. CURRAN AND HENRY K. BEECHER
EXPERIMENTATION IN CHILDREN*

* * *

One of the authors (H.K.B.) has been in correspondence with the British Medical Research Council concerning this statement. He asked for further information regarding the legal precedent or authority upon which the "strict view" of English law was based, since no legal citations had been provided in the original statement. The inquiry was referred to Sir Harvey Druitt, KCB, who answered by letter dated Dec. 16, 1968. Sir Harvey has allowed us to refer to and to quote from his letter. First, he writes that the legal position taken in the statement of the Research Council was based upon his advice. He then continues, "I am confident about

* Report of the Medical Research Council for 1962-63 (Cmd. 2382) 23-24 (1963). Reprinted by permission.

* 210 *Journal of the American Medical Association* 77, 81 (1969). Reprinted by permission.

the correctness of that statement, but I cannot cite any statute or decided case which is exactly in point." The letter concludes with the following summary paragraph:

It follows from the foregoing that a parent's right to assault his child is in law strictly limited. No doubt the parent has the right to consent to a doctor carrying out upon his child medical procedures which are thought to be for the child's benefit. But I am confident that the parent has no legal authority to consent to medical procedures being carried out on his child for the advancement of scientific knowledge or for the benefit of humanity, if those procedures "are of no particular benefit to" the child and "may carry some risk of harm."

* * *

NOTE 3.

R. E. W. FISHER
CONTROLS*

It is a matter for regret that the use of normal children (or children suffering from some irrelevant disease) as controls in clinical research appears to be increasing.

No medical procedure involving the slightest risk or accompanied by the slightest physical or mental pain may be inflicted on a child for experimental purposes unless there is a reasonable chance, or at least a hope, that the child may benefit thereby.

If this is true—and I hope that there are few doctors in this country who would disagree—then it must surely be difficult to justify the use of two hydrocephalic infants reported in the paper by Dr. Doxiadis and his colleagues, and the use of a normal control by Dr. Bickel and his colleagues. Both papers appeared in your issue of October 17.

It may be, of course, that there were some good reasons for the use of these children which have not been made clear. If so, the authors owe it to themselves to explain.

NOTE 4.

K. S. HOLT
CONTROL†

It is quite reasonable that Dr. Fisher should raise the question of the use of normal children or children suffering from some irrelevant dis-

ease as controls in clinical research. There are extreme opinions on both sides, but I feel most of us adopt a policy between the two—somewhere in the grey between the rather theoretical white and black. My own working policy, which differs slightly from that expounded by Dr. Fisher in the second paragraph of his letter, is that no procedure should be carried out involving risk or discomfort without a reasonable chance of benefit to that child or other children; and this principle was followed throughout our work. The crux of the matter is contained in the last sentence of Dr. Fisher's letter—we owe it to ourselves to explain our actions. Surely we all weigh these matters most carefully in our own consciences.

NOTE 5.

AMERICAN MEDICAL ASSOCIATION
ETHICAL GUIDELINES FOR CLINICAL
INVESTIGATION*

* * *

Minors or mentally incompetent persons may be used as subjects [in nontherapeutic situations primarily for the accumulation of scientific knowledge] only if:

- i. The nature of the investigation is such that mentally competent adults would not be suitable subjects.
- ii. Consent, in writing, is given by a legally authorized representative of the subject under circumstances in which an informed and prudent adult would reasonably be expected to volunteer himself or his child as a subject.

* * *

NOTE 6.

PRINCE V. MASSACHUSETTS
321 U.S. 158, 170 (1944)

MR. JUSTICE RUTLEDGE delivered the opinion of the Court:

[Appellant and her nine year-old niece, of whom she was custodian, were devout Jehovah's Witnesses. For allowing her niece to sell the sect's literature publicly, appellant was convicted under state statutes which prohibited "boys under twelve and girls under eighteen" from selling newspapers and magazines "in any street or public place" and also prohibited others from per-

* 2 *The Lancet* 993 (1953). Reprinted by permission.

† 2 *The Lancet* 993 (1953). Reprinted by permission.

* *Opinions and Reports of the Judicial Council*. Chicago: American Medical Association. 9-11 (1969). Reprinted by permission. See pp. 845-846 *supra*.

mitting such children to engage in these activities. She attacked the statutes' validity on equal protection and freedom of religion grounds.]

* * *

... Parents may be free to become martyrs themselves. But it does not follow they are free, in identical circumstances, to make martyrs of their children before they have reached the age of full and legal discretion when they can make that choice for themselves. ...

* * *

NOTE 7.

DAVID DAUBE TRANSPLANTATION—ACCEPTABILITY OF PROCEDURES AND THE REQUIRED LEGAL SANCTIONS*

* * *

Children should on no account be donors, and there should be no cheating by maintaining, for example, that the child would suffer a trauma if he were not allowed to give his twin a kidney or whatever it might be. The psychologist who alleged this danger is presumably identical with the one whose little daughter did not eat. He asked her what she wanted and she said "Daddy, I want a worm;" so he went into the garden and got a worm. She said "No, it must be a hairy one;" so he went again and got a hairy one. She then said "It must be cooked," so he cooked it. She said "Daddy, you must eat half it it;" he overcame his nausea and ate half of it. Then she burst into tears and said "That was the half I wanted!" The likelihood of a trauma, incidentally, will be greatly lessened if the law leaves not the shadow of a doubt that a transplantation is here out of the question: the case will then be no different from where a twin dies from pneumonia—bad enough, but with no scope for offer of a sacrifice, disappointment, self-torture.

I would, however, advocate extending the age of consent of donors downwards to roughly the age of conscription; that is why I referred to children in this context instead of to minors. I believe I owe this idea to Professor Woodruff with whom I discussed the subject a few years

ago. From an age when we encourage or even compel a person to lay down his life for his country, he should also be allowed to make a potential sacrifice for a near relation. This would mostly be seventeen or eighteen years. Of course, conscription does not exist everywhere: there are countries which do not contemplate war. I suppose marriage might count as an equivalent, which would give us about the same age. A friend observed to me that refusal to allow children to give organs will hamper medical progress. If this is so, it is regrettable, but medical progress must then be hampered; it might be impeded more seriously if the prohibition were not enforced and if, after some mishap, there were an indiscriminate public reaction. Anyway I do not believe anyone has the right to dispose of an organ from the body of a living child simply because this is a child.

* * *

[ii]

*The Editors of the British Medical Journal Experiments on the Fetus**

The statement by Mr. Norman St. John-Stevas that "aborted live fetuses have been sold for medical experiments" has understandably caused some consternation. In a few words it raises at least three issues of great concern to the medical profession. These are, firstly, the use of living human organisms, not merely their tissues, for experiments; secondly, the sale of them; and, thirdly, the medical context. ...

... That to save a mother's life or preserve her health one "human life" in that sense must on occasions be sacrificed is the justification for terminating pregnancy or even (though very rarely nowadays) destruction of the baby during parturition. But a clear implication of this ethical precept is that a distinction must be drawn between fetal tissues and the fetus as a living organism: the doctor's ethical obligations are different in the two circumstances. The use of tissues would not seem to raise any special problems, and the question of consent by the mother hardly arises if cells from disorganized fetal tissues that would otherwise be incinerated are used for experimental purposes. But what of a living fetus, removed by hysterotomy after perhaps several months' development?

* G. E. W. Wolstenholme and Maeve O'Connor, eds.: *Ethics in Medical Progress—With Special Reference to Transplantation*. Boston: Little, Brown and Co. 198-199 (1966). Reprinted by permission of J. & A. Churchill, London.

* 1 *British Medical Journal* 433-434 (1970). Reprinted by permission.

The question when human life begins is if anything more difficult than the much-discussed problem of when it ends. Yet the time may now have come when it must be seriously considered in relation to experiments in fetal physiology. . . .

A legally recognized human life is protected by the law of murder. That law protects only human beings who have been born alive—that is (in England), totally extruded from the body of the mother and having a circulation independent of the mother. Legal authorities give little assistance when considering the degree to which the criminal courts might interfere in the conduct of experiments on a fetus. Nor does the Infant Life (Preservation) Act of 1929 provide a definite answer. That Act created the offence of child destruction committed by anyone who wilfully causes a child to die "before it has an existence independent of its mother," and so it would probably not apply to a fetus killed after a short existence linked to a machine. But in any event the offence is committed only if the child was "capable of being born alive." While the Act provides that evidence of 28 weeks of gestation or more shall be *prima facie* proof that the child was capable of being born alive, it does not provide that this is the only possible evidence of that fact. Consequently, until science has advanced so far that it can be proved that a particular fetus was capable of being reared by machine to a fully independent life, the criminal law seems unlikely to intervene to protect its life provided it was lawfully detached from the mother.

* * *

The rearing of fetuses from a previable state to one of independent life is no longer a remote possibility, while the experimental work that must precede it has been carried out for some time on animals. Though the sale of fetuses, if it has ever been conducted, must surely be summarily condemned, thorough discussion of the ethical and legal aspects of the work itself is greatly needed and should be initiated soon, perhaps jointly by the B.M.A. and the Royal College of Obstetricians and Gynaecologists. The government is to set up an advisory group "to consider the ethical, medical, social, and legal implications of using fetuses or fetal material in research," and meanwhile the Department of Health has informed approved abortion clinics that they must not supply fetuses for research purposes. The general public must be heard on these debatable issues, and the medical profes-

sion has an obligation to assist lay people to understand the medical implications as well as to formulate its own collective thoughts. . . .

b.

Deciding about the Ambit of Experimentation?

Leon R. Kass

*Freedom, Coercion, and Asexual Reproduction**

* * *

Our first experience with nuclear transplantation in human beings will almost certainly come on a small scale. The first attempt to clone a man will be an entirely voluntary undertaking on the part of a few people. No social coercion will be required; on the contrary, government and law need contribute only silent acquiescence.

Consider a likely first case. A husband and wife, each a carrier of a debilitating recessive genetic disease wish to have a child. They are unwilling to run the risk of having a child with the disease, a risk facing them in normal procreation. The husband is opposed to adoption; the wife very much wants to bear her own child. Knowledgeable about asexual reproduction by means of nuclear transplantation, they ask the experimental geneticist and his obstetrical colleagues to provide them with a child by cloning either husband or wife. The geneticist sees a natural marriage between his scientific interest in the outcome of the transplantation and his desire to help the couple have a healthy child. Confident as a result of much success in cloning chimpanzees, and encouraged by his opportunity to do good, he decides to risk the first human experiment.

What issues of freedom and coercion are raised by such a case? The existence of the technique of nuclear transplantation permits the couple to have a child without fear that it will acquire the disease for which they are both carriers. The right to procreate is for this couple a right they are not fully free to exercise: they are inhibited by a proper anxiety. Nuclear transplantation offers a new opportunity, and thus enhances their freedom. In the absence of societal and legal prohibitions, they will be free to use their new freedom.

Should the law remain silent? It can be

* Unpublished manuscript 9-16, 21-24 (1970). Printed by permission of the author, who retains all rights.

argued that the use of nuclear transplantation in this instance, or in any other instance, should be prohibited, not because of any evil present in this case but because of evils likely to result from the widespread practice of cloning. In other words, the first case can be considered objectionable not in itself but for what it might lead to. Yet one can argue, on the other hand, that the possibility or even likelihood of future abuses of a technological development does not justify preventing the use of a technique on a proper scale, for proper ends, by appropriate men. . . . In considering these arguments we may agree that the likely social and moral costs of future widespread use and abuse need to be weighed in deciding about the first case. We might even insist that methods for controlling future use be developed before we permit first use. Nevertheless, an appropriate verdict would seem to require an evaluation of the merits of the specific case itself, setting to one side its importance as a precedent.

In my view, this hypothetical first attempt to clone a man—or any other proposed first case—can be criticized on ethical grounds even when it is considered singly and apart from its importance as a first case. Any moral assessment of this procedure, no less than of any other procedure, must consider the person on whom it is performed, in this case, the unborn child-to-be that develops from the egg with transplanted nucleus. In other words, the attempt to clone a man is an experiment on a human subject, albeit a potential one, and as such, should conform to our standards of ethical experimentation, standards which at minimum require the free consent of the human subject. My previous statement that “the first attempt to clone a man will be an entirely voluntary undertaking” was misleading. It can never be entirely voluntary; the will of one of the participants, a participant of at least equal rank despite his merely potential existence, can never be consulted. That the asexually reproduced individual might give consent in retrospect—or at least would not protest his origin—would be insufficient to establish the morality of performing the transplantation in the first place.

On first glance, it might seem that the argument just presented calls into question the morality of normal procreation. However, without minimizing the responsibility of parents for bringing a child into the world, we can recognize that normal procreation is never an experiment performed to produce *that particular* child. (Prop-

erly understood, procreation is not an experiment at all, despite its uncertain outcome; the distinction is between generating and making, between nature and art). In the language of genetics, all parents are responsible for the decision to generate a new genotype, but not for the particular genotype generated. Any child born naturally can perhaps legitimately complain about his having been generated without his consent, but he cannot hold his parents responsible for his particular genotype. Such a claim might justly be made by a person with genetic disease whose parents had foreknowledge that exercise of their right to procreate would result in a diseased child. If we acknowledge the justness of this claim where chance has played a large role and where probably only a single gene is involved, how much more just the claim against complete determination of genotype without consent?

The arguments made here do not speak to and hence do not weigh against interventions *in utero*, even genetic engineering *in utero*, where such interventions are for the purpose of correcting specific diseases or defects found to be present in the fetus. These interventions would be forms of therapy, and as such would be subject to the ordinary ethical standards of medical practice in children and in others incapable of giving their own consent. . . .

* * *

What are the reasons for asserting that the consent of the clonant cannot be assumed, for the above first case or for any other first case? What are the likely and legitimate grounds of his possible retrospective objection? In short, what's wrong with cloning? One issue is that of identity and individuality. The problem can be illustrated by exploiting the ambiguity of the word “identity”: the clonant may experience serious concerns about his identity (distinctiveness) because his genotype, and hence appearance, stands in a relationship of identity (sameness) to another human being.

The natural occurrence of identical twins does not weaken an attack on the artificial production of identical humans; there are many things which occur by accident that ought not to be done by design (Who would justify the deliberate creation of an earthquake or the deliberate production of birth defects?) In fact, the problem of identity faced by identical twins should instruct us and enable us to recognize how much greater the problem might be for someone who was the “child” (or “father”) of

his twin. I cannot improve upon Paul Ramsey's reflections on this subject:

Growing up as a twin is difficult enough anyway; one's struggle for selfhood and identity must be against the very human being for whom no doubt there is also the greatest sympathy. Who then would want to be the son or daughter of his twin? To mix the parental and the twin relation might well be psychologically disastrous for the young. Or to look at it from the point of view of parents, it is an awful enough responsibility to be the parent of a son or daughter as things now are. Our children begin with a unique genetic independence of us, analogous to the personal independence that sooner or later will have to be granted them or wrested from us. For us to choose to replicate ourselves in them, to make ourselves the foreknowers and creators of every one of their genetic predispositions, might well prove to be a psychologically and personally unendurable undertaking. For an elder to teach his "infant copy" is a repellent idea not because of the strangeness of it, but because we are altogether too familiar with the problems this would exponentially make more difficult.*

* * *

Fabrication is a second major issue. Is it not reasonable to suppose that the first clonant might resent the trademark "Made by the Departments of Genetics and Obstetrics, Brave New University School of Medicine"? Can we assert the natural right of an individual not to be manufactured? Again, we face a strange question, one which could not have been imagined in earlier discussions of natural rights.

This question needs to be clarified by emphasizing that the issue of fabrication goes far beyond any similar issue attending artificial insemination or even "test-tube fertilization." Both of these techniques are sexual, even if only in the genetic sense. The particular genotype which results is the product of chance, even if both egg and sperm are taken from selected donors. Cloning is manipulation with a vengeance; it means the virtual elimination of chance. . . .

* * *

To return to our cloned individual. To claim for him or for us the right to an indeterminate origin is not merely a sentimental preference for "the natural" or "the accidental." On the contrary, it reflects a prudent judgment about alternative unpredictable masters. The right not to be

manufactured protects the individual against the far greater capriciousness of the human artificer.

* * *

C.

Deciding about Harm?

Susan W. Gray

*Ethical Issues in Research
in Early Childhood Intervention**

In a sense this paper . . . examine[s] the ethical issues involved in research on the effects of planned intervention early in a child's life. In another sense, however, I am presenting here a somewhat personal account of over a decade of involvement in intervention research with young children from low-income families. . . .

* * *

Intervention research . . . imposes some special characteristics of its own. It is necessarily longitudinal—that is, it takes place over a considerable period of time. Typically many changes, some intentional and others not, are introduced into the system—the child and his world. The objectives are apt to relate to motivational characteristics and also to various facets of intellectual competence. Thus, the program may touch not only the persons who are its specific targets but also those with whom they live and associate. The effects are intended to be lasting and substantial. . . .

A decade ago developmental "interveners" were seldom questioned about their motives and general intentions. It was usually taken for granted that a program that had clear implications for human welfare originated from positive motives. Today questions arise, particularly from members of minority groups, concerning such motivation. The majority of these questions have little to do with methods of research, but rather with intervention as such, whether in a service or a research program. . . .

Some objections center on the rights of parents. There is certainly no question from the legal standpoint that the parent is completely responsible for the child and has a full right to grant or withhold consent for the preschool child's participation in any program—up to a point. . . . The more difficult question perhaps is whether the parents' rights extend to decision-making with respect to the intervention program itself and in-

* Paul Ramsey, *Fabricated Man*. New Haven: Yale University Press 71–72 (1970).

* 18 *Children* 83–89 (1971). Reprinted by permission.

clude the right to dictate the program's methods and goals. This is not an easy issue to resolve. . . .

Other questions go beyond the parents' rights. One criticism leveled at developmental interveners these days is often put this way: How do you dare to work simply with young children when the basic problem is the entire social system?

This question, of course, implies a certain lack of distinction between a child development worker's professional role and his civic role. Asking a developmental intervener to work to change the whole social system is about as inappropriate as asking a thoracic surgeon why he does not give up the practice of lung surgery and instead work on outlawing cigarettes and certain pollutants in the atmosphere. The answer must be that it is highly appropriate for the professional person to engage in social action in his role as a citizen, but to expect him to devote his entire time to such efforts ignores the ethical imperative for using most productively his particular competence in promoting human welfare.

* * *

In his civic role the citizen-scientist can appropriately work to change the social system or environment that has created some of the problems to which his research addresses itself. In his scientific role, his first concern ethically should be to carry on his research to the best of his ability.

Another broad issue that comes under the general questioning by the public today has to do with the goals and values of the intervener. The issue typically is brought up by members of minority groups or persons who see themselves as spokesmen for minority groups. Many of their questions are highly relevant. The usual accusation is that interveners are promoting a white middle-class model of what is appropriate behavior when dealing with other ethnic groups. Obviously, intervention programs can confound, or can be perceived as confounding, elements of social class and race, for the representation of minority groups—especially the black, the Spanish-speaking, and the American Indian—in the low-income segment of the population is disproportionately high.

Developmental interveners are often accused of working with a theoretical model based on an assumption of deficiency in the subject. In theory we all speak about cultural differences; in practice many of us are concerned with cultural deficiencies. Today these terms are laden with

emotion and provoke bitter criticism. In a sense the accusation is just.

There are two ways, however, to look at cultural deficiencies. One is to take the view that a given culture simply tends to be deficient; some cultures are better—presumably in God's eyes—than others. Few social or behavioral scientists would defend such a stand. The other view, a broader one, emphasizes cultural differences among segments of our society but looks at and attempts to remedy the "deficiencies" of a given subculture in relation to a specific societal demand. If we accept the point of view that the technological civilization of the 1970's rewards the person who can read more than the person who cannot read, then we have a case for intervening to correct a specific deficiency—if a person wishes to take advantage of these rewards. Some subcultures have child-rearing practices that make learning to read more of a problem for their children than it is for children generally. . . .

The issue of cultural differences versus cultural deficiencies is, of course, confounded with the failure to distinguish the differences in social class. A few years ago a great deal of professional attention was being directed towards the concept of a "culture of poverty." Those who espouse this concept believe that patterns of coping develop in extreme poverty and that certain of these patterns are institutionalized—that is, they are adaptive to living in poverty but may be maladaptive to moving out of poverty. . . .

* * *

The confounding of social class differences with true cultural differences has led to problems in planning intervention programs and in observers' interpretations of these programs. How we resolve these problems is probably going to depend in part upon our view of how we should deal with cultural differences.

We could follow the old American philosophy of a melting-pot society. Today, however, many minority groups are becoming less and less willing to be melted down. We could ignore cultural differences—a rather unsatisfactory approach since it does not work. We could use cultural differences to build a bridge for meeting the demands of the larger society.

This last approach is the one used by many of the more carefully planned intervention programs. The child is taken "where he is." His first reading materials, for example, are based upon experiences that are familiar to him. So far so good; most interveners would "buy" this in rela-

tion to certain skills and areas of understanding that are regarded as necessary for a person to have in our ever-contracting globe. The problem is how far interveners should go in this direction.

The more thoughtful intervention programs today, as well as the general trends in our society, seem to reflect a move toward a degree of "cultural pluralism." Ideally, under cultural pluralism many different groups live in the same society with mutual respect, and mobility from group to group is possible not only over an extended period of time but also immediately.

* * *

My suggestion for resolving these issues is certainly not unique, but it is one with which I can live. It is that an appropriate goal in intervention programs is to make possible more options for the individual in his childhood and in adulthood.

One of the most characteristic aspects of poverty is that the poor have no options. The extremely poor must live hand to month, day by day, because they are at the mercy of external circumstances; they cannot take advantage of opportunities nor can they plan ahead. In a very different way, certain cultures tend to restrict individual experiences regardless of socio-economic class. Take, for example, the Amish. In the view of the "old order" Amish, education should be simply teaching the child to read well enough to read the Bible and to cipher well enough to figure simple quantities on the farm. There is some evidence that the Amish children experience adjustment problems in school because of the discrepancies between the school's and their families' values. The way of life of the old order Amish has much to recommend it, but many people would question a view of education that systematically limits the options for the coming generation.

A society that maximizes options may be one having a degree of cultural pluralism but enough commonality in the education of the young to make a range of choices available to all. This approach should not be regarded as based on a belief that the schools and society are always right or that early childhood intervention alone can resolve their problems. Clearly, throughout society, including the schools, many changes are needed to widen the options for young people. The research intervener, however, may appropriately make his scientific contribution by developing knowledge that can be used to improve the ability of young children and their parents to take advantage of these options as they

become available or to open up more options themselves.

* * *

Let us look now at some specific ethical principles. Paramount among these is the importance of remembering that in intervention research *you can't do just one thing*. In attempting to make relatively large and enduring changes in a child and his world, we generally take as the point of entry the child himself, although we may take the mother and child together. However, no matter what the point of entry, when one is trying to make profound changes in a system, one must work with due regard to all the aspects of that system, including the relationships involved. Furthermore, one cannot ethically terminate an intervention program without making whatever provision possible for some type of continuation or sustaining treatment. Herein lies the reason for the increasing emphasis in intervention programs on work with parents and for the establishment of Follow Through programs to pick up in the first grade where Head Start leaves off.

Another principle is the avoidance of the invasion of privacy. . . . What one family regards as intrusion may be interpreted simply as friendly interest by another family. A person can easily learn not to pry; it is not so easy to identify the line between intrusion and an appropriate interest in the concerns of the person with whom one is working.

Another problem associated with the invasion of privacy is that work with young children and parents from poverty-stricken homes is good newspaper copy. [I]t is difficult to provide public recognition of the needs of the poor without some invasion of privacy, particularly by local news sources. Our solution, not always successful, has been to avoid all publicity until a study has been completed. We have, however, felt an obligation to communicate findings that might be helpful to others, always avoiding the release of any identifying data. It is not always possible, however, to avoid premature publicity. The only solution we have found is to work with reporters of local newspapers and TV stations to try to help them understand why it is important to withhold publicity at a particular time.

Another important ethical principle—one not always honored—is to show respect for the dignity of the individual, whether a little child or an adult. This seems obvious. But persons with a strong middle-class bias are not always able to respect persons whose ways are different

from their own. It is not always easy for an inexperienced, middle-class worker to hide an aversion to clutter or to conceal annoyance over complete apathy in the face of a solvable problem. Consequently, a research director must exercise extreme caution in selecting staff members, to be sure that they can show true respect.

* * *

A well-known ethical principle requires that "informed consent" be obtained from the child's parents and from the child himself if old enough to understand. . . .

Much of our research is carried on with children who are far too young to understand. The answer, we say, is to inform and get counsel from the parent, by which we usually mean the mother. Well and good, but how can one really inform the parent if the parent has very limited understanding of the principles of child development? Still, one must try to give the parent as great an understanding of the goals and methods of the program as possible. If the principle of informed consent were applied literally, however, most intervention research would have to cease.

My own answer to the dilemma of informed consent is this: intervention researchers should inform the mother as best they can and then should work with her over a period of time to make more options available to her in her interactions with her child. Of greatest importance, perhaps, are efforts to help the mother increase her understanding of and competence in carrying out the acts that will be instrumental in achieving her own goals for the child.

Thus, informed consent in intervention research involves a collaborative approach. It also involves another principle: one must be very careful not to raise false hopes. The best guide is complete honesty with the parent.

Another ethical dilemma facing the developmental intervener derives from the discrepancies in the values between generations. We know next to nothing of the future of the infants with whom we work. . . . Since the future is largely unknown, the major emphasis of an educational program for any human being might well be placed on the development of the qualities and characteristics that make learning possible. Perhaps the only thing we know about life 20 years from now is that the competencies required of people will be different from those required today.

* * *

d.

Deciding about Interests of Science and Society?

[i]

The Editors of the New England Journal of Medicine
"Judgment Difficult"*

* * *

Since infants and young children cannot be expected to comprehend the procedures to which they may be subjected, parental permission has been accepted as a substitute for that of the subject, and the World Medical Association's Draft Code of Ethics on Human Experimentation . . . provides that parents should have complete freedom to make decisions on behalf of children. One may even question the moral legitimacy of such freedom and, in the light of present knowledge of the way in which parental responsibility is sometimes discharged, this could sometimes be of little value in protecting the human rights of the individual. Children in institutions and not under the care of relatives, according to the Code, should not be the subject of human experiment. Certainly a procedure must be really innocuous in most cases and relatively so in the remainder, and the expected reward in terms of potential benefit to the individual and all mankind must be the greater, the greater the risk; the desired end should always be of sufficient value to justify the means. . . .

[ii]

Ross G. Mitchell
The Child and Experimental Medicine†

* * *

The former practice of subjecting "charity children," orphans, or mentally defective children to procedures which would be considered undesirable for more fortunately placed children is wholly objectionable and morally indefensible. By the same token, however, there is no fundamental reason why children in hospital should be considered ineligible, since no unethical experiment should be contemplated in any case. There are certain disadvantages in this practice, however, apart from the obvious scientific one that children in hospital are seldom "healthy." The

* 269 *New England Journal of Medicine* 479 (1962). Reprinted by permission.

† 1 *British Medical Journal* 722, 725-726 (1964). Reprinted by permission.

hospital is a friendly and homely place to the paediatrician and others who spend their lives in it, but it may be terrifying to some young children, who appear docile and cooperative but are really fearful and resentful. Unnecessary investigation must be kept to a minimum in such children, so that they are generally unsuitable for experimental investigation unless this is essential for their recovery. On the other hand, many older children really enjoy life in hospital and are pleased to be the center of attraction in the ward. After years of working in children's wards, one learns to recognize the different reactions of children and the meaning of different sorts of behavior—this is one further attribute of the paediatrician as investigator, that he knows which patients are emotionally suited to participation in experimental research. Special care must be taken, of course, that children in hospital are not used in preference to other more suitable children simply because they are accessible, and the difficulties inherent in obtaining observations on healthy control subjects must be faced squarely, even at the cost of greatly increased effort and expense.

. . . Sometimes it is suggested that experiments of doubtful propriety are permissible on babies with severe malformations. To me, this is an affront to the whole concept of the individual as a person, and I do not believe that any experiment should be carried out on a malformed child which would place the malformed child in a separate category, thus creating two types of human being and paving the way for Hitlerian ideas of inferior beings.

* * *

2.

In Administering Research

a.

Who Should Participate, within What Structure, in State Regulation?

[i]

Strunk v. Strunk
445 S.W. 2d 145 (Ky. 1969)

OSBORNE, JUDGE.

The specific question involved upon this appeal is: Does a court of equity have the power to permit a kidney to be removed from an incompetent ward of the state upon petition of his com-

mittee, who is also his mother, for the purpose of being transplanted into the body of his brother, who is dying of a fatal kidney disease? We are of the opinion it does.

The facts of the case are as follows: Arthur L. Strunk, 54 years of age, and Ava Strunk, 52 years of age, of Williamstown, Kentucky, are the parents of two sons. Tommy Strunk is 28 years of age, married, an employee of the Penn State Railroad and a part-time student at the University of Cincinnati. Tommy is now suffering from chronic glomerulus nephritis, a fatal kidney disease. He is now being kept alive by frequent treatment on an artificial kidney, a procedure which cannot be continued much longer.

Jerry Strunk is 27 years of age, incompetent and through proper legal proceedings has been committed to the Frankfort State Hospital and School, which is a state institution maintained for the feeble-minded. He has an I.Q. of approximately 35, which corresponds with the mental age of approximately 6 years. He is further handicapped by a speech defect, which makes it difficult for him to communicate with persons who are not well acquainted with him. When it was determined that Tommy, in order to survive, would have to have a kidney the doctors considered the possibility of using a kidney from a cadaver if and when one became available or one from a live donor if this could be made available. The entire family, his mother, father and a number of collateral relatives were tested. Because of incompatibility of blood type or tissue none were medically acceptable as live donors. As a last resort, Jerry was tested and found to be highly acceptable. This immediately presented the legal problem as to what, if anything, could be done by the family, especially the mother and the father, to procure a transplant from Jerry to Tommy. The mother as a committee petitioned the county court for authority to proceed with the operation. The court found that the operation was necessary, that under the peculiar circumstances of this case it would not only be beneficial to Tommy but also beneficial to Jerry because Jerry was greatly dependent upon Tommy, emotionally and psychologically, and that his well-being would be jeopardized more severely by the loss of his brother than by the removal of a kidney.

Appeal was taken to the Franklin Circuit Court where the chancellor reviewed the record, examined the testimony of the witnesses and adopted the findings of the county court.

A psychiatrist, in attendance to Jerry, who

testified in the case, stated in his opinion the death of Tommy under these circumstances would have "an extremely traumatic effect upon him" (Jerry).

The Department of Mental Health of this Commonwealth has entered the case as *amicus curiae* and, on the basis of its evaluation of the seriousness of the operation as opposed to the traumatic effect upon Jerry as a result of the loss of Tommy, recommended to the court that Jerry be permitted to undergo the surgery. Its recommendations are as follows:

It is difficult for the mental defective to establish a firm sense of identity with another person and the acquisition of this necessary identity is dependent upon a person whom one can conveniently accept as a model and who at the same time is sufficiently flexible to allow the defective to detach himself with reassurances of continuity. His need to be social is not so much the necessity of a formal and mechanical contact with other human beings as it is the necessity of a close intimacy with other men, the desirability of a real community of feeling, an urgent need for a unity of understanding. Purely mechanical and formal contact with other men does not offer any treatment for the behavior of a mental defective; only those who are able to communicate intimately are of value to hospital treatment in these cases. And this generally is a member of the family.

In view of this knowledge, we now have particular interest in this case. Jerry Strunk, a mental defective, has emotions and reactions on a scale comparable to that of normal persons. He identifies with his brother Tom; Tom is his model, his tie with his family. Tom's life is vital to the continuity of Jerry's improvement at Frankfort State Hospital and School. The testimony of the hospital representative reflected the importance to Jerry of his visits with his family and the constant inquiries Jerry made about Tom's coming to see him. Jerry is aware he plays a role in the relief of this tension. We, the Department of Mental Health, must take all possible steps to prevent the occurrence of any guilt feelings Jerry would have if Tom were to die.

The necessity of Tom's life to Jerry's treatment and eventual rehabilitation is clearer in view of the fact that Tom is his only living sibling and at the death of their parents, now in their fifties, Jerry will have no concerned, intimate communication so necessary to his stability and optimal functioning.

The evidence shows that at the present level of medical knowledge, it is quite remote that Tom would be able to survive several cadaver transplants. Tom has a much better chance of survival if the kidney transplant from Jerry takes place.

Upon this appeal we are faced with the fact that all members of the immediate family have recommended the transplant. The Department

of Mental Health has likewise made its recommendation. The county court has given its approval. The circuit court has found that it would be to the best interest of the ward of the state that the procedure be carried out. Throughout the legal proceedings, Jerry has been represented by a guardian ad litem, who has continually questioned the power of the state to authorize the removal of an organ from the body of an incompetent who is a ward of the state. We are fully cognizant of the fact that the question before us is unique. Insofar as we have been able to learn, no similar set of facts has come before the highest court of any of the states of this nation or the federal courts. The English courts have apparently taken a broad view of the inherent power of the equity courts with regard to incompetents. *Ex parte Whitebread* (1816), 2 Mer. 99; 35 E.R. 878, L.C. holds that courts of equity have the inherent power to make provisions for a needy brother out of the estate of an incompetent. This was first followed in this country in New York, *In the Matter of Willoughby, a Lunatic*, 11 Paige 257 (NY 1844). The inherent rule in these cases is that the chancellor has the power to deal with the estate of the incompetent in the same manner as the incompetent would if he had his faculties. This rule has been extended to cover not only matters of property but also to cover the personal affairs of the incompetent. . . .

* * *

. . . Testimony in this record shows that there have been over 2500 kidney transplants performed in the United States up to this date. The process can be effected under present techniques with minimal danger to both the donor and the donee. Doctors Hamburger and Crosneir describe the risk to the donor as follows:

This discussion is limited to renal transplantation, since it is inconceivable that any vital organ other than the kidney might ever be removed from a healthy living donor for transplantation purposes. The immediate operative risk of unilateral nephrectomy in a healthy subject has been calculated as approximately 0.05 per cent. The long-term risk is more difficult to estimate, since the various types of renal disease do not appear to be more frequent or more severe in individuals with solitary kidneys than in normal subjects. On the other hand, the development of surgical problems, trauma or neoplasms, with the possible necessity of nephrectomy, do increase the long-term risks in living donors; the long-term risk, on this basis, has been estimated at 0.07 per cent. These data must, however, be considered

in the light of statistical life expectancy which, in a healthy 35-year-old adult, goes from 99.3 per cent to 99.1 per cent during the next five succeeding years; this is an increase in risk equal to that incurred by driving a car for 16 miles every working day (Merrill, 1964). The risks incurred by the donor are therefore very limited, but they are a reality, even if, until now, there have been no reports of complications endangering the life of a donor anywhere in the world. Unfortunately, there is no doubt that, as the number of renal transplants increases, such an incident will inevitably be recorded.*

* * *

We are of the opinion that a chancery court does have sufficient inherent power to authorize the operation. The circuit court having found that the operative procedures in this instance are to the best interest of Jerry Strunk and this finding having been based upon substantial evidence, we are of the opinion the judgment should be affirmed. . . .

STEINFELD, JUDGE (dissenting):

Apparently because of my indelible recollection of a government which, to the everlasting shame of its citizens, embarked on a program of genocide and experimentation with human bodies I have been more troubled in reaching a decision in this case than in any other. My sympathies and emotions are torn between a compassion to aid an ailing young man and a duty to fully protect unfortunate members of society.

The opinion of the majority is predicated upon the authority of an equity court to speak for one who cannot speak for himself. However, it is my opinion that in considering such a right in this instance we must first look to the power and authority vested in the committee, the appellee herein. KRS 387.060 and KRS 387.230 do nothing more than give the committee the power to take custody of the incompetent and the possession, care and management of his property. Courts have restricted the activities of the committee to that which is for the best interest of the incompetent. . . . The authority and duty have been to protect and maintain the ward, to secure that to which he is entitled and preserve that which he has. . . .

* * *

The majority opinion is predicated upon the finding of the circuit court that there will be

* Hamburger and Crosneir, "Moral and Ethical Problems in Transplantation," in *Human Transplantation* 37 (Rapaport and Dausset ed. 1968).

psychological benefits to the ward but points out that the incompetent has the mentality of a 6-year-old child. It is common knowledge beyond dispute that the loss of a close relative or a friend to a 6-year-old child is not of major impact. Opinions concerning psychological trauma are at best most nebulous. Furthermore, there are no guarantees that the transplant will become a surgical success, it being well known that body rejection of transplanted organs is frequent. The life of the incompetent is not in danger, but the surgical procedure advocated creates some peril.

* * *

Unquestionably the attitudes and attempts of the committee and members of the family of the two young men whose critical problems now confront us are commendable, natural and beyond reproach. However, they refer us to nothing indicating that they are privileged to authorize the removal of one of the kidneys of the incompetent for the purpose of donation, and they cite no statutory or other authority vesting such right in the courts. The proof shows that less compatible donors are available and that the kidney of a cadaver could be used, although the odds of operational success are not as great in such a case as they would be with the fully compatible donor brother.

I am unwilling to hold that the gates should be open to permit the removal of an organ from an incompetent for transplant, at least until such time as it is conclusively demonstrated that it will be of significant benefit to the incompetent. The evidence here does not rise to that pinnacle. To hold that committees, guardians or courts have such awesome power even in the persuasive case before us, could establish legal precedent, the dire result of which we cannot fathom. Regretfully I must say no.

NOTE

WILLIAM J. CURRAN
A PROBLEM OF CONSENT—KIDNEY
TRANSPLANTATION IN MINORS*

During 1957 the Supreme Judicial Court of Massachusetts issued three highly significant opinions in declaratory judgment proceedings in a developing area of medical science: the homotransplantation of functioning tissue. . . .

* * *

* 34 *New York University Law Review* 891, 893-898 (1959). Reprinted by permission.

In each of the three cases, the court relied on the testimony of a psychiatrist. . . . The use of psychiatric evidence in support of a finding such as this is similar to the method used in the famous school segregation case, *Brown v. Board of Education*, where the Supreme Court was strongly impressed with the evidence of the bad psychological and cultural effect of "separate but equal" school facilities on Negroes in the South. The use of this technique in *Brown* has received generally praiseworthy comment, but the writer cannot help but recall the masterly critique of this portion of the segregation decision by Edmond Cahn. Professor Cahn questioned the value of much of the "scientific proof" produced by the social scientists in their famous special brief in that case. . . . Many years before, [Charles C.] Moore issued similar complaints about the "new science" of psychology and what he felt to be its much too ambitious claims to usefulness in the courts. Basically, he said the psychologists were merely offering common sense in technical jargon, a common sense which had been used in the courts for years. One can see the same objections being made to the psychiatric opinions in the kidney transplant cases. It hardly seems that psychiatric evidence is necessary to convince anyone that a healthy identical twin would suffer a grave emotional impact on the death of his twin brother. This statement does, of course, rest on an important assumption on which psychiatric opinion may be valuable. It assumes that the donor twin is within normal intelligence levels and experiences normal emotional responses. And yet, every lawyer knows that courts make their own judgments on issues of this type every day without expert testimony. In the kidney transplant cases, for example, the justice presiding at each hearing determined for himself by questioning of the donor twin whether or not the twin was intelligent enough to understand the nature and consequences of the operation and fully and freely consented to it. This determination was equally as difficult and as technical as the question of sustaining a "grave emotional loss" on the death of the sick twin.

* * *

In the instant case, we see a rather unique involvement of community and professional judgments in a narrow issue, i.e., whether a minor should be allowed to donate a kidney to a twin sibling under very serious circumstances. The family and both twins are involved and must

understand and consent. The hospital and the surgeons are vitally concerned. The court steps in as a "community" representative, more or less, and it relies on another professional judgment, that of a psychiatrist, in reaching its conclusion. The ubiquitous declaratory judgment procedure is used to accomplish this result, and with, as is becoming more and more usual in these proceedings, no real controversy or likelihood of litigation between the parties.

* * *

. . . What would the situation be if the twins were willing to go through with the operation, but the parents refused? . . . In the ordinary case of parental refusal to allow medical procedures on their children, many states have legislation allowing a state agency, usually a Child Welfare Department, to take temporary custody of the child as a "neglected child" for a period sufficient to obtain the needed treatment. These statutes are limited to cases of very serious emergency treatment, however. It is doubtful that they would cover taking custody of the healthy twin unless some theory of benefit such as that suggested in these opinions prevailed.

[W]e keep coming back to the issue of a lack of direct therapeutic benefit to the healthy twin. We might have been more satisfied had the court met it more directly. Actually the benefit found by the court with the aid of the psychiatric evidence is more the prevention of possible detriment than it is the conferring of a positive gain. As life will have it, this is brought to mind most strongly today by the fact that of the transplants attempted in these cases only one has survived to this date. The younger children who received the kidneys . . . died some months after the operations.

* * *

[ii]

Joseph D. Cooper

*Creative Pluralism—Medical Ombudsman**

The clamor for practical application of discoveries of biomedical knowledge grows louder. Medical researchers are being told they must release the secrets of their laboratories to physi-

* *Research in the Service of Man—Hearings on Biomedical Development, Evaluation of Existing Federal Institutions before the Subcommittee on Government Research of the Senate Committee on Government Operations, 90th Congress, 1st Session 46-61 (1967).*

cians for the public benefit. This poses quite a problem for the research community which must ask itself: What are we holding back?

The situation is not an unexpected one. Sooner or later, an impatient public was bound to ask for delivery on promises made recurrently that the conquest of innumerable diseases would be achieved quickly if only enough were spent in a hurry.

* * *

... In our haste to win the medical wars—society's haste—and to enjoy promised fruits of conquest, we are adventuring beyond prudent limits of risk. The hope becomes the theory which leads to selective discovery of evidence to support the wish, while contrary evidence which might slow the pace is ignored or rationalized away. This naturally stems from single-minded advocacy which sometimes has led to great gains, but more often has blocked or retarded action along other avenues of progress.

What is wrong is the absence of mechanisms for obliging proponents of action to offer evidence, in reasonable depth, to independent judges who do not have causes to espouse. Consequently, it has been too easy for bold new programs in the medical sector to come into being without scientific bases for promises or hope that benefits could or would materialize. Once activated these new programs become irreversibly committed because of public promises, dependence of program personnel on continuity of support, and force of legislation.

As an example of prematurity and the lack of constructive challenge which once was more dominant in scientific discourse, I will discuss the national program to prevent a rare disease called phenylketonuria, a disease which often results in mental retardation.

* * *

Phenylketonuria, more commonly called PKU, is a genetically acquired disease commonly associated with mental retardation, although some phenylketonuric babies grow up to be normal or bright without treatment. Apart from, or in addition to, retardation, the child may have postural peculiarities, convulsive or jerking movements, and a characteristic musty body odor, among other symptoms. PKU belongs to a disease category called "inborn errors of metabolism". . . .

For the symptomatic child and its parents, PKU is a calamity. For society generally, PKU

is a rare disease. The incidence of the disease is estimated, on the high side, about 1 out of every 10,000 births. On the low side, the incidence has been estimated at 1 in 25,000 or lower. A true figure cannot really be given due to errors of diagnosis which may yield either false positives or false negatives and to difficulties of projecting statistically from small samples. . . .

The institutional population of phenylketonurics is also relatively rare, having been estimated at considerably less than 1 percent (0.793 percent). . . .

Why, one may ask, is this disease so much in the public view, despite its relative rarity? The reasons mainly are these:

1. Universally, mothers are fearful of having a child with a birth defect. . . .

2. Close to 6 million Americans are mentally retarded in varying degree. Mental retardation is the single largest category of childhood disease. . . . A broad base of missionary interest is to be found, therefore, among parents and lay voluntary groups.

3. A medical breakthrough in PKU and other metabolic disorders associated with retardation was hailed both symbolically and practically as an opening wedge—as a gain which would be followed by other breakthroughs which eventually would reduce the incidence of mental retardation. A national PKU crusade was therefore organized by voluntary health agencies, working through government agencies and state legislatures, partly to control this disease and partly to bolster the spirits of those who seek anxiously for additional gains.

4. There existed a small but active group of physicians and medical researchers who had begun to build investigational interests and careers around the phenomena of the "inborn errors of metabolism." Some—not all—of the more actively disposed of these medical personalities involved themselves in the promotion of the PKU program. They became the advisers to legislators, government administrators, and voluntary health organizations. Out of the fusion of their own professional convictions and career interests emerged a professional evangelism.

5. The public was eager for delivery of new medical breakthroughs which it had been promised and for which it had been primed through the successive miracles of the sulfonamides, antibiotics, and poliomyelitis vaccines. . . .

I shall review now some of the things known about PKU. Phenylketonuria is a metabolic defect transmitted genetically as a Men-

delian recessive factor. This disease was first recognized and described in 1934. Detection at birth was difficult because the development of the child with phenylketonuric symptoms progresses quite normally during the first few months of life. Thereafter, intellectual growth is retarded. This is believed to be caused by the failure of a liver enzyme to metabolize the amino acid phenylalanine whose excessiveness in the bloodstream causes brain damage.

For some years after this disease had been defined and was made recognizable, medical science could offer little more than identification and explanation. A major advance which permitted widespread screening economically was the development of a simple urine test. This test was not wholly satisfactory because the presence of phenylpyruvic acid, a spillage byproduct of the excessive phenylalanine, was not readily detectable until the baby reached 6 to 8 weeks of age. At that time it was no longer under hospital control and less amenable to screening and the commencement of dietary control. Prompt therapeutic management during the first weeks of life is believed by many to be essential to prevent development of a brain lesion, the cause of retardation. Robert Guthrie, of Children's Hospital, Buffalo, developed a blood test which utilized only a few drops of blood taken by simple puncture from the baby's heel when it is only 4 or 5 days old. This afforded hospital control of the procedure. It is at the heart of today's mass screening programs which have been instituted in many states.

The development which really fired the imagination, which offered the hope of cure not only for PKU retarded but for other victims of inborn errors of metabolism, was the reported impression that a special diet, low in phenylalanine, apparently prevented or limited the retardation of intellectual growth and other phenylketonuric symptoms. From a public health standpoint, therefore, the formula for action seemed clearcut: put every newborn child through a PKU screening test and then take all who are found to be PKU positive and put them on the special diet. This is the simplistic model now widely adopted for the detection and treatment of PKU. It is the model which it is hoped will be useful in the treatment of many other metabolic disorders.

The belief that effective control of a genetic disorder—of PKU—has been achieved was electrifying. The bandwagon quickly took on a heavy load—several voluntary health agencies, several

federal agencies, and medical researchers, among others. "PKU" became a household word. Interest in screening for other metabolic diseases was heightened. . . .

People soon began discussing a new problem: What would happen when salvaged PKU patients grew up and procreated? Would they then add to the pool of defective genes in the total population? This, however, was a deferrable problem to be faced later. Meanwhile, in relatively short order, 37 states, as of November 1966, passed PKU screening laws. The American Medical Association also endorsed screening programs, as had other groups, but it did not favor legislative requirements for them.

Thus, the consensus was that an excellent medical model was available for the management of PKU and that screening and treatment should proceed accordingly. Only here and there were voices raised in protest against the legislative approach. Even fewer scientific challenges were expressed as to the validity of the medical model. I use the word "expressed" deliberately, because as I explored the PKU program I was to learn that many who had doubts had not expressed them. I also learned that the source of consensus was traceable to a rather small group of people who were in substantial agreement among themselves. The same people appeared time after time on professional programs throughout the country. They reinforced each other in their convictions, sincerely and earnestly held.

* * *

The evidence of a faculty medical model I will now present covers diagnostic validity and reliability, control and effects of treatment, and readiness of the PKU program to be put into a service status for the public.

The diagnostic finding of a high phenylalanine content in the blood does not in itself establish the infant as phenylketonuric. Neither does the finding of a low serum phenylalanine level necessarily predict the absence of PKU. Guthrie and associates reported that about 85 percent or more of presumed positives turned out to be false positives. Presumably, the false positives are eliminated through use of confirmatory tests, but the literature offers no assurance that existing tests, used generally, will exclude all false positives. . . .

The blood phenylalanine test is given in the hospital before discharge of the newborn; usually when 4 days old. The recommended pro-

cedure is that all infants be tested again at age 4 weeks, so that false positives and false negatives might then be rechecked. What happens to those babies who were put on low phenylalanine diets very early? How does a later test reveal them to be false positives or false negatives if already on diet? What happens to non-PKU children falsely diagnosed so to be? It has been suggested that when put on low phenylalanine diets, their own body proteins break down through catabolic action to release blood phenylalanine intake whereas more would actually be needed.

While Dr. Guthrie has reported, on the one hand, that 85 percent of his initial positive screenings are false upon recheck, other investigators have . . . claimed that the Guthrie test has a potential of 53 percent false negatives. So, on the one hand the test pulls in too many babies, and, on the other, it is claimed to bypass too many.

One of the problems with which we are here confronted is that the most meager data have been used in projecting the incidence of disease, the validity and reliability of diagnostic screens and the clinical value of the dietary treatment. The efficacy of the dietary substance used to feed PKU babies, Lofenalac, was originally demonstrated through experience with only six cases as a basis for obtaining FDA approval in 1958.

The trouble is in the difficulty of collecting enough new cases in any one clinical center to provide an adequate statistical base for study. Thus, the last time I checked on experiences in the District of Columbia, which has a screening program, only one confirmed case had been found in 2 years.

* * *

Consider the reactions of the parents who are told that their children are or might be retarded and will require additional tests over a period of time which will narrow the field down to only a fraction of those screened out. How does the imparting of this information change their lives? What traumata are thereby induced and at what cost? Even as to children who are eventually adjudged to be PKU-negative, are the lingering doubts in parents' minds ever dispelled?

* * *

One of the more recent uncertainties is whether "Phenylketonuria" is a single disease or a spectrum or collection of many different diseases each of which would require its variant

of treatment. This is a matter for more profound conjecture than it has been given, particularly in view of our tendency to identify diseases and their cures through rather simplistic models.

Consequently, children who test out to be phenylketonuric, in terms of blood chemistry, may grow up to be normal in all respects. Under present screening and treatment procedures, they would be put on a diet which might very well do them harm. On the other hand, some children who develop normally on a PKU diet might have developed even more normally without the diet.

A factor which impairs the ability of scientists to conduct research, even to know whether or not the low phenylalanine diet is beneficial, is that when an entire universe—all babies who show up as PKU positives—is put on the diet, no control groups are left for comparison. We do not know whether any children under dietary management who do not become retarded would have remained normal under ordinary diets. Untreated children with high phenylalanine levels have been found with intelligence in the normal and high normal range.

* * *

Earlier, I mentioned the widely held belief that diagnosis and treatment within the first weeks of life are important in order to prevent brain damage. Some recent work by Fuller, a psychologist of New York, suggests otherwise. She found that, taking all phenylketonurics (within her study) as a group, the earlier they were placed on the low phenylalanine diet, the less impaired they were. This would possibly support the views on early diagnosis and treatment, but let us face that one further after looking at some more of Fuller's findings.

Some PKU babies started on early control showed marked retardation. On the other hand, some children started on the diet after 3 years of age—long after brain damage should have occurred—showed great improvement to the point of little or no retardation. Furthermore, in a study of siblings on PKU diets, a significant proportion started at a later age showed better improvement than their sisters or brothers who were started at younger ages.

The implications are profound. It is not improbable that measured improvement is in part, at least, the result of an intervention factor—the giving of individual attention to children who previously had been abandoned by society—rather than to biochemical effects of withhold-

ing an amino acid from the diet. The intervention factor, which may in this case be response to attention and training, is known among psychologists as the "Hawthorn effect."

* * *

... Now I will take up problems of treatment, especially as related to child safety. Very little attention has been given to deleterious effects of treatment, including the incidence of death attributable to induced dietary insufficiency. Other side effects and complications of the PKU diet, which consists solely of an unpalatable preparation from which phenylalanine has been removed include skin lesions, refractory anemia, bone changes, vomiting, lethargy, appetite failure, poor weight gain, retarded growth, and miscellaneous symptoms of malnutrition.

Recently, investigators found that the immune responses of PKU children to certain infectious diseases were lowered by dietary treatment. Wooley has argued that PKU patients saved from idiocy might become schizophrenic when taken off their diets later in life. The Food and Drug Administration informed me it had no knowledge of deaths. The Children's Bureau informed me it had no evidence of fatalities occurring as a result of treatment. Yet references to treatment-induced death are indeed to be found in the medical literature.

* * *

A reported case of death, as an example, was attributed to megaloblastic anemia of nutritional origin. A phenylketonuric infant was started on a low-phenylalanine diet at age 2 weeks, suffered serious setbacks resulting in three hospital readmissions, and died at age 7 months. The reference to this death was published in a bibliography of the Children's Bureau.

As a commentary on public attitudes, one must observe that if any drug company were actively promoting the PKU program, which is not the case, it would be hoisted on the nearest lamppost if deaths were involved.

One of the problems in treatment, related to adverse reactions, is the need for exquisite balancing of nutrient intake to metabolic changes in the growing infant and child. Phenylalanine is an essential amino acid. It is necessary for growth, repair of tissues, and physical survival. The blood content or serum phenylalanine levels must be checked regularly to guide dietary management.

* * *

From all experience—even poor experience—lessons ought to be taken. One big lesson from the PKU situation is that one should not commit any major endeavor on a broad scale without first having undergone pilot testing. Inevitably, such testing leads to correction of assumptions and procedural techniques. We did not have this in the PKU program. Rather, the cry went out that society owed it to every child to have a PKU test at birth and that it would be unethical to deprive any child of the dietary treatment once he had been diagnosed as phenylketonuric.

Just how the PKU program was determined to be service-ready ought to be examined, in order to learn more lessons therefrom. Mandatory PKU screening first became law in Massachusetts. As near as I can determine, universal screening was originally introduced in order to find cases for research programs, although I am sure the researchers must have felt this would also lead to public benefit.

At no point, however, has the public ever been told that the PKU program is still mainly investigational and that almost the entire population of newborn infants has been converted into a national laboratory of clinical research with attendant risks. Few physicians and hardly any parents have been made aware of these risks and of all the reasons for screening.

The claim has been made that the physician is still free to decide the course of treatment for the patient, the infant. Theoretically this may be so, but the specter of the malpractice suit must exert a powerful stimulus to prescribe in accordance with the cultural mores for these are what influence the court. Already, there have been two malpractice suits in which physicians have been charged with failure to treat.

The inauguration of screening programs was well along when the Committee on Fetus and Newborn of the American Academy of Pediatrics published the following criteria for screening of newborn infants for metabolic disease:

1. Does the seriousness of the disorder justify screening?
2. Is therapy for the disease in question available?
3. Is there a clearly identifiable segment of the population with an increased incidence of this disease?
4. Is it possible to perform reliable screening during the first few days of life?
5. Can the screening test be performed in a routine service laboratory?

6. Is the test acceptable to the physician and to a majority of parents?

7. Is the cost of the test acceptable?

8. Are there acceptable medical facilities prepared to confirm diagnosis and consult about the institution of therapy?

* * *

To underscore the state of confusion as regards PKU and to show how sharply opinions are divided even with the American Academy of Pediatrics, the following is quoted from a heretofore unpublished report of its Committee on Nutrition to the Children's Bureau, dated July 30, 1965:

1. The objectives and ways and means for implementing such wide-scale screening programs remain to be evaluated as do the methods for following through of patients with heritable metabolic diseases detected by such programs.

2. The beneficial effects of good dietary management of any of the heritable metabolic diseases, detected in these programs or elsewhere, have yet to be proven unequivocally. Under the circumstances, the committee felt that caution was indicated in launching widespread screening programs until practical therapeutic programs, the effects of which are predictable in the majority of children participating, have been designed.

3. It must be demonstrated with certainty that any normal children who receive these restrictive diets through inadvertence or because of misdiagnosis will not suffer irreparable neurological or physical damage.

* * *

[A]lthough most of this discussion has pertained to PKU, I am less interested in that rare phenomenon than in how decisions are made affecting public health and welfare. The PKU affair happens to be a well-contained example of how not to proceed. It also enables us to derive lessons from establishment workings, for there happens to be a PKU establishment.

* * *

The PKU establishment embraces lay and professional personalities in academic institutions, hospitals, public health departments, the federal government, and voluntary health agencies. It has erred, I believe, in not submitting itself to the discipline of independent critique—in not opening the channels of doubt and criticism. The principal federal agency involved is the Children's Bureau. Of course, it has been involved in PKU establishment affairs and has, I believe, committed errors of its own, but to be

critical of it on that score would be unfair. The Children's Bureau has done a tremendous job in developing clinical programs and aids in the area of mental retardation, overshadowing the PKU activity in importance.

The Children's Bureau is to be commended, in fact, for its efforts to promote constructive dialog through numerous symposia in which divergent points of view have often been expressed. Nevertheless, the Children's Bureau has been dominated as to PKU by a small group of outside program proponents who have also been the source of guidance of federal and state legislators, who have dominated the professional literature, who have advised lay voluntary groups, and who have been the main recipients of federal grants for PKU activity. I criticize none of the members of this establishment individually, but collectively there seems to be a fair case for saying that their mutual enthusiasm has led them to block outside challenges to unbridled program execution beyond the state of knowledge.

* * *

Reversal is hard to achieve in the government, because it implies lack of good judgment. This is unfortunate. As we move more deeply into the inner fastnesses of medical science, we had better be prepared to reverse gears without implications of dishonor.

* * *

What do I propose?

1. *As to mechanisms of advice:*

Any one solution, such as some independent ombudsman or office of review in the executive or legislative branches, would be insufficient. Rather, we need a return to old-fashioned scientific pluralism. We need open, constructive conflict of ideas from which truth may emerge. We should not discourage advocacy, dissidence, and special pleading. One approach is to dilute the concentration of advisory sources. The same people or program sources should not at once guide legislative and executive branches, from within and without, while also dominating voluntary and professional society channels. Let us round out our pluralisms and at least occasionally have some spirited debates over both ends and means, right out in the open.

2. *As to program choice and priorities:*

The making of choice becomes more diffi-

cult as more is learned about situations and problems. On the whole, reliance must be placed on the professional judgments of the experts and the administrators. Legislators must also play a part in choice, for they thereby bring in the popular view—provided it is really that—as opposed to the dominance of professionalism. Yet choice must be subject to criteria-based review, taking into account total needs and total resources. Thus, if PKU programs are still investigational, should we not limit their scope while resources are deployed to improvements in more prevalent areas of mental retardation?

3. *As to application of knowledge:*

Before particular disease targets are selected for widespread preventive or therapeutic application, there must first be a base of adequate knowledge derived through fundamental and controlled clinical research. Consistent with advances in clinical experience protracted pilot tests should be conducted in one or more states under controlled, scientifically modeled conditions, in order to derive adequate experience. Progressively, as wider field trials are conducted under varying conditions, independent medical judges without personal cause should evaluate progress. Then, assuming that the program demonstrates its worthiness, it should be expanded at a rate consistent with the development of adequate clinical and laboratory facilities and professional manpower.

The public should be fully informed as to whether a program is investigational or service-ready. Evaluations against criteria of benefit should be continuous.

The need for developing informational bases as prerequisites for action is just as important in all other areas of public medicine, whether in the regulation of drugs or in the extension of medical services to the public.

4. *As to legislative prescription of medical practice:*

Legislative enactments of medical practice should be limited to assuring good practice, to protecting the public against hidden or unseen external hazards, and to protecting the rights of patients, especially the incompetent. Laws cannot specify action, when individuals are biochemically and biosocially unique and when the knowledge of medicine undergoes constant change. Laws cannot substitute for the professional judgments of physicians.

* * *

NOTE

STANDARD DIET FOR PKU MAY IMPAIR INTELLIGENCE*

By producing profound malnutrition, treatment of phenylketonuria in early life with the standard low-phenylalanine diet may cause, rather than prevent, permanent intellectual impairment, a Canadian investigator reported . . . to the Society for Pediatric Research.

A more liberal allowance of phenylalanine and protein to insure satisfactory growth and development appears to result in improved functioning, said Dr. William B. Hanley, of the University of Toronto.

* * *

Dr. Hanley and co-workers in Toronto became "dissatisfied" with the results of low-phenylalanine diet therapy about two and a half years ago when they observed that nearly all phenylketonurics started on the diet in the first few months of life had poor weight gain and linear growth and some showed evidence of serious malnutrition. Moreover, ultimate I.Q.'s were not as high as had been anticipated despite early diagnosis and seemingly adequate treatment.

"Studies of children in underdeveloped countries had revealed that protein malnutrition in early infancy may produce intellectual impairment," Dr. Hanley said. "We wondered whether our treatment was producing mental retardation by too vigorous restriction of phenylalanine and protein."

When dietary therapy of PKU was introduced a decade ago the aim was to maintain fasting serum phenylalanine within a normal range of 1 to 3 mg. per 100 ml., he recalled. Subsequently values of up to 6 mg. per 100 ml. were allowed since it was felt the original limitation might be too strict.

But Dr. Hanley and associates found that 3 of 19 children put on either regimen within the first six months of life had required hospitalization for severe illness between four and nine months, showing classic signs of malnutrition, deficient growth, hypoproteinemia, and anemia. The other 16 showed less severe "but definite and prolonged evidence of malnutrition."

* * *

* *Hospital Tribune* 1, 18 (June 3, 1968). Reprinted by courtesy of *Hospital Tribune*.

[E]ffects of early malnutrition on mental development were . . . longer-lasting, Dr. Hanley said. Four are definitely retarded, eight are rated "dull normal" and two are of "borderline" intelligence. Only five are mentally normal.

* * *

b.

Who Should Participate, within What Structure, in Professional Regulation?

[I]

*Protocol for Clinical Studies to Be Approved
by the Yale Medical School Clinical
Investigation Committee (1969)**

<i>Title of project</i>	Evaluation of Drug Therapy in Hyperkinetic Behavior
<i>Chief Investigator</i>	Daniel S. Rowc, M.D.
<i>Other Investigators</i>	Frederic P. Anderson, M.D., Ethelyn H. Klatskin, PH.D., John V. Federico, M.D., Gary R. Wanerka, M.D.
<i>Description of Study</i>	1) <i>General goals and pertinence</i> 2) <i>Procedures</i> 3) <i>Possible hazards to the subjects</i>

Children with hyperkinetic behavioral disturbances have long represented a problem of management to the physician faced with their care. Previously employed pharmacological, environmental, and therapeutic approaches have not been wholly successful in management of this entity. The pharmacological approach, however, offers the best opportunity of achieving a positive impact in this area.

The goal of this study is to evaluate the effectiveness of two different drug regimens and counseling as opposed to counseling and placebo medication. The effect will be measured by the evaluation of hyperactivity, attention span, behavior, and aggressiveness before and during the course of the study.

Sixty patients between 7 and 10 years of age will be selected from the out-patient pediatric services of the Yale-New Haven Medical Center and from the educable, retarded children in classes of local school systems. The prospective patients, all of whom will be in the I.Q. range 60-80, will be evaluated by a clinic pediatrician and psychologist to adjudge whether each prospective patient fulfills the criteria for the hyperactive behavior syndrome. Patients with sei-

zure disorders, chronic renal or hepatic disease, history of allergy, or sensitivity to the benzodiazepines or amphetamines will be excluded.

The sixty patients selected for the study will be divided into three treatment groups. The groups will receive *d*-amphetamine and placebo, *d*-amphetamine and diazepam, and placebo, respectively. The study will be double blind. Patients will be seen semimonthly and evaluated for the effects of the medication. For this purpose, report forms for the physicians, parent, and teacher will be utilized. At the completion of the study period data will be statistically reviewed.

Side effects which may be anticipated with diazepam include drowsiness, ataxia, and dizziness; with *d*-amphetamine include appetite loss, irritability, increased hyperactivity, epigastric distress, and wakefulness. These will be recorded. In most instances these are dose related and may be avoided by dosage adjustment.

Why must this study be done in humans?

To assess the effect in the group most in need. Non-human subjects are not applicable to this study.

Subjects for the Study

(Approximate number, type of subject, how consent is to be gained, medical supervision).
Subjects under age 21 must have parental consent.

Sixty patients, selected from the out-patient pediatric service at the Yale-New Haven Medical Center and educable, retarded children in classes of local school systems. Consent will be gained through direct contact with the parent and explanation of the study and goals. All patients will be under the medical supervision of the pediatricians involved in the study.

* * *

PATIENT CONSENT FORM FOR PARTICIPATION IN A CLINICAL INVESTIGATION PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN HOSPITAL

Description of Project: The project being undertaken, and the one for which your child is a prospective participant, is to evaluate the use of specific drugs in the management of hyperkinetic behavior. Children with this type of behavior characteristically are those who are overactive, difficult to manage, tend to be dis-

* Reprinted by permission of the investigator who retains all rights.

ruptive in the school classroom, and have short attention spans.

Children with this pattern of activity have long represented a most difficult management problem for the physician faced with their care. Previous programs of drugs, counseling, and psychiatric management have not proved to be completely successful. At this time, we are planning to study the effects of several newer drugs employed in this area of concern.

Of course, in any study employing and evaluating medications, not all patients will be receiving the drug. In order to have a means of comparison, some patients will be receiving a placebo, or "sugar pill," which would resemble the real medication. Eventually, however, all children would benefit from any positive results which might emerge from the study. If we are able to prove that there is a benefit from the use of these medications, then, of course, all participants would be able to use the drug. During the course of the study even the physicians involved will not know which patients are actually receiving the drugs; thus there will be no bias in the interpretation of the results.

The drugs being used are both available commercially and no longer in the "experimental" stage of testing. Of course, as with any medication, there can be undesirable side effects. One of the drugs is diazepam (Valium), which on occasion can cause drowsiness, dizziness, and instability of gait; the other drug is *d*-amphetamine (Dexedrine), which on occasion can cause appetite loss, increase in overactivity, irritability, and wakefulness. In the case of both drugs, such side effects can easily be controlled simply by reducing the dosage. We will be making a careful effort to prevent any side effects from occurring.

Authorization: I have read the above and agree to the participation of _____

(name or names and how related)

in the project described above. Its general purposes, potential benefits, and possible hazards and inconveniences have been explained to my satisfaction.

Signature

Date

(Physician)

[ii]

Melvin Lewis, Audrey T. McCollum,
A. Herbert Schwartz, and Jerome A. Grunt
*Informed Consent in Pediatric Research**

* * *

In view of the difficulties involved in determining the meaning of informed consent, we suggest the following safeguards for children being considered for participation in medical research:

1. The nature of the research design and all risks to the child should be assessed by a review committee that includes pediatric investigators who are not involved in the research as well as the pediatric investigator who is to conduct the study. This will provide safeguards against the investigator's inevitable bias and gaps in knowledge.

2. The review committee should include a professional person especially equipped to assess the psychological risks to the child. This person would have to be aware of those areas of development especially vulnerable to impairment at the child's developmental stage, have the interviewing skill required for assessing the child's degree of vulnerability, and understand the kinds of stress likely to be provoked by the research procedures.

3. The investigator should have a series of personal interviews with the parents and at times with the child to build a relationship of trust, and establish an understanding of the research goals and methods and of the risks involved.

4. When the investigator lacks the skill or experience necessary for preparing the parents and the child for the research, correcting their misconceptions about it, and dealing with the child's reactions as the admission date approaches, a social worker and a psychiatrist may be called upon to help fulfill these functions, in supplementary preadmission interviews.

5. The investigator, research director, nurse, social worker, and psychiatrist should plan in advance for the child's care in the hospital since special arrangements may be required to prevent impaired development.

6. The research team should include a pediatrician, nurse, child psychiatrist, child psychologist, or social worker to provide a continuing evaluation of the psychological reactions of

* 16 *Children* 143, 148 (1969). Reprinted by permission.

the child and his parents to the research procedures and to train research personnel in the early recognition of emotional stress and ways of dealing with it.

7. The activities of all the staff members on the research team should be coordinated in regularly held interdisciplinary conferences.

8. Follow-up care should be provided to deal with whatever reactions to the research procedures may occur after the child's discharge from the hospital.

9. Parents and staff members should have an understanding of what parts of the psychological information revealed during the research are to be shared with other members of the staff and what parts will remain in confidence; and all staff members should understand the need for discretion in divulging such information.

c.

Should Research Design and Scientific Merits Be Evaluated?

Nancy Bayley

*Implicit and Explicit Values in Science as Related to Human Growth and Development**

* * *

. . . Leon Yarrow is now [studying] the effects on the infant of separation from the mother. A number of psychologists and psychiatrists hold that such separation is likely to have devastating effects on the infant's development. There are others who question the great importance to the infant of the changes in mother-figures. When there is the possibility of damage to the child as would be the case if the first-named group of theorists is correct, we do not just set up an experiment in which, say, we induce a group of mothers to exchange babies. We can, however, test the hypothesis without making such a drastic experiment. We can find conditions in which the child, by force of circumstances, is separated from his mother. What Yarrow has done is to seek out such cases and to study them by observation in their homes. Through the cooperation of adoption agencies, he is able to observe infants who live in foster care homes with the foster mother before the change to an adoptive home, and then to observe them with the adoptive mother afterward. The effect

of the child's age on the nature of his adjustment to change is studied by comparing those who were placed at different ages during the first year: before 3 months, 3 to 6, 6 to 9, and 9 to 12 months of age. The babies can also be compared according to the kinds of mother-child relations that are established, and according to their emotional adjustment in the two or three years subsequent to adoption. Another group of babies placed directly in adoptive homes, from the hospital, is being studied, as adoptive controls.

* * *

d.

Should Consent Be Supervised?

[1]

William McD. Hammon, Lewis L. Coriell, and Joseph Stokes, Jr.

*Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis**

The principal purpose of the experiment . . . was to determine whether gamma globulin, as prepared for and furnished by the American National Red Cross for measles prophylaxis, would protect against the paralytic manifestations of poliomyelitis when administered in reasonable dosage before the onset of illness. A secondary purpose was to determine, if protection were afforded, the duration of protection in the dosage selected for the experiment. . . .

* * *

This study appeared to have considerable, immediate importance, since epidemiological studies had led to no hope of control in the near future by breaking the infection chain. Furthermore, no active immunizing agent was available, and no specific therapeutic drug or antibiotic was known, while the incidence of paralytic poliomyelitis appeared to be increasing. Information obtained from animal experiments suggested strongly that human gamma globulin might give temporary protection. It was available in limited quantities and could be produced in much larger amounts. Since the effectiveness of gamma globulin in man could be determined only through actual administration to human beings and since its safety had been previously determined through use in well over one million cases of measles and hepatitis, a

* *Merrill-Palmer Quarterly* 121-126 (Spring 1956). Reprinted by permission.

* 150 *Journal of the American Medical Association* 739-747 (1952). Reprinted by permission.

human field test under suitably controlled conditions was believed to be indicated.

* * *

For reliable evaluation of results, essentially alternate controls to receive an inert, safe material resembling gamma globulin would be necessary. Only this type of test would withstand critical scientific scrutiny and be accepted universally as a final evaluation. If all volunteers were inoculated with gamma globulin, the uninoculated group could not serve as comparative controls for many reasons. Fear, motivating volunteering, would bring a higher proportion of children from areas or groups known to be most heavily exposed. Economic, social, and racial differences might readily influence response to public clinics. These and other factors would render the two groups dissimilar. Better cooperation in reporting suspected cases would probably occur among the inoculated than the uninoculated, and our own clinicians as well as physicians of the community could not entirely avoid being influenced in making a diagnosis in questionable cases if they knew that the patient had received an injection of gamma globulin. Thus, bias could not be avoided. Furthermore, among those not receiving injections at the clinics, an unknown number might receive injections of gamma globulin from others, so the control group would not be entirely uninoculated, as planned.

Almost every conceivable variation to avoid "control" inoculations was suggested and carefully considered, but had to be ruled out as endangering the success of the test. This was the most debated problem in planning, because it introduced a novel approach in evaluating immunization in man. It was readily recalled that, had typhoid and rabies vaccines been originally tested in this manner, years of uncertainty might have been saved and we might not be in our present, unenviable quandary regarding the efficacy of these immunizing procedures after a great many years of routine application. . . .

In order that no member of the team could be biased by a knowledge of what was injected and that no favoritism or yielding to pressures to obtain the active material for selected children could occur, it was decided to arrange a random distribution of all the vials when they were packed and to give each child the first unit of inoculum presenting in the box in order of serial number and packaging. All units would look alike, and the serial number of the table

would be the only means of identification. Fifty units of the same size would be packed in a box, 25 of gamma globulin and 25 of control inoculum, all numbered serially as a single series. . . . In this way gamma globulin and control groups should be comparable, and no knowledge of the type of agent used could influence the mother, physician, or consultant in reporting, hospitalizing, or making a final diagnosis, or the physical therapist in grading the degree of muscle involvement.

* * *

The consent form to be signed by the parent would be carefully worded with legal assistance. It should explain accurately the purpose and procedure of the study. It would be printed in the newspapers and read over the radio so that all parents could be fully informed and understand what they would sign before coming to the clinic. We were anxious that everyone would understand that half the children would receive control material. The text of the consent form was as follows:

FORM OF CONSENT

I have been informed that Dr. William McD. Hammon, Professor of Epidemiology of the Graduate School of Public Health of the University of Pittsburgh, with the financial support of the National Foundation for Infantile Paralysis, Inc., and with the cooperation of the _____ County, and _____ State Health Departments, has inaugurated in _____ County, _____ a project which aims at the injection of a large number of children for test purposes in connection with the study of Infantile Paralysis and its causes and remedies. For the purpose of that test, it is proposed that a solution of gamma globulin or a solution of specially prepared gelatin be injected into a buttock of each of the children. The method of identifying the substance injected into each child is such that the person administering the injection does not know which one is being used at the time. To assist this project, I hereby consent that either one of the preparations above mentioned may be injected into the buttock of my child

(Name of Child)

Signed: _____

(Father or Mother)

(Relationship to Child)

(City or Town)

Witness: _____

Date: _____

* * *

Following selection of a city for a field trial and after obtaining the support of all official agencies and medical groups, a public announcement of the decision would be made. The widest possible local publicity would be desirable at this time. Press and radio releases would be prepared in advance to insure that full and factual information be available. At a special conference of reporters, editors, radio, and television program directors from this city and any nearby larger city with significant local coverage, this material would be released and fully discussed. The date of opening the clinics, their locations, hours of operation, the age group of children to be included, and the estimated closing day of clinics would be announced. So that the scientific aspects and background of the study would be appreciated by the press, radio, and others, we would try to anticipate and answer through previously prepared and mimeographed releases all questions that might arise.

It was believed that since parents were being asked to bring their children for an unusual type of test, every attempt should be made to explain completely all scientific details of the project and to withhold nothing. National publicity would be avoided whenever possible, since it could not contribute to the success of the local study and might hinder subsequent studies in other areas. However, it was realized that wire services would pick up the story, and national publicity could not be avoided. Local leaders of the women's organizations of the community would be approached to recruit a large group of women volunteers to assist in the clinics.

* * *

The public attendance at the clinics was so much greater than expected that several changes had to be made at the end of the first day. The house-to-house canvass was called off, since it was obviously unnecessary. Since almost every syringe and needle was used on the first day, instead of half as planned, provisions had to be made to wash, repack, and autoclave all 1,800 every night. The nearest autoclaves of adequate size were in Salt Lake City, nearly 50 miles away.

Instead of running for five or six days as planned, all clinics were closed in three and one-half days, because the supply of biologicals was exhausted. . . . Hundreds of people were turned away when the clinics were closed on the fourth day. There were indications that 75 to 90 percent of the population had planned to partici-

pate and would have done so had supplies been adequate. . . .

* * *

[ii]

Liz Roman Gallese

*Medical-Ethics Panels Are Set Up to Resolve Dilemmas on Research**

* * *

In cases involving young children, especially those who are mentally retarded and unable to understand a research project, obtaining patient consent is all but impossible. . . . The consent of both young patients and their parents is often required. Yet research with such children is practically the only way to obtain certain scientific information.

The ethics committee at [the] Massachusetts General [Hospital] recently wrestled with this dilemma. Scientists know that certain types of cancer trigger a high level of calcium in the blood that can kill the patient far faster than the cancer itself. They also suspect that the amount of calcium in a person's blood may be at least partly regulated by calcitonin, a recently discovered hormone produced by the thyroid gland. This opens the possibility of using calcitonin to control calcium levels and thus greatly prolong the patient's life. Scientists also suspect that calcitonin may have other and as yet undefined therapeutic values.

But first scientists are trying to nail down the fact that calcitonin does indeed control calcium and how it does so. To prove this, the scientists need a group of normal children whose thyroids produce calcitonin and a group of children without thyroids producing this hormone so that the two groups can be compared.

Dr. Alberto Hayek, a Harvard University researcher who is working on the calcitonin study, proposed using mentally retarded children in an institution affiliated with Massachusetts General for the group without thyroids. This upset the ethics committee. During a committee meeting to consider Dr. Hayek's written proposal, members posed question after question.

"Why does he wish to use mentally retarded children?" one ethics committee member asked.

"Why use institutionalized children, who

* *The Wall Street Journal* 1, col. 6; 17, col. 3 (April 14, 1971). Reprinted by permission of *The Wall Street Journal*.

constitute a captive group?" another member asked.

"Can't other subjects be found who are intelligent enough to give consent to the study?" a third member asked.

The committee framed its questions in a letter.

In a written reply to the committee and in a later interview, Dr. Hayek said other subjects aren't suitable.

"Only one in every 30,000 babies is born without a thyroid gland and more than half of these have an IQ far less than 90. The result is that many of the members of this very tiny group are in institutions for the mentally retarded. There is virtually no place else to find them."

Dr. Hayek also emphasized that the study, while tedious, would pose very little risk to the children. The project involves three-hour calcium infusions into the bloodstream and blood samples taken every half hour to check calcitonin levels so doctors can assess the relationships between the two chemicals.

The ethics committee finally agreed to approve the project but only after appointing a physician-advocate—a move that is increasingly being used at research hospitals.

The physician-advocate, who is not one of the researchers, is named to represent the children's interests. His duty is to make sure that full information is given to parents when their consent is asked, that undue risks are avoided and that every safety precaution available is taken. He can withdraw the patients he represents from a research project if he thinks they are taking too great a risk.

* * *

NOTE

THE MASSACHUSETTS GENERAL HOSPITAL HUMAN STUDIES—GUIDING PRINCIPLES AND PROCEDURES*

During the course of the first years that this small guide was put to use, it became apparent that the problem of protecting the rights and welfare of children and other incompetent individuals had not been given sufficient attention. . . . As a result and in line with the intent of the Trustees' Advisory Committee on Research and the Individual . . . the guidelines have been re-

vised by the Committee in agreement with suggestions by the Committee on Research and its Subcommittee on Human Studies.

* * *

A. *Studies for the benefit of others, with no direct benefit for the subject involved*

* * *

3. When a procedure is not for the diagnosis or treatment of his own condition, this must be made clear to the patient. When the subject of the study is a child or an incompetent individual, informed consent must be obtained from parents or legal guardian. If the subject has reached an age of understanding, every effort must be made to obtain his consent as well. In this context a subject under sixteen years of age will be considered a child.

* * *

6. A safeguard is to be found in the practice of having at least two professionally qualified persons involved in experimental situations: First there is the physician or other person concerned with the care of the subject; his primary interest is the subject's welfare. It is of utmost importance in experimental situations involving children or incompetent individuals that this person serve as the subjects' advocate. Second there is the investigator whose interest is the sound conduct of the investigation. Perhaps too often a single individual attempts to encompass both roles.

* * *

B. *Experimental diagnosis or therapy for the direct benefit of the patient whether or not there is benefit for others*

* * *

5. It is recognized that certain forms of psychological testing of achievement may involve subjects who are children and that in such testing, informed consent may unduly bias the result. Since these tests as a rule are for the benefit of the subject, strict adherence to the requirement for informed consent may not be justified. In times of uncertainty, review by the investigator's peers would be in order.

C. *Volunteers, normal and patient*

* * *

3. An individual cannot soundly volunteer for an experiment unless he first understands

* Boston: The Massachusetts General Hospital 6, 8-9, 11-12 (2d ed., 1970). Reprinted by permission.

what he is volunteering for, as well as the degree of inconvenience and risk involved. Here again the problems raised by studies of normal children must be considered with special care. Informed consent of parents or guardian and, if feasible, of subjects must be obtained. If such would unduly bias the study or if other uncertainties exist, review by the investigator's peers would be in order.

e.

Should Harm Be Assessed?

[i]

Ross G. Mitchell

*The Child and Experimental Medicine**

* * *

... When deciding whether an experiment is justifiable, the old question: "Would you subject your own child to this?" is still a good yardstick for most moderately minded people. It should be remembered, however, that some zealots may be prepared to submit their own families to indignities which the average man would consider excessive. The experiment referred to above, in which Oliver injected his own son with a crude extract of endocrine glands, is a well-known example.

* * *

[ii]

C. Henry Kempe

The Battered Child and the Hospital†

* * *

At least 700 children are killed every year in this country by their parents or parent surrogates. Thousands more are permanently injured, physically or mentally. In the week before this article was prepared, nine young victims of serious abuse were seen here at Colorado General Hospital, and it is a rare week indeed in which four or five new cases do not come to our attention. From some of our early work on case-finding, it is our impression that at least 15 percent of all children under age five who come into the emergency room fall into the battered category. Data such as these suggest that the problem of the abused child and the

abusing parent is one of the most important "epidemic" diseases in the U.S.

* * *

3.

In Reviewing Decisions and Consequences

a.

Through Public Scrutiny?

Statement of Representative

Cornelius E. Gallagher—

*September 29, 1970**

* * *

I want to welcome you here today to our hearing into Federal responsibility in promoting the use of amphetamines to modify the behavior of grammar school children. The indications are that these drugs are now being widely employed to ameliorate the effects of what is called minimal brain dysfunction (MBD) in children. One of our witnesses today has been quoted as saying that the use of this type of therapy will "zoom" from its current usage in approximately 200,000 to 300,000 American children today.

These amphetamines, such as Dexedrine and Ritalin, apparently do not act the same in children as they do in young adults, according to some authorities. Instead of being "speed" and accelerating the individual's activity pattern, proponents of the program claim that amphetamines slow down the child and make him controllable both in the classroom and at home. This use of stimulants to calm children termed hyperactive is called the "paradoxical effect" and it is but one of the many paradoxes which this hearing is designed to explore. Let me list a few contradictory implications.

First, and a distressingly obvious paradox, is the effect of accelerating this use of amphetamines on our extensive national campaign against drug abuse. From the time of puberty onward, each and every child is told that "speed kills" and that amphetamines are to be avoided. Yet, this same child has learned that Ritalin, for example, is the only thing which

* 1 *British Medical Journal* 722, 725-726 (1964). Reprinted by permission.

† *Hospital Practice* 44 (October 1969). Reprinted by permission.

* Materials in this section are reprinted from *Hearings on Federal Involvement in the Use of Behavior Modification Drugs on Grammar School Children before a Subcommittee (The Right to Privacy Inquiry) of the House Committee on Government Operations*, 91st Congress, 2d Session 1-74 (1970).

makes him a functioning member of the school environment and both his family and his doctor have urged the pills on him.

* * *

Second, I am very concerned [that] the fact that the child . . . has been undergoing drug therapy becomes a permanent part of the child's school record, to be recalled and available to anyone who wishes to see it. We may well break the child's MBD-induced hyperactive behavior pattern, but by freezing on the record the fact that it took drugs to do it, we cast a cloud of suspicion over the child's future. . . .

A third paradoxical effect is directly related to the jurisdiction of this subcommittee of the Committee on Government Operations. We are charged with the responsibility of determining whether Federal funds are spent in an economical manner and whether the operations of Federal agencies are conducted efficiently. We have learned that Federal funds have been used to support various experimental programs and studies concerning the use of drugs to treat learning disabilities in children. Assisted by this infusion of tax dollars, it has become apparent that biochemical medication and an alteration of the learning environment is considered as part of a "new wave" approach to public education in the United States by many persons both in and out of the Government.

Not only has this issue never been subjected to full public discussion and understanding, but I am deeply concerned about the possibility that an overreliance on drug therapy could spread far beyond its apparently valid applications and thus denigrate the novel learning methods which have also been explored by the use of Federal funds. In so many areas which the Privacy Subcommittee has explored, we have seen a dependence on quick and inexpensive solutions offered by the new technology without adequate attention being paid to the slower and perhaps more costly methods which would preserve the sanctity of human values and the precious resources of the human spirit.

This point is made well in a telegram I received recently from a parent who lists 10 drugs given his child in one year. He says, "Testing proved child creatively gifted, no classroom available. My state has hundreds of gifted and creative children on prescribed drugs as result of refusal to provide proper education facilities."

And here we come to what is perhaps the

greatest paradox in this entire program and why I am convinced that public discussion must take place before the use of behavior modification drugs "zooms." As the father of four, I am well aware of the occasional frustrations which come from the fact that children do not simply sit quietly and perform assigned tasks. Based on my personal experience, I believe that children learn with all their senses, not just with their eyes and ears. For childhood is an exploratory time and the great energy of children propels them into situations which may look frivolous or counter-productive to more restrained adults, but which are the sum and substance of the child's learning experience. I do not think I am overstating the case when I say that the learning environment for the young child is the total environment and every experience is a learning experience.

Obviously, this unstructured passion for all the events in a child's world is regarded as unruly and disruptive, particularly in overcrowded classrooms. I fear that there is a very great temptation to diagnose the bored but bright child as hyperactive, prescribe drugs, and thus deny him full learning during his most creative years.

While we intend to hear from the Food and Drug Administration about the legal guidelines for the use of such drugs in children and the warnings they require to be printed on the packages, I am deeply concerned about the mislabeling of the child and packaging an ill-conceived program as an answer to our ills in the education of our children.

In addition, are there reliable medical guidelines which can be universally and absolutely applied to separate the normally active child from a clinically diagnosed hyperactive child?

* * *

Public men must investigate the uses of science and research and decisions must not be made solely on the expertise of those connected with a new technology. In the past we have tried to excise the potentially toxic elements from the beneficial tonic of technology; that is the purpose of this hearing today.

Before calling our first witness, I want to place in the hearing a portion of the preliminary report I received last Friday, September 25, from the General Accounting Office. This shows almost \$3 million in Federal funds have been expended solely by the National Institute of

Mental Health in grants in the conduct of research of learning disabilities and, as part of each study, behavior modification through the use of drugs.

This document, focusing only on grant awards by the NIMH of the Department of HEW shows nine grants totaling nearly \$3 million. Of that figure, the General Accounting Office reports \$965,000 has been granted since the beginning of 1970.

* * *

NOTES

NOTE 1.

TESTIMONY OF DR. THOMAS C. POINTS,
DEPUTY ASSISTANT SECRETARY FOR HEALTH
AND SCIENTIFIC AFFAIRS, HEW, AND
DR. RONALD LIPMAN, CHIEF, CLINICAL
STUDIES SECTION, FDA—SEPT. 29, 1970

* * *

DR. POINTS: Hyperkinesis is recognized by the medical community as one of the more common behavior disorders of childhood which, when diagnosed by a competent physician or medical team, lends itself to safe and effective drug treatment, given, of course, adequate medical supervision. While this treatment should not be "forced" upon the parent, neither should it be denied to those children whose parents willingly give permission for such treatment. In most cases, proper drug treatment will provide symptomatic relief and will reduce the personal unhappiness of the child while enabling him to profit from the educational experience and from other forms of therapy such as psychotherapy, family counseling, and remedial reading.

While it seems clear that there is some diagnostic heterogeneity in children labeled as hyperkinetic, this syndrome, in addition to the key symptom of overactivity, usually includes many of the following symptoms: short attention span, low frustration tolerance, aggressive-hostile behavior, and hyperexcitability. The syndrome is frequently accompanied by impairment in perception, conceptualization, language, and memory. A neurological examination typically reveals minimal signs of neurological impairment.

Most clinicians feel that the hyperactivity per se is outgrown by adolescence. However, the few follow-up studies that have been reported suggest that hyperkinetic children who have not received treatment and/or whose treatment

has been limited to either individual or group psychotherapy show as adults, a disproportionately high incidence of diagnosed psychoses and sociopathic personality. Conversely the percentage of hyperkinetic children whose adjustment was characterized as evidencing "no psychiatric disease" (21 percent) was quite low relative to a matched control group (60 percent). It should be noted that the hyperkinetic children comprising this sample of roughly 250 children were not mentally retarded, nor were they psychotic at the time of the original diagnosis.

* * *

The present consensus of expert opinion regarding the treatment of hyperkinetic children is that Ritalin (methylphenidate) and Dexedrine (dextroamphetamine) are the drugs of choice. Although Ritalin and Dexedrine are considered stimulants, they have a calming and quieting effect in hyperkinetic children in striking contrast to their exciting, stimulating effect in adults. Given under competent medical supervision, these drugs are regarded as safe and clinically effective in a very high percentage of hyperkinetic children. While children report that they feel better when receiving these drugs, we are aware of no evidence to suggest any feeling of euphoria and no evidence to suggest that these drugs are addicting in children.

The therapeutic efficacy of the stimulant drugs is evidenced both behaviorally (there is reduced overactivity, impulsiveness, temper outbursts, aggressiveness) and on such cognitive tasks as arithmetic, spelling, paired-associate learning, recognition, maze learning, etc. This improvement is obvious to the physician, parents, teachers, peers, and to the child himself. Moreover, there is evidence to suggest that the stimulant drugs do not "dull" the child or decrease his activity level in appropriate situations such as free play; rather these drugs enable the child to sit still and attend in those situations, such as in the classroom, where this behavior is both appropriate and, indeed, necessary if the child is to profit from the education experience and not become a school dropout.

* * *

MR. GALLAGHER: How do you select the children?

DR. LIPMAN: Children are typically referred either from the report of the parent seeking help for the child, from the child's physician

or pediatrician, or on the recommendation of a teacher and then the child may go through the route of seeing the school psychologist and then being referred on.

None of these studies are done directly in the school system.

MR. GALLAGHER: What qualifications would a teacher have to make this kind of diagnosis to nominate a child for this kind of study?

DR. LIPMAN: I think typically what may happen is the teacher will see that the child is extremely inattentive in class, extremely restless. The child is not performing up to the level of intellectual ability that the child has.

The child seems personally unhappy, unable to get along with his or her peers. The child is continually in motion, continually getting into things, and in general their academic performance does not come up to what their intellectual abilities would suggest it should.

MR. GALLAGHER: Couldn't it also be similarly a result of a poor teacher or a bright child who is beyond the point of concentration because the class is dull?

DR. LIPMAN: I would say that the role of the teacher is not to diagnose the medical syndrome.

MR. GALLAGHER: But that is where the child begins the treatment, diagnosed by some teacher, isn't that a fact? It comes from the public school system, as opposed to a parent who may take a child to a doctor?

DR. LIPMAN: I think the role of the teacher is really a referral function. That the diagnosis should be properly made by a skilled medical person or a medical team.

* * *

MR. GALLAGHER: . . . The thing in these programs that troubles me is the number of children involved. How many children would you say today are being treated—we have seen quoted a figure of some 200,000 to 300,000 children. Would that be correct? More? Less?

DR. LIPMAN: Well, if you restrict it to amphetamine and to Ritalin, I would say that figure is probably high. It would probably be closer to about 150,000 to 200,000. That is just a rough estimate. . . .

* * *

MR. GALLAGHER: Then further you state, "I think the results of the last few years of research will soon reach the nation's doctors. The pediatricians will begin using them." In effect,

what will happen is it will zoom as word of its success spreads throughout the nation's medical community.

Where do you think it will zoom to 5 years from now?

DR. LIPMAN: I didn't use the term "zoom." I said it would probably increase.

MR. GALLAGHER: I think your enthusiasm led to the word "zoom."

DR. LIPMAN: I guess really some evidence that we have indicates that child psychiatrists tend to be using more of the stimulant drugs than pediatricians. I think the more recent studies that are well controlled and meet scientific standards have strengthened the earlier clinical reports and I think as the scientific validity of the treatment of children with hyperkinesis with the stimulant drugs as part of their total treatment program becomes better known and better accepted by the medical community, that there probably will be some increase. Now, where it will go, I don't know.

MR. GALLAGHER: Do you think that it should be allowed to increase or zoom or whatever word we want to use, on the basis of the follow-up studies which involve, as I recall, some 250 children out of 200,000 or 150,000 or 300,000, whatever is the correct figure? Are we justified at this point in further funding the use of amphetamines for children?

DR. LIPMAN: . . . I think we need more knowledge in these areas and I think the studies that we are currently supporting are directed to developing that knowledge.

* * *

MR. GALLAGHER: If we don't have it, then should the program be allowed to grow? This is one of the points of our inquiry. If there is not this amount of scientific dedication around at this time, why are we allowing this to grow in the proportion that it appears—to use your own words here, whatever they indicate—if we don't have any real follow-up studies in light of all of the evidence that we do have of the effect of the drug culture on American children today?

DR. LIPMAN: Well, the follow-up study by Connors which is the only one I can really talk to with any—

MR. GALLAGHER: Yes, but Dr. Connors has been involved in this for some time. He is obviously a dedicated scientist to this thing. Where do we have some other dedicated scientist who may question this? This is the point. An adversary development may well produce a more

valid opinion, no matter how dedicated the people may be. Are we doing any of that before we begin to zoom?

* * *

MR. GALLAGHER: In these studies that you have concluded and Dr. Conners' study, what is the addiction percentage of children in these programs, or the dependency percentage? Say out of 150,000 children?

DR. LIPMAN: As I mentioned, Mr. Gallagher, the results of Dr. Conners' study are still preliminary, in the first 67 cases he examined, there have been no instances of diagnosed alcoholism or drug addiction.

MR. GALLAGHER: Sixty-seven out of 150,000. That is all we have looked at? That is not a real basis to give additional millions of dollars to these programs, if all we know is 67, and when the whole bulk of the medical industry is trying to tell us, and all parents are trying to say, that amphetamines are so widely used they become the basis of addiction.

* * *

MR. WYDLER: I want to go back to something more fundamental here so I can get a point clear in my mind.

We are giving some school children these drugs. What is the purpose of it?

Is it to make that child learn better or more?

Is it to make it easier for his classmates to learn more because he becomes more amenable to the learning process and less disruptive, or is it to help the teacher possibly control the class?

For what purpose are we giving these drugs to children in school? . . .

DR. POINTS: . . . It is mainly to improve their learning.

* * *

MR. WYDLER: What evidence do we have that that has worked?

DR. POINTS: There are several reports over the years that in these true hyperkinetic children, their arithmetic improves, and so forth.

These true hyperkinetic diagnosed children, treated with these drugs, have increased their learning capacities and improved their social adjustment.

* * *

MR. ROSENTHAL: . . . What percentage of our children suffer from MBD?

DR. LIPMAN: The estimates we have are

from 3 to 10 percent of those up to 12 years of age.

* * *

NOTE 2.

STATEMENT OF JOHN HOLT,
EDUCATIONAL CONSULTANT AND
LECTURER AT HARVARD UNIVERSITY—
SEPTEMBER 29, 1970

One of my concerns has been the lack of real knowledge as to the nature and effects of the use of these drugs. What actually happens when a child is given these drugs? A mother brings a child to a doctor and says, "Doctor, my child is doing this or that, he won't sit still at meals, he fights with other children, he doesn't pay attention to me when I talk, et cetera, et cetera." Does the doctor himself observe any of this behavior? He does not. Does he have any way of knowing the history of the child and the mother, whether there is anything in her way of dealing with the child that might cause the child's behavior? He does not.

Does he fulfill his minimum responsibility as a physician by giving the child a thorough enough physical examination to be reasonably sure that there is not some other somatic cause for the child's behavior—bad hearing or sight, other body malfunctions, muscular or nervous injury, tension, pain, hypoglycemia, protein or vitamin deficiency, allergies, glandular disturbances? In the cases I have heard of, he does not. Does he test in any way the hypothesis that it might be something other than brain damage in the child that is causing the mother to describe him as she does? For the most part, he does not.

Might not one of the causes be the fact that we take lively, curious, energetic children, eager to make contact with the world and to learn about it, stick them in barren classrooms with teachers who on the whole neither like nor respect nor understand nor trust them, restrict their freedom of speech and movement to a degree that would be judged excessive and inhuman even in a maximum security prison and that their teachers themselves could not and would not tolerate? Then, when the children resist this brutalizing and stupefying treatment and retreat from it in anger, bewilderment, and terror, we say that they are sick with "complex and little-understood" disorders, and proceed to dose them with powerful drugs that are indeed complex and of whose long-run effects we know little or nothing, so that they may be more ready to do the asinine things the schools ask them to do.

* * *

Given the fact that some children are more energetic and active than others, might it not be easier, more healthy, and more humane to deal with this fact by giving them more time and scope to make use of and work off their energy?

In addition to the educational questions, there are two other areas that we must consider. First, the social response of the child, and second, the kinds of pressure that the parents are subjected to.

In the first instance, what I think we can say, and with great certainty, is that if we think a child is strange, treat him as if he were strange, and tell him he is strange, he will begin to think of himself as strange and will act more and more strangely. I have known some such children myself. They often talked and acted as if they had a license to act crazy, to do what other children were embarrassed or ashamed or forbidden to do. This, in turn, added to their reputation of strangeness, and so around in a vicious circle.

Further, in a community where parents are under enormous pressure to have their children look well and do well, in school and everywhere else, where people justify their lives through their children's accomplishments, the parents of these children are out of the rat race, off the hook. Other people might have to agonize—"What have I done? What must I do?"—when their son or daughter has failed in school, misbehaved, and broken windows. But not these other parents, for they have the perfect answer—their child has a medical label, so it is not their fault, there is nothing for them to do about it, and how lucky it is that there are these experts here to look after their poor darlings. Everyone is taken care of, except, of course, the child himself, who wears a label which to him reads clearly enough "freak," and who is denied from those closest to him, however much sympathy he may get, what he and all children most need—respect, faith, hope, and trust.

* * *

NOTE 3.

TESTIMONY OF DR. JOHN E. PETERS,
CHILD STUDY CENTER, UNIVERSITY OF
ARKANSAS MEDICAL CENTER—
SEPTEMBER 29, 1970

* * *

MR. GALLAGHER: . . . What we are really doing is looking at the total effect on our children.

DR. PETERS: My concern is not the general-

ity of our children but these particular children that these parents bring to me. This is my concern.

MR. GALLAGHER: We have a broader responsibility to the children of our country. What a doctor recommends is the doctor's business, but not when our government is sponsoring it.

* * *

MR. GALLAGHER: Do you feel the diagnostic procedure used today is sufficient and adequate?

DR. PETERS: I think it is clear to us, particularly in, say, the middle-class home where the nutrition and the psychological environs have been what we might call healthy. I think it sometimes is not clear in the culturally deprived. We do not know which it is.

MR. GALLAGHER: But you feel that you can at least detect it and properly diagnose it as this, as MBD. Can a country doctor do this?

DR. PETERS: If I had the chance to teach him, yes.

* * *

MR. GALLAGHER: In your judgment then, is more research required in this area or do you feel we have adequate knowledge now to properly train and carry out the treatment?

DR. PETERS: Well, I think we have adequate knowledge to treat as we are now, but I think we need much more research because we need to know much more about what is going on in the brain, what is happening in these children, what is different about them, how the medication is affecting them, and more than anything we need other educational approaches as ways of handling them too.

* * *

b.

Through Professional Evaluation?

[i]

*Report of the Conference on the Use of
Stimulant Drugs in the Treatment of
Behaviorally Disturbed Young School Children**

On January 11–12, 1971, the Office of Child Development and the Office of the Assistant Secretary for Health and Scientific Affairs, Department of Health, Education, and Welfare, called a conference to discuss the use of stim-

* Daniel X. Freedman, M.D., Chairman. Washington, D.C.: Department of Health, Education, and Welfare (1971).

ulant medications in the treatment of elementary school-age children with certain behavioral disturbances. In convening the conference, the Office of Child Development was aware of public concern about the increasing use of stimulant medications (such as dextroamphetamine and methylphenidate) in treating so-called hyperkinetic behavior disorders. Were these drugs—so widely misused or abused by adolescents and adults—truly safe for children? Were they properly prescribed or were they used for youngsters who, in fact, need other types of treatment? Is emphasis on medications for behavior disorders misleading? Might this approach tempt many to oversimplify a complex problem, leading to neglect of remedial social, educational or psychological efforts on the part of professionals, parents, schools and public agencies?

In order to clarify the conditions in which these medications are beneficial or harmful to children, to assess the status of current knowledge, and to determine the best auspices for administering these drugs to children, a panel of fifteen specialists was invited to meet in Washington. The panelists were from the fields of education, psychology, special education, pediatrics, adult and child psychiatry, psychoanalysis, basic and clinical pharmacology, internal medicine, drug abuse and social work. The panel's task was to review the evidence of research and experience and to prepare an advisory report for professionals and the public.

* * *

We know little about definitive causes. The disorder has been ascribed to biological, psychological, social or environmental factors, or a combination of these. There is speculation that the core set of symptoms—those affecting control of attention and motor activity—may have their origin in events taking place before the child is born, or during the birth process, or they may be related to some infection or injury in early life. The neurological and psychological control of attention is an important but incompletely researched topic, as are the nutritional, perinatal and developmental factors. Thus, in many instances, it is not yet possible even to speculate as to original causes.

Usually, the excessive activity and attentional disturbances are less apparent after puberty. Specialists citing experience and some fragmentary research data believe that treatment enables many to lead productive lives as adults, while severely afflicted children who remain un-

treated may be significantly at risk for adult disorders. Extensive research is still required on these points. Because the ages of 5 to 12 are crucial to the child's development and self-image, treatments which permit the child to be more accessible to environmental resources are warranted and useful.

In diagnosing hyperkinetic behavioral disturbance, it is important to note that similar behavioral symptoms may be due to other illnesses or to relatively simple causes. Essentially healthy children may have difficulty maintaining attention and motor control because of a period of stress in school or at home. It is important to recognize the child whose inattention and restlessness may be caused by hunger, poor teaching, overcrowded classrooms, or lack of understanding by teachers or parents. Frustrated adults reacting to a child who does not meet their standards can exaggerate the significance of occasional inattention or restlessness. Above all, the normal ebullience of childhood should not be confused with the very special problems of the child with hyperkinetic behavioral disorders.

The diagnosis is clearly best made by a skilled observer. There unfortunately is no single diagnostic test. Accordingly, the specialist must comprehensively evaluate the child and assess the significance of a variety of symptoms. He considers causal and contributory factors—both permanent and temporary—such as environmental stress. He distinguishes special dysfunctions such as certain epilepsies, schizophrenia, depression or anxiety, mental retardation or perceptual deficiencies. The less severe and dramatic forms of hyperkinetic disorders also require careful evaluation. Adequate diagnosis may require the use not only of medical, but of special psychological, educational and social resources.

* * *

We will now turn to various concerns about hazards and abuses when stimulant medications are used for children. For example, concern has been expressed that the medical use of stimulants could create drug dependence in later years or induce toxicity. This subject touches on the rights of the child to needed treatment, as well as risks to both the child and the public, and requires continued intensive scrutiny.

One should not confuse the effects of intravenous stimulants and the high dosages used by drug abusers with the effects or the risks of the low dosages used in medical therapy. In the dosage used for children, the questions of acute or

chronic toxicity noted in the stimulant abuser are simply not a critical issue. Unwanted mental or physical effects do rarely appear in children; cessation of therapy or adjustment of dosage quite readily solves the problem.

Thirty years of clinical experience and several scientific studies have failed to reveal an association between the medical use of stimulants in the pre-adolescent child and later drug abuse. Physicians who care for children treated with stimulants have noted that the children do not experience the pleasurable, subjective effects that would encourage misuse. They observe that most often the child is willing to stop the therapy, which he views as "medicine." Thus, the young child's experience of drug effects under medical management does not seem to induce misuse. The medical supervision may "train" him in the appropriate use of medicines. . . .

* * *

It is sometimes suggested that treated children may not be able to learn normal responses and master adjustments to the stresses of everyday life. These fears are understandable but are not confirmed by specialists who have experience with the conditions and the situations in which medications are properly used. For the correctly diagnosed child, these medications—if they work at all—facilitate the development of the ability to focus attention and to make judgments in directing behavior. Such children can acquire the capacity to tolerate and master stress. The medications, in these circumstances, help "set the stage" for satisfactory psychological development.

The hyperkinetic behavioral disturbance is a form of disorganization that creates great stress in the afflicted child. The use of therapeutic stimulants for this disturbance should not be equated with the misuse of medication aimed at allowing a normal child or adult to avoid or escape the ordinary stresses of life.

Under no circumstances should any attempt be made to coerce parents to accept any particular treatment. As with any illness, the child's confidence must be respected. The consent of the patient and his parents or guardian must be obtained for treatment. It is proper for school personnel to inform parents of a child's behavior problems, but members of the school staff should not directly diagnose the hyperkinetic disturbance or prescribe treatment. The school should initiate contact with a physician only with the parents' consent. When the parents do give their approval, cooperation by teach-

ers, social workers, special education and medical personnel can provide valuable help in treating the child's problem.

* * *

Pharmaceutical companies producing stimulants or new medications which may become useful for hyperkinetic disorders have a serious obligation to the public. These medicines should be promoted ethically and *only* through medical channels. Manufacturers should not seek endorsement of their products by school personnel. In the current climate, society can best be served if industry refrains from any implicit urging that nonspecialists deal with disorders and medications with which they are unfamiliar. Professionals and the news media can play useful roles by not pressing for treatments in advance of their practical availability.

Our society has not as yet found complete solutions to the problem of the delivery of special health care. When available treatments cannot be confidently and appropriately delivered by physicians, they are perhaps best withheld until such treatments can be provided—especially with milder dysfunctions. This is not to say that severely afflicted hyperkinetic children should not or cannot receive available medical treatment. But until systems of continuing professional education and ready access to consultants are financed and perfected, some judgment about the pace at which unfamiliar treatments can be widely fostered is required. Finally, we must recognize that it is not only the scarcity of trained personnel, but factors such as poverty and inadequate educational facilities which prevent accessibility to individualized treatment.

In preparing this report, the committee was repeatedly struck by our lack of information in many crucial areas. The facts are that children constitute well over half our population, but receive a disproportionately low share of skilled research attention. We have noted the difficulties in arriving at accurate methods of diagnosis and the importance of launching careful longitudinal and follow-up studies. The investigation of causal factors lags. Such factors as perinatal injury, environmental stress or the development of the neurological and psychological controls of attention require study. Variations in different socioeconomic and ethnic groups must be considered in order to arrive at better definitions of behavior properly regarded as pathological. All such research efforts would have aided us in assessing the numbers of affected children and in recom-

mending designs for more effective treatment programs.

Clinical pharmacologists have repeatedly found that drugs may act differently in children than in adults. To use medicines of all kinds effectively in children, more specialists must be trained in drug investigation—pharmacologists who can develop basic knowledge about the action of drugs in the developing organism. There is the obvious need for better and more precisely targeted drugs for the whole range of severe childhood behavior disorders. This requires intense research and training efforts. Such efforts provide the means for developing, testing and delivering better treatment programs. There is a similar need for research in the techniques of special education and also a need to make these techniques available to children who can benefit. It would appear to be a sound federal investment to conduct such research and training.

In summary, there is a place for stimulant medications in the treatment of the hyperkinetic behavioral disturbance, but these medications are not the only form of effective treatment. We recommend a code of ethical practices in the promotion of medicines and candor, meticulous care and restraint on the part of the media, professionals and the public. Expanded programs of continuing education for those concerned with the health care of the young, and also sustained research into their problems are urgently needed.

* * *

[ii]

Stephen Goldby

*Experiments at the Willowbrook State School**

You have referred to the work of Krugman and his colleagues at the Willowbrook State School in three editorials. In the first article the work was cited as a notable study of hepatitis and a model for this type of investigation. No comment was made on the rightness of attempting to infect mentally retarded children with hepatitis for experimental purposes, in an institution where the disease was already endemic.

The second editorial again did not remark on the ethics of the study, but the third sounded a note of doubt as to the justification for extending these experiments. The reason given was that some children might have been made more susceptible to serious hepatitis as the result of the

administration of previously heated icterogenic material.

I believe that not only this last experiment, but the whole of Krugman's study, is quite unjustifiable, whatever the aims, and however academically or therapeutically important are the results. I am amazed that the work was published and that it has been actively supported editorially by the *Journal of the American Medical Association*. . . .

* * *

. . . Is it right to perform an experiment on a normal or mentally retarded child when no benefit can result to that individual? I think that the answer is no, and that the question of parental consent is irrelevant. In my view the studies of Krugman serve only to show that there is a serious loophole in the Draft Code [of the World Medical Association], which under General Principles and Definitions puts the onus of consent for experimentation on children on the parent or guardian. It is this section that is quoted by Krugman. I would class his work as "experiments conducted solely for the acquisition of knowledge," under which heading the code states that "Persons retained in mental hospitals or hospitals for mental defectives should not be used for human experiment." Krugman may believe that his experiments were for the benefit of his patients, meaning the individual patients used in the study. If this is his belief he has a difficult case to defend. The duty of a pediatrician in a situation such as exists at Willowbrook State School is to attempt to improve that situation, not to turn it to his advantage for experimental purposes, however lofty the aims.

* * *

If Krugman and Giles are keen to continue their experiments I suggest that they invite the parents of the children involved to participate. I wonder what the response would be.

NOTES

NOTE 1.

THE EDITORS OF THE LANCET
REPLY TO GOLDBY*

Dr. Goldby asks *The Lancet* a question it ought to have faced long ago. The journal's eagerness to discuss all the events in the elucidation

* 1 *The Lancet* 749 (1971). Reprinted by permission.

* 1 *The Lancet* 749 (1971). Reprinted by permission.

tion of the spread of hepatitis left it exposed to these criticisms, which we accept. The Willowbrook experiments have always carried a hope that hepatitis might one day be prevented there and in other situations where infection seems almost inevitable; but that could not justify the giving of infected material to children who would not directly benefit. Dr. Krugman and Dr. Giles argue that "the artificial induction of hepatitis implies a 'therapeutic' effect because of the immunity which is conferred." It is hard to accept that view, even when applied to a school where a very high proportion of children will, in existing conditions, be infected anyway.

NOTE 2.

SAUL KRUGMAN
EXPERIMENTS AT THE
WILLOWBROOK STATE SCHOOL*

Dr. Stephen Goldby's critical comments about our Willowbrook studies and our motives for conducting them were published without extending us the courtesy of replying in the same issue of *The Lancet*. Your acceptance of his criticisms without benefit of our response implies a blackout of all comment related to our studies. This decision is unfortunate because our recent studies on active and passive immunization for the prevention of viral hepatitis, type B have clearly demonstrated a "therapeutic effect" for the children involved. These studies have provided us with the first indication and hope that it may be possible to control hepatitis in the institution. If this aim can be achieved, it will benefit not only the children, but also their families and the employees who care for them in the school. It is unnecessary to point out the additional benefit to the world-wide populations which have been plagued by an insoluble hepatitis problem for many generations.

* * *

... Viral hepatitis [at Willowbrook] is so prevalent that newly admitted susceptible children become infected within 6 to 12 months after entry in the institution. These children are a source of infection for the personnel who care for them and for their families if they visit with them. We were convinced that the solution of the hepatitis problem in this institution was dependent on the acquisition of new knowledge leading to the development of an effective immunizing

agent. The achievements with smallpox, diphtheria, poliomyelitis and more recently measles represent dramatic illustrations of this approach.

It is well known that viral hepatitis in children is milder and more benign than the same disease in adults. Experience has revealed that hepatitis in institutionalized, mentally retarded children is also mild, in contrast with measles which is a more severe disease when it occurs in institutional epidemics involving the mentally retarded. Our proposal to expose a small number of newly admitted children to the Willowbrook strains of hepatitis virus was justified in our opinion for the following reasons: 1) they were bound to be exposed to the same strains under the natural conditions existing in the institution, 2) they would be admitted to a special, well-equipped and well-staffed unit where they would be isolated from exposure to other infectious diseases which were prevalent in the institution; namely, shigellosis, parasitic infections and respiratory infections. Thus, their exposure in the hepatitis unit would be associated with less risk than the type of institutional exposure where multiple infections could occur; 3) they were likely to have a subclinical infection followed by immunity to the particular hepatitis virus; and 4) only children with parents who gave informed consent would be included.

The statement by Dr. Goldby accusing us of conducting experiments exclusively for the acquisition of knowledge with no benefit for the children cannot be supported by the true facts.

NOTE 3.

JOAN P. GILES
HEPATITIS RESEARCH AMONG
RETARDED CHILDREN*

No man has yet known absolute right or absolute wrong. We are grateful to those who would have us review, to examine our ethics. Let us go back.

The institutional problem does not begin with endemicity and its morbid toll. It begins with heredity, pre- and postnatal infection, pre- and postnatal trauma. So do its ethics. The compounding of moral decisions that precede institutionalization gives us pause. The geneticist, weighing adverse chance with fact and figures, advises that a handicapped child should not be conceived; the parents, informed, accept or re-

* 1 *The Lancet* 966-967 (1971). Reprinted by permission.

* 1 *The Lancet* 1126 (1971). Reprinted by permission.

ject such advice. The therapeutic abortionist, equally fundamental, equally weighing adverse chance with fact and figures, advises that a handicapped fetus should not be born; the parents, informed, accept or reject such advice. The obstetrician, knowledgeable though fallible, makes decisions according to his best judgment: the parents, informed, accept or defer to his decisions. The pediatric surgeon must do the same, weighing knowledge and success against adverse chance; the parents, informed, accept or reject his advice. The physician, religious leader or social worker who advises removal of the retarded child from the home his presence disrupts must weigh the repercussions of moral responsibility. The parents who accept this advice must answer to their conscience. In each case the skilled, the knowledgeable physician, informs, advises; in each case, from before conception to day of admission to an institution, it is the parents who ultimately decide: an awesome precedent. The physician does not make the moral judgment. He stands by, ultimately human, to accept or reject parental decision. If he cannot accept, he refers. If he accepts, he acts.

* * *

We too are dealing with facts, with adverse chance, with, to be specific, our problem: endemicity of hepatitis. We too must await the ultimate parental decision: controlled or uncontrolled exposure, immunity safely by design through minimal disease, or by natural endemic exposure, ill-timed perhaps, with the adverse chance of complicating with respiratory disease, shigellosis, Coxsackie or Echo viruses—the compounded infections which threaten survival. We are physicians, dedicated to life, to support, to teach, to grow with our knowledge, to offer more because of this knowledge; and because of overwhelming circumstances we knew that action was warranted. We too believe that it is the duty of the pediatrician to attempt to improve the situation. Put back the knowledge gained and we must deal, in conscience, with ignorance. This too begets reaction. We could have stepped over disease and been blamed for not caring. As a matter of record instead we have slowly and carefully advanced. The population has been among the earliest to have been vaccinated against measles and rubella, and soon shigellosis. Now the encouragement of promise against serum hepatitis.

Yet are we faced with the conflict to truths. The ethical relativism, honest and honorable

within the environment we are dedicated to serve, is questioned. The truth is that our conscience does not inhabit a germ-free area and the children were sick upon it. Our actions are dissected by words and the result is fatuous.

A farmer may pull up corn seedlings to destroy them, or he may pull them up to set them in hills for better growing. How then does one judge the deed without the motive?

We are advised to improve the situation; of what is the situation but a child (and retarded at that), and a virus (whose only constancy is its love-affair with the human host), and society (who puts them together and departs)? In our honesty we cannot separate the child from the situation of which he is an integral part: both cause and effect. To do so is a trick of words.

And what of knowledge? A physician brings to the care of a patient all the knowledge of which he is possessed (much of it born of controversy now forgotten), and learns from each patient to whom he ministers. In our honesty, we have learned. We cannot separate knowledge from the child, no more than deed from motive, or child from situation.

* * *

Now examine the accusation that "infected material" is injected into children, and let us discuss knowledge, and *degree* of infectivity, and resultant gain. Yes gain, and to the child. For the half-truth of the accusation is that we proceed blind and wanton for our own unspeakable advantage. The thought shames us for here is proof that you have never known us, that you have not come the three thousand miles to know what you condemn, nor walked with us even the first mile. For here is truth: you cannot clinically tell the newly admitted child from the child injected, at the height of response, from the child whose response is over, except for the fact that those who have been with us longer, by virtue of our care, are better adjusted, better nourished, and more scheduled within their capabilities. And immune, and this is a measurable fact. Your assumption is of illness. We have seen more reaction to countless vaccines than to the procedure we have so carefully controlled.

Truth is many things: the truth of parents, realistic after trial; the truth of critics, idealistic and apprehensive of what they have not seen and do not know; there is the truth of those whose judgment has led to action, and the truth, acknowledged, that there are no absolutes. There is the final truth that above all else man must help

man, and the knowledge that each may approach by a different path, in conscience.

NOTE 4.

THE EDITORS OF THE JOURNAL OF THE
AMERICAN MEDICAL ASSOCIATION
PREVENTION OF VIRAL HEPATITIS—
MISSION IMPOSSIBLE?*

Letters to the editor of *Lancet* harshly criticized Krugman and his colleagues for their studies. . . . One writer (Goldby) was "amazed that the work was published and that it has been actively supported editorially by the *Journal of the American Medical Association*. . . ." In pious tone, *Lancet's* editor supported Goldby's view. . . .

* * *

This issue of *The Journal* carries the most recent report from Krugman's group and, as it turns out, *Lancet's* editor would have been well advised to keep his pen away from paper. The evidence is now in; viral hepatitis, type B (MS-2) can be prevented by active immunization induced by inoculation of an inactivated preparation of MS-2 serum.

Mission accomplished!

c.

Through Governmental Action?

Medical Notes in Parliament
Ethics of Clinical Investigation†

The conduct of clinical trials in hospitals and the right of the patient to be informed and to give or withhold his consent were discussed in the House of Commons on February 16. It was raised by MR. STEPHEN SWINGLER (Newcastle-under-Lyme, Lab.). . . . He put forward two principles: medical experiments on patients should not be conducted unless there was a chance of patients benefiting; and clinical experiments in hospitals should not be conducted unless the consent of the patients had been freely given. . . .

In the Bristol case, he said, penicillin was administered to newly born babies for the purely scientific purpose of observing their reaction to penicillin and to establish the properties of the preparations. The penicillin was not required by

the babies, and there was no question of its having any beneficial effect on the babies. It had been established by the Minister of Health on inquiry that the consent of the parents was not sought. In his opinion, even if consent had been given, the experiment was ethically dubious. [In the same issue of the *Journal* in which the experiment was reported there was a report of a speech by a distinguished doctor to a meeting of the Royal Society of Medicine about the uses and abuses of antibiotics, in which he was reported to have said that a doctor should think twice before prescribing the first-ever dose of penicillin to any patient.

* * *

MAJOR W. J. ANSTRUTHER-GRAY (Berwick and East Lothian, Con.) was concerned that all consideration of the parents appeared to have been overlooked. He quoted extracts from the *Journal* report, and said that he had no doubt the experiment was quite harmless. There was a note at the foot of the article in which a lot of people were thanked. But the parents were not only not thanked, they were not even consulted.

MR. IAN MACLEOD, Minister of Health, said it was admitted that the consent of the parents should have been asked for. The people responsible, who were of the greatest authority and competence, regretted very much—as he did—that that was not done. What the House was discussing was whether such experiments were proper, and whether any action should be taken by the Minister in these matters. He disagreed with Mr. Swingle's proposition that it would be wrong and unethical for any clinical investigation to be carried out which would not immediately benefit the person concerned. If it was to add to future knowledge he did not see how that could be so. The reward to those who tried to catch the common cold at the Salisbury research unit was not that they would derive direct benefit themselves, but that the general pool of knowledge might be increased and others helped in the future. The answer to Mr. Swingle, therefore, was that babies yet unborn might benefit from this continued thrusting forward to new frontiers.

There were two propositions with which he thought most of the House would agree. First, there was bound to be clinical investigation and experiment. If that were not so, knowledge of surgery and medicine would not have changed over the centuries. Second, only the clinician in charge could say what was right and proper

* 217 *Journal of the American Medical Association* 70-71 (1971). Reprinted by permission.

† 1 *British Medical Journal* 546-547 (1955). Reprinted by permission of the editor.

and what safeguards were needed in the action he took. Mr. Swingler had asked, in questions on February 14, that before further clinical experiments on children were undertaken the nature of such experiments should be reported to the Ministry of Health so that the medical staff of the Ministry could ensure that there were adequate safeguards against harmful effects; and also that the Minister should issue a directive to hospital management committees on the ethical principles involved. That was in his (Mr. Macleod's) view a wrong conception of the duty of the Minister of Health. He thought it would be wholly improper for him to try to lay down what ethical and medical principles should govern the conduct of professional men in the work they undertook at hospitals.

In this instance there was undertaken an experiment which all those concerned, who were of the highest capability, were quite certain was completely harmless. If a small child of his, or a child of any age, was in hospital, and he was told by people of the standing, for example, of professor of medicine and child health at the university concerned, "We are interested to know the effects of a perfectly safe clinical investigation; it may very well be that we can learn from what is done, and as a result can drive still lower the infant mortality rate," he would be more than ready to give his consent.

The common sense of the matter was that where a clinician intended to undertake an investigation which was so novel as to amount to an experiment he would be wise to seek consent from the patient or parent for what was proposed. But he was absolutely convinced that it would be quite wrong for a Minister of Health to issue directives on a matter that was essen-

tially one of medical ethics to those concerned. He was sure it was best to leave the matter to the profession, and not to have a lay Minister interfering in a matter that was very precious to those professionally concerned.

MR. SWINGLER said he appreciated why the Minister should resist the idea that he should himself go into this matter and issue a directive. But in view of the complexity of the situation, did he not think it was the duty and responsibility of the heads of the medical profession to give some ethical guidance? As it had been brought to his attention that there were cases where, for example, consent had not been obtained, and where experiments were being conducted which had nothing to do with actual treatment, would he not use his good offices to ask the heads of the medical profession to give some guidance on that?

MR. MACLEOD said that was a very different matter and one with which he was in some sympathy. If he had the slightest reason to believe that the position was not fully understood, then he would informally—and it could only be informally in a matter like this—draw the attention of those responsible to what had been said. The Medical Research Council sent out a confidential memorandum rather on those lines. If he had any reason to believe that the position was not completely clear, and that it was desirable for these things to be drawn to the attention of those responsible, then of course he would not object at all to what he might call an informal notification from himself. Of one thing he was clear: no directive must come from the Ministry of Health on a matter of this delicacy.

* * *

CHAPTER THIRTEEN

Experimentation with Captive Subjects

The prosecutors at Nuremberg maintained that the use of political and military prisoners for experimental purposes constituted a “crime against humanity.” The defense tried to meet this argument by presenting evidence, especially from American sources, of the longstanding practice of enlisting prisoners in research projects. Heated exchanges ensued about the capacity of any captive person to participate in research on a truly voluntary basis.

From these debates emerges a broader and more basic question for the entire human experimentation process: What persons or institutions should be authorized to formulate, administer, and review decisions to allow investigators to recruit subjects who are vulnerable to external pressures? Since these subjects are usually the “captives” of state institutions, the decision to experiment with them, as with uncomprehending subjects, must be grounded in public policy and cannot be left solely to the discretion of investigators. Although the case materials in this chapter focus primarily on prisoners, the issues they raise apply in varying degrees to other captive groups, *e.g.* soldiers, the economically disadvantaged, and persons in hospitals and other non-penal institutions.

In studying these materials, consider the following questions:

1. What groups should be defined as “captive” for research purposes? Is vulnerability to “external pressures” the most important cause for concern?
2. Should external pressures be taken as a characteristic common to all human activity and thus deemed of no special significance to decisions in human experimentation?

3. To what extent are external pressures strengthened or weakened by making rewards for participation in an experiment explicit or leaving them implicit?

4. If permitted, should the use of captive patient-subjects be restricted to research which aims to benefit them or attempts to learn more about the conditions which made them members of the captive group?

5. Should captive subjects be permitted to participate in research if non-captive subjects could be selected instead?

6. If research is permitted on captive groups generally, should any sub-group be specifically excluded from participation in research?

7. What impact might the widespread use of prisoners for research have on the administration of justice?

A.

Case Studies of Prisoners and Soldiers as Patient-Subjects

1.

Richard P. Strong **Vaccination against Plague***

Although the question of protective inoculation against plague has received considerable attention during the past few years and prophylactics for the disease have been recommended . . . apparently no successful experiments have been made on human *vaccination* against the malady—i.e., protective inoculation in which the living attenuated pest bacillus has been employed. . . . In 1781, Samoilowitz, a Russian physician, inoculated himself with plague pus, suffered a mild attack of the disease, and so became immune. Therefore, he recommended that a lint compress previously saturated with the pus from a plague bubo be bound upon the arm of the person to be immunized. The skin of the individual was not to be abraded. Other observers attempted similar experiments; but many of these resulted disastrously; thus, Cerutti performed such inoculations on six persons, five of whom died of plague. Because of these results this method of immunization obviously was soon abandoned and has not since been employed. . . .

* * *

In 1902 and 1903 Kolle and Otto inoculated eighteen guinea pigs subcutaneously with an attenuated culture of the pest bacillus. The organism was an old laboratory culture in which the

reduction of the virulence had, in some unknown manner, taken place during its growth on artificial media. Buboos, which later discharged and healed and in the pus from which a few bacilli were present, developed in the animals, but they showed no other evidence of sickness and subsequently entirely recovered. The animals were reinoculated two, three, and eight months later with one-twentieth to one-fiftieth dose of a pest culture (of which one one-hundredth dose represented the fatal dose for a normal guinea pig). Seven of the animals remained alive.

* * *

In December of the past year (1904) Kolle and Otto in further detail reported upon the immunization of guinea pigs with the attenuated pest bacillus. Among thirty-four of these animals immunized with such a culture, of which none died during the process of immunization, twenty-one were reinoculated with a virulent organism one to four months after their vaccination, and of this number sixteen (76 per cent) remained alive, and five died. Nine other guinea pigs were inoculated with the avirulent culture, and at the same time with plague immune serum; all proved to be immune upon reinoculation with the virulent pest bacillus. The organism with which these vaccination experiments were performed possessed so little virulence that from two to three living, agar slant cultures, when injected into a guinea pig of 250 grams' weight, did not cause the death of the animal. . . .

* * *

* 1 *Phillipine Journal of Science* 181, 184-187 (1906). Reprinted by permission.

In the present paper it is merely my desire to call attention to the fact that vaccination in man can with safety be performed with attenuated cultures of the living plague organism, and therefore only the human inoculations undertaken with one strain of this bacillus will be referred to. The organism in question possesses so little virulence that in a series of twelve guinea pigs and thirty monkeys inoculated with from one to two entire agar slant cultures, not one succumbed from the effects of the inoculation. It was with this culture that the first experiments were performed in human beings. Since I believe that the guinea pig is an equally if not even a more susceptible organism than man to the pathogenic action of the plague bacillus, it was presumed that, if this animal could invariably withstand the action of such large amounts as two whole agar slant cultures of the organism, much smaller quantities could be inoculated into human beings with safety, and, indeed, before performing the experiments on man, I felt thoroughly convinced of this fact; nevertheless, the human inoculations were performed as carefully and with as much deliberation as possible.

* * *

The first injections were carried on upon prisoners under sentence of death; in the first case one-hundredth dose of the attenuated culture was inoculated subcutaneously without any noticeable effect. After ten days, ten other individuals were inoculated with the same dose, in order to demonstrate that no special natural immunity against the plague organism had been existent in the first instance. In this manner the amount of living organisms given was gradually increased, a single person being first inoculated with the larger dose and then, after it had been observed that no unfavorable effects occurred, from five to ten other persons were also treated with the same amount of the vaccine. This method of procedure was adopted in order to minimize the danger of inoculating a very susceptible individual with a dose which might prove disastrous. It was argued that if ten persons selected at random withstood the inoculation of a certain amount of the organism without developing unfavorable symptoms, a single individual, also selected at random, could probably receive a slightly larger dose without great danger. In this manner as mentioned the dose was gradually increased until one whole agar slant was inoculated. No attempt has been made to inject a larger amount of the organism, since

from experiments performed on animals it has been concluded that a sufficient immunity in man will probably result from an inoculation of this quantity. Up to the present time forty-two persons have been injected with this large dose (one twenty-four hour agar slant culture) of the living bacillus, and, although the inoculations which I include in this report were all performed more than two months ago and the individuals treated have been under constant surveillance, I have no accident to report.

Surprising as it may seem, the injection of these large amounts of the living plague organism have not given rise to any very severe reactions. . . .

* * *

NOTE

RESEARCH ON THE KINETICS OF THE GERMINAL EPITHELIUM IN MAN

In an article published in 1964,* Heller and Clermont reported their investigation of "the dynamic processes taking place in the seminiferous epithelium of man." The study was conducted with eight previously vasectomized "inmate volunteers" at the Oregon State Penitentiary who ranged in age from 20 to 42 years. When Dr. Heller analyzed his subject population, he found that

they were a rather uniformly mixed group of northern Europeans. They were Irish, Scots, English, and French mixed (and one French Canadian). We are now looking for other volunteers from other racial groups. I found a splendid full-blooded American Indian volunteer, and the preliminary studies suggest that at 16 days and at 31 days he falls right where he should be. I have a negro volunteer at present. Other ethnic groups are absent from the Oregon State Penitentiary; I cannot find anybody with a full-blooded semitic background. There are no Japanese, there are no Chinese, but there are many of Filipino origin and we are searching for such a volunteer.

Bilateral testicular biopsies were performed by first administering local novocaine anesthesia (the testes remaining uninjected). After the scrotal skin had been incised, a 0.5-1.0 cm cut was made in the tunica "and the testicular tissue was separated from the tunica by lateral undercuts. External pressure on the testis was avoided.

* Carl G. Heller and Yves Clermont: "Kinetics of the Germinal Epithelium in Man." G. Pincus, ed.: *20 Recent Progress in Hormone Research*. New York: Academic Press 545 (1964).

Due to internal pressure, the underlying seminiferous tubules protruded above the tunica and were severed by a stroke of a razor blade parallel to the surface of the testis."

To determine the duration of the spermatogenic process, radioactive thymidine (thymidine- H^3) was introduced directly into the testicular matrix. This procedure was first tested in rats before being applied to men. The injection sites were marked by a black silk suture to facilitate their identification for subsequent repeated biopsies.

In another experiment, a normal healthy subject was injected intramuscularly with 4000 I.U. of chorionic gonadotropin every second day for thirty-five days. Subsequently 10 mc. of thymidine- H^3 was injected intratesticularly and some time later a biopsy was obtained.

The authors concluded "that neither a steroidal hormone nor chorionic gonadotropin has affected the rate of development of the germ cells; the rate of spermatogenesis in man therefore appears to be a biological constant in confirmation of Ortavant's conclusion derived from . . . studies on the ram."

2.

Arthur L. Mattocks and Charles C. Jew Assessment of an Aversive "Contract" Program with Extreme Acting-Out Criminal Offenders*

* * *

The drug succinylcholine (Anectine) has been widely used during recent years by medical practitioners as a muscle relaxant in proper dosages. Succinylcholine, when injected intravenously, results in a brief muscle paralysis and respiratory arrest. Administered in sufficient dosage, the patient goes through a sensation of suffocation similar to drowning although he remains fully conscious of the experience (temporary paralysis and apnea). This experience, to some, can be a highly frightening experience which psychologists would term "aversive."

* * *

Concerned with the inability to prevent self-destructive and/or assaultive behavior among extreme acting-out patients despite psychotherapy, phenothiazine tranquilizers, anti-depressant

drugs, therapeutic milieu, electro-shock therapy and other resources, a program of Anectine treatment as a last resort was initiated at the California Medical Facility [CMF] in January, 1967. The first case was a patient who had continued inexorably to mutilate himself and imperil his life by swallowing six- to nine-inch sharpened metal wires which required multiple laparotomies. He then persistently reopened his laparotomy wounds and shoved pieces of wood and metal under his skin. The use of Anectine treatment prevented the patient from harming himself for many weeks which led to the continuation of the program to handle similar patients who posed a constant serious threat to themselves (self-mutilation, suicidal attempts) or to others (assaults on other inmates or staff) for whom all available treatments within the institution have been exhausted and failed to alter their behavior. The conceptual scheme was to develop a strong association between any violent or dangerous acting-out behavior and the drug Anectine (and its frightful consequences) such that it would be an effective suppressant to further contemplation or commission of these acts.

The Anectine program was begun in January, 1967 and continued until April, 1968. During that time, sixty-four inmates participated by signing a treatment contract with the institution's Special Treatment Board.[†] The aversive cues

[†] . . . On five patients, consent was not received from the patient himself, but was granted by the institution's Special Treatment Board. Thus, these five patients were included in the treatment program against their will.

* * *

It is interesting to note that although only five of those interviewed in the present study were signed up involuntarily for the aversive treatment program, eighteen indicated they involuntarily signed the treatment contract indicating that they felt some implied pressure to do so in the doctor's request. Related to this is the fact that a sizable number of the patients perceived the motive of the doctor as one of punishing them even though the medical staff exerted efforts to assure the patients that this was not to punish but to help the patient control his own behavior. While the staff was successful in convincing a majority of the subjects interviewed of their helpful intentions, it is clear that in the environmental context, and with the experiential background of the subjects in the type of population used in this study, such efforts are not apt to meet with total success.

* * *

* Unpublished manuscript (1971). Printed by permission of the authors who retain all rights.

of the drug were described by the medical staff as each individual become involved in the program. The contract emphasized that he would receive an Anectine injection *if, and only if*, he indulged in behavioral acts such as (1) violently attacking others, (2) serious self-mutilation, or (3) suicidal attempts, but he would receive no injection if he did not commit such acts. It was therefore up to him whether he ultimately would receive an injection since this was determined by his own behavior.

As it will be seen later in the study, only a small portion of the patients involved in the program actually had violated their contracts and received Anectine injections. The actual administration followed closely the patients' acting-out behavior. Because the administering procedure is also a crucial part of the aversive program, it is outlined here as it was described by one of the medical staff administering the program:

Our technique is simply to administer 20 to 40 mg. of succinylcholine intravenously with oxygen and an airway available, and to counsel the patient while he is under the influence of the drug that his behavior is dangerous to others or to himself, that it is desirable that he stop the behavior in question, and that subsequent behavior of a nature which may be dangerous to others or to himself will be treated with similar aversive treatments. During the entire time, oxygen is administered so that there is no danger of anoxia and . . . there is no pain accompanying the procedure, only cessation of respiration for a period of approximately two minutes duration. We have been very careful to explain to all individuals involved that they will suffer no permanent ill effects, that the treatment is safe as long as it is given by competent medical personnel, that it will not cause pain, and that at all times they will be supervised closely so that they need not worry about ill effects of the treatment.

How severe is the Anectine experience from the point of view of the patient? Sixteen likened the experience to dying. Three of these compared it to actual experiences in the past in which they had almost drowned. The majority described it as a terrible, scary, experience. Nearly all of these subjects based their descriptions not only upon what the doctor had told them, but either on personal experience or the first-hand description from patients who had had an Anectine injection. Again, two patients denied the experience bothered them at all, and two were non-committal. It would seem therefore that the perception of the aversive consequence by the patients was of sufficient severity to warrant consideration of this factor as a possible explanation for the inhibition of aggressive behavior. [From an earlier draft of the same paper.]

Most of the sixty-four patients in the program were housed in the acute treatment area due to their recurring pattern of extreme and potentially dangerous behavior both to themselves and others. Nearly all could be characterized as angry young men who directed their anger impulsively outwards in attacks on others, or inwardly towards themselves, or exhibited both types of behaviors at various times. The average age of the subjects was twenty-five years and the mean time at the institution was fifteen months. The frequency and repetition with which they engaged in these dangerous behaviors cannot be overstated. Examples of violent behavior of two of the patients read as follows:

He was a twenty-four-year-old committed to prison for murder 2nd originally, who, while he was in the county jail, hanged his cell partner. On being sent to the California Department of Corrections he was placed in an adjustment center where he engaged in self-mutilative efforts which gained him admission to the institution hospital. While there he murdered another time (a defenseless psychotic prisoner) and was sent forthwith to us for psychiatric observation while he was waiting to stand trial. His stay at our institution was without self-mutilation or assault under the promise of Anectine treatment and he received no treatments.

Another patient under the treatment program was considered by institution officials as very dangerous. He had killed one man and assaulted another with a bayonet (commitment offense). During his stay in the institution he accumulated twenty-three violations of rules necessitating thirteen placements in administrative segregation and/or isolation. He had threatened officers and recently "stabbed" another inmate a few days ago.

Three months prior to the termination of the program, an evaluation strategy was developed by the CMF Research Unit to assess the impact of the Anectine program. The evaluation goals were to determine: (1) whether Anectine had an impact in inhibiting the continued repetition of suicidal, homicidal, and self-mutilative behavior(s), (2) whether a generalization effect will occur leading to the overall reduction of undesirable behavior, including those not specified within the treatment contract, and (3) whether the response to Anectine differs according to the type of commitment offense of the patient.

At the time of the data collection most of the patients had been under the Anectine "contract" for at least three months. Considering the frequent repetition of aggressive behavior among this population, the results shown tend to sug-

gest Anectine is highly effective in inhibiting the commission of "contract" behavior in that only twenty-eight percent (18) of the population had received one or more injection of Anectine. Seventy-two percent (46) had not committed any of the specified acts and did not receive an injection of Anectine. This constitutes an improvement in that they fulfilled the treatment contract. While there is no way in which one can accurately estimate the number of assaults, stabbings, self-mutilations, and suicidal attempts inhibited through the use of the Anectine program, a fact not to be ignored is that fifty-seven percent of the patients were able to be assigned later to a psychiatric program or sufficiently stabilized for transfer to other prisons for programming.

Indeed, at the time of the evaluation, sixteen of the participants had been transferred to other penal institutions for programming. The remaining thirty-five were interviewed and their disciplinary records reviewed. . . .

* * *

A most unexpected result from the Anectine program data is the differential effect it has upon different types of criminal offenders, which came to light through comparing increases and decreases in disciplinary infractions among offense types. Patients who committed "crimes against persons" (i.e., robberies, homicides, assault, sex, rapes) responded entirely differently to the Anectine program than patients who committed crimes against property (fraud, theft, tax evasion, etc.) The former offense types tended to decrease while the latter tended to increase the overall number of disciplinary infractions as a result of the Anectine "contract."

* * *

This type of program seems to be particularly useful in institutions where the concern is to inhibit highly dangerous behavior through the temporary application of an aversive stimulus in which more effective alternatives are not to be found. However, extreme caution needs to be exercised in the use of Anectine because more knowledge is certainly needed to understand the subsequent anxiety and the side effects derived from its usage, especially the "paradoxical" effects of punishment in which the use of aversive stimuli may increase the rate of the punished behavior when the aversive stimulus is removed. In addition, not everyone in the program had considered the Anectine program "aversive." In subsequent interviews with some of the patients

who received Anectine injections, several indicated that they enjoyed undergoing the Anectine experience. In a similar vein, nine persons not only did not decrease but had actually exhibited an increase in their overall number of disciplinary infractions. Thus, careful selection as to who may be included in programs of this nature seems mandatory because the application of aversive stimuli to inhibit one or a series of behaviors may be highly effective to some patients, ineffective for some, and for still others may stimulate an increase in behaviors which the aversive stimuli were intended to inhibit.

3.

William R. Brink, C. H. Rammelkamp, Jr., Floyd W. Denny, and Lewis W. Wannamaker Effect of Penicillin and Aureomycin on the Natural Course of Streptococcal Tonsillitis and Pharyngitis*

The problem of determining the efficacy of therapy of acute streptococcal infections of the upper respiratory tract is difficult, for these infections are of short duration and are usually not severe. Only by controlled studies in which an attempt is made to quantitate the occurrence of symptoms, physical signs and fever is it possible to conclude that this disease has been affected favorably. The present study was undertaken to determine the relative efficacy of penicillin and aureomycin in the treatment of group A hemolytic streptococcal respiratory infections. For this purpose 475 patients with exudative tonsillitis or pharyngitis were studied by clinical, bacteriologic and serologic methods.

The investigation was conducted in Francis E. Warren Air Force Base, Wyoming, between March 8 and April 30, 1949. During the period of study streptococcal respiratory infections were epidemic with rates of ten to thirteen hospitalized cases per 1,000 men per week.

All patients admitted to the base hospital with respiratory symptoms or fever were examined within a few hours by a physician from the Streptococcal Disease Laboratory. If exudate of any degree was observed on the tonsils or pharyngeal mucosa, the patient was admitted to the study ward. Selection for the treated and control groups was determined by the air force serial number. While penicillin was being eval-

* 10 *American Journal of Medicine* 300-308 (1951). Reprinted by permission.

uated, patients whose serial numbers ended in an even digit received intramuscular injections of procaine penicillin. . . . Patients whose serial number ended in an odd digit served as controls and received no treatment.

One week after concluding the study of penicillin, aureomycin therapy was employed. Patients with serial numbers ending in the digits one and three were given no specific treatment. All other patients with exudative tonsillitis and pharyngitis received one gram of aureomycin. . . .

While in the hospital the patients received no antipyretics but were given small doses of codeine for severe headache.

* * *

There was a total of 198 patients who received no treatment; 197 received penicillin and 80 were treated with aureomycin.

* * *

The relative frequency of feverishness, headache and loss of appetite was similar in the three groups; sore throat, however, occurred somewhat less frequently in those who received penicillin than in the other two groups. This was also associated with a decreased incidence of tenderness of the cervical lymph nodes in the patients who later received penicillin. There was a distinct difference in the incidence of edema of the soft palate, the control group exhibiting less swelling of the palate and uvula than the group receiving aureomycin or penicillin.

* * *

. . . Penicillin or aureomycin treatment resulted in a more rapid disappearance of symptoms than occurred in the control group of patients. Aureomycin was more effective than penicillin although the differences were not marked. The prevalence of anorexia was about equal in the three groups throughout the period of observation. Nausea and vomiting were especially prevalent among those patients receiving aureomycin, 51 per cent having these complaints. In the untreated group 35 per cent complained of nausea or vomiting during the course of the illness. Loose stools occurred in 45 percent of the patients receiving aureomycin whereas only 15 per cent of the control group exhibited this symptom.

Treatment instituted early in the course of illness resulted in a more rapid recovery than when therapy was delayed. . . . Patients treated

with aureomycin within the first twenty-four hours of onset of illness no longer complained of sore throat after the fourth day whereas on the sixth day 8 per cent of the control group still had this symptom. Penicillin therapy instituted after the first twenty-four hours of illness resulted in only a slightly more rapid disappearance of sore throat than occurred in those who received no treatment.

. . . Following treatment with either aureomycin or penicillin there was no marked improvement in the physical signs. However, in almost every instance individuals receiving treatment improved somewhat more rapidly than those serving as controls. Aureomycin appeared more effective than penicillin in this regard, but the differences cannot be considered significant.

* * *

Suppurative complications were unusual. There were ten (5 per cent) patients with peritonsillar cellulitis in the control group, thirteen (6.5 per cent) in the group receiving penicillin and four (5 per cent) in the group treated with aureomycin. In two of the patients being treated with penicillin peritonsillar cellulitis developed after therapy was instituted.

The number of patients in whom signs of otitis media developed is not known but 6.5 per cent of the control group complained of an earache beginning twenty-four hours or more after hospitalization. This is in contrast to 2 per cent of the patients treated with penicillin and 1 per cent of the aureomycin-treated group in whom earache developed after the institution of treatment.

There were seven instances of definite acute rheumatic fever developing within ten to thirty-five days following the acute streptococcal illness. Five of these patients were in the control group which received no treatment and two developed in patients treated with penicillin. No rheumatic fever occurred in those patients treated with aureomycin. No instance of acute nephritis was observed.

* * *

The fact that acute rheumatic fever developed in only two patients receiving penicillin and five patients of the control group suggests that penicillin may prevent rheumatic fever. The two cases occurring following penicillin were the only instances observed in a much larger study of 698 patients treated with this drug and is in contrast to seventeen instances of the disease

among 702 controls who received no specific therapy. This study established that penicillin is an effective agent in the prevention of rheumatic fever when administered during the preceding acute streptococcal infection. The fact that no

case of rheumatic fever followed the acute infections treated with aureomycin suggests this drug may also prevent the subsequent development of acute rheumatic fever.

* * *

B.

Appraising the Role of the Participants*

1.

In Formulating Policy

a.

Deciding about Choice of Subjects?

[7]

John D. Arnold, Daniel C. Martin,
and Sarah E. Boyer

*A Study of One Prison Population
and Its Response to Medical Research†*

* * *

It will be our goal to discuss the act of volunteering for medical research and its relationship to the social structure of the prison system. From previous studies, it was noted that communication between potential volunteers in prison and the experimenters, who belong to free society, was an obvious problem. In general, members of prison groups have a low verbal ability. The type of language of the prison inmates is very often specialized. Along with the technical difficulties overlying the use of language, the usual difficulties with informed consent are accentuated in the prison setting. Additionally, information originating in free society is often considered suspect by the prison population. A great many explanations can be called on to account for this, but for our purpose, it is important simply to recognize that a credibility gap does exist.

In a recent study of a prison population, we found two major factors contributing to the availability of a subject: the type of prison and the value scale of the prisoner. It is difficult for

members of the free-living society to visualize the condition of most penal institutions. [I]t is necessary to understand the general condition of prisons in order to examine more closely the volunteer and the volunteering process. The second portion of our study concerns itself with the value scale by which prisoners judge risk, reward and social merit.

We have analyzed the inmate's views of the prison system in this study (county jail), as well as his view of other prison systems (federal and state penitentiaries) in which he has also resided.

The federal prisons, according to our inmates, are the best run institutions. Prison discipline is usually good, and the aberrant behavior of prisoners seen in other prisons is less common. Inmates also indicate that federal prisons offer more opportunities for employment during incarceration and that many federal institutions have active and intensive rehabilitation programs.

The prisons in the state systems vary widely. Some are considered to be well run, while others are described as chaotic and dangerous. The long-term character of imprisonment in the state system leads to the development of certain social phenomena. In the state prisons there is a tendency toward the formation of powerful social cliques. Admission to these influential social groups depends almost entirely upon individual behavior. Street relationships have little or no influence on a prisoner's membership in an organized social clique. Preservation of street relationships within the state penitentiary system is often difficult. Prisoners rank state institutions as good when they offer job opportunities and when the prison supervision is effective. Prisons considered chaotic and dangerous are those where supervision is lax or indifferent.

The county and city jail systems have a character quite different from that of either the state or federal prisons. In county and city prisons, street associations are often a binding

* This appraisal section focuses on captive subjects. For a fuller exposition of the factors requiring appraisal, consult section D of Chapter Eleven, beginning at p. 818 *supra*.

† 169 *Annals of the New York Academy of Sciences* 463-469 (1970). © The New York Academy of Sciences, 1970. Reprinted by permission.

social force. In county jails, street relationships are sometimes transferred intact from the street to a given area of the jail. Depending upon the orientation and size of the jail, these street relationships can become powerful forces operating within the institution. Membership in these cliques, unlike the cliques in state prisons, is dependent entirely upon whom the prisoner knew while he was on the streets. If a prisoner in a county jail has no friends from the street serving time with him, he more than likely will find himself considered an outcast by the organized groups. Such outsiders are subject to the whims and sometimes the abuse of the clique.

Supervision in county jails often is less effective than it is in the other groups of prisons. Because of inadequate supervision, the powerful cliques are difficult to control. Effective supervision is further hampered by the poor physical facilities typical of many of our county jails. Perhaps of greatest importance is the fact that very little constructive activity is normally provided in county jails. As a result of so much inactivity, there is less competition for the time and interest of the prisoners. Therefore, medical research in these institutions is given a competitive advantage.

The medical research conducted in the county jail of this study falls into two general categories. The first includes all of those studies concerned with the treatment of malaria, and it is referred to by staff and prisoners alike as the "malaria project." The second category is concerned with a variety of drugs and their effect on certain body functions. This group, taken collectively, is always called "the drug studies." Prisoners who volunteer for either type of research must meet certain criteria before they can be accepted for any of the studies.

Eligibility requirements were set up by the project director and the jail warden. These considerations include the kind of crime committed, the type of previous convictions, and the time remaining on the prisoner's sentence. Prisoners who volunteer for either type of research must have received their sentences and have at least six months of jail time remaining. Volunteers are individually screened by the project director to see if they meet all the physical requirements of the project.

A prisoner who volunteers and is accepted for the research project moves into the special project area. This area differs from the other parts of the jail because the volunteers are

treated more like members of a free society. Clean linens are provided, beds instead of bunks are installed, the quality of the food is better, and food is available to the volunteers 24 hours a day.

During the past five years several studies of our prison population have been conducted. Our most recent study was developed in three phases designed to examine the attitudes and motivation of prisoners toward volunteering. Phase I includes open-ended in-depth interviews of a group of 14 volunteers. From these data a semistructure interview schedule was developed. During Phase II, this interview was administered to all of our volunteers ($N=13$) on all of the research projects during the first week of April, 1969. Phase III consisted of interviews conducted with 15 prisoners from all areas of the jail who had no present or previous affiliations with any of the research studies. The data for this paper are drawn primarily from our most recent study. However, we have used supporting information taken from previous clinical research conducted during the past 12 years of work, including six years in a state prison and six years in a county jail.

We had assumed that living conditions in the other areas of the jail would influence a prisoner's decision to volunteer. During the open-ended interview conducted in the beginning of this study, the volunteers were asked to describe the living conditions in the jail. Their remarks, taken collectively, described the jail living conditions as "impossible situations." When asked if this influenced their decision to volunteer for medical research, more than 50 percent indicated that their decision to volunteer was based in part on their desire for better living conditions.

It was an assumption of our present study that street relationships would be an influential factor in the volunteering process. In an attempt to establish a correlation between street relationships and volunteering, the volunteer subjects were asked how many inmates they then knew were people they had formerly known in the streets. Only three prisoners in our sample had known any of the other prisoners from the street. These three respondents did not consider this relationship a strong one. Further questioning of our volunteer subjects indicated that the majority of them considered themselves "loners."

The loner, by definition, had not belonged

to any organized group. According to our study, the outcasts from the street cliques often sought membership in the only group that would take them—the research project. In effect, the medical research project provided a new environment.

There is another force operating within the prison system that influences medical research. This additional force is far less acceptable than inadequate supervision, constructive use of time, living conditions, or street associations. This less acceptable force is the general level of fear that exists in many city and county and state prisons. One of the more graphic descriptions of this was given by Davis, who studied sexual assaults in a county jail. This prison also had a medical research project that provided a haven from fear, as well as offering financial and other rewards.

* * *

Our volunteers stated that it was safer in the research project than it was elsewhere in the jail. In the volunteers' words, "You could trust people on the project," and, "There was less tension among the volunteers than among the other prisoners." The volunteers felt they could go to sleep in the research project without being afraid someone would "hust you in the head" or "set fire" to their bunks while they slept. All of the prisoners who did not volunteer, but who knew about the research project, agreed that there was probably less tension on the project than there was in their tanks. When asked why they believed this to be true, volunteers and nonvolunteers agreed that it was because the prisoners on medical research had something constructive to do with their time. As one volunteer said, "We are too busy to get into trouble." Seventy-five percent of the volunteers said that being on the project had helped keep them out of trouble while they were in jail.

Value Scales

One of our special interests has revolved around the problems of the value scale by which prisoners judge risk, reward, and social merit. To some degree, prisoners have their own value scale for the things that compete for their time. This is so because they have relatively few competing proposals. In their arid existence, some activities that are of little interest to free-living individuals are highly regarded by prison inmates. This fact alone gives every time-use proposal that is offered to their group a stronger

appeal than it might have among free-living groups.

There is an element in their way of life that we have also considered. That element is risk taking. This consideration is not unusual, for many of these men are dedicated professional criminals. Their professional lives are often devoted to activities that expose them to personal risk. The form and amount of risk taken by them is rarely seen among free-living people. To the degree that volunteering requires risk taking, certain inmate groups may endow this activity with status. This may be especially true if there is actual physical danger in the activity.

The prison inmate has two standards of risk. One applies to the period of incarceration (short-term risk) and the other applies to the time he is free-living (long-term risk). There is something about the state of imprisonment or the environment of a prison that alters a subject's view of risk. For instance, 12 of a group of 13 volunteers indicated that the apparent risk of adverse physical effects had little negative influence on their decisions to volunteer as long as they were in jail. In some instances, it constituted an attraction for volunteering. On the other hand, when confronted with a hypothetical experiment with the same risk considerations as that of the malaria project, of these same volunteers, only eight indicated that they would not be willing to face these same risks when free-living. Most of the free-living people whom we have interviewed would also not accept risks of this magnitude.

There is a small proportion of our volunteers that has included the element of risk in their life styles. From another group of 14 volunteers, three inmates expressed *no* concern about long-term risks, because they rarely planned ahead for anything. As an example, one prison volunteer indicated he would volunteer for anything, regardless of the risk. As a professional thief, he regarded life as just one long chance. Because of this attitude, he viewed his long-range survival with much doubt.

This last group of prisoners is the exception, rather than the rule. However, both of our volunteer groups demonstrated rather curious behavior with regard to family consultation concerning their volunteerism. If they informed their family, they always minimized the risk. They did this even though they themselves had a high estimate of adverse physical effects. When questioned about this discrepancy, they usually

indicated that it was immaterial whether or not there would be a recurrence of their malaria as long as they were under the protection of the program. This introduced another factor that plays a major role in volunteerism. This is the factor of a substitute parent.

One of the most striking factors influencing concern about risk was the protection provided by the research team. There develops by the volunteer an almost parental view of the research physician. In part, the research team has replaced the real family. Many prisoners would say, "I would do anything the doctor tells me to." Not only does this relationship remain strong in prison, but it tends to carry over after discharge. Some discharged prisoners attempt to use members of the research team for moral and medical support after leaving prison.

Money is as important in most jails as it is outside them. However, the value scale is different because money is much more difficult to obtain. In some jails money is contraband, but it undoubtedly circulates in all penal systems. Having money during one's incarceration enables one to buy certain privileges that are otherwise unavailable. But the need for money is most acute at the time a prisoner is to be released. The adjustment to a free-living society is made with greater ease when the returning prisoner has some financial independence. With rare exceptions, no provision has been made for the prisoner in terms of financial support. His first problem is to make a score soon after discharge. It is a fairly common consensus inside the prison that a return to crime, at least briefly, is the only way to manage during the early discharge period.

At present, one alternative to scoring is to be a prison volunteer. This provides the individual with a chance to gain financial independence for the critical period immediately following his release. Even with these opportunities, money earned by the volunteer is often spent while the inmate is in jail, and the inmate still leaves jail penniless. To whatever degree money may diminish the pressures on a newly discharged inmate to commit a crime, the payment for participation in medical research should be considered as a possible help in crime prevention.

Another prison force leading to participation in medical research is, surprisingly enough, the desire to do something worth while. It takes very little search of the *curriculum vitae* of these men to realize how little they have done for fam-

ily, friends, and society. A large proportion of those interviewed expressed a desire to make a positive contribution to society. The opportunities to satisfy this wish are often limited by the prisoner's dearth of skill.

In one part of this study volunteers were asked to respond to a set of statements by indicating those phrases that most clearly described their own feelings about volunteering. This group indicated that their participation in the malaria project would be a direct help to the servicemen in Vietnam. Several of the volunteers had been in military service or had relatives in it, and they felt they were making a positive effort toward eventual control of malaria. Others on the project stated that since they had experienced malaria, they would be able to help members of their family or friends if there would ever be an "outbreak of malaria" in the United States. It mattered little to them that there is no real likelihood of this happening. All of the volunteers interviewed, with the exception of three, felt that by volunteering they were doing something worth while. Volunteerism, therefore, offers them a sense of satisfaction, and this feeling is frequently expressed by the volunteers both before and after an experiment.

One other aspect of the study concerned the fringe benefits of volunteering. The volunteers were divided in their opinions regarding this issue. Half of our prisoners believed that by volunteering for medical research, they had improved their chances for obtaining a job once they were released from prison. Only a very few of this group felt that volunteering had increased their opportunity for early paroles. Examination of nonvolunteers indicated that they held the same views concerning the fringe benefits of volunteering. Ninety-two percent of the group indicated that the experience as human subjects would have no bearing on their life styles once they were again members of the free society.

In this study we made no attempt to chart the steps in the decision-making process. We asked our volunteer subjects how they had first learned about the research project. Most of them had heard about the project either from other inmates or from the nurses who went around and asked for volunteers. The volunteers were asked to try to remember what the other inmates had told them about the project. Remarks from the other inmates regarding the project could be placed on a continuum ranging all the

way from "they kill people down on malaria" to "medical research is the best way to do your jail time." The volunteers were asked what effect these remarks had on their decisions to volunteer. All of the volunteers, with one exception, indicated that the remarks of the other prisoners had no influence on their decisions to volunteer. Again, this is probably because this particular sample was made up of loners.

Although at various times we have had volunteers only from the "loners," this is not invariably so. At other times the jail cliques have strongly supported the program. At these times we can almost always identify the role of a single enthusiast who has great personal influence over a group of inmates. As we have indicated earlier, these groups are usually built around the street relationships.

If strong figures can turn on the flow of volunteers, they can also turn it off, except for those men whom we have called "loners."

We are also interested in knowing if the decisions to volunteer were made quickly, or if the prisoners thought for a long time before deciding.

About half of our group made up their minds to volunteer for medical research the same day they heard about the project. When asked if this decision had been an impulsive one, most of the volunteers responded that it had been made on impulse. Those volunteers who took a month or longer to make up their minds did not consider their decisions impulsive, but, on careful analysis, the long delays were often due to the fact that the prisoners were waiting for their jail time. We could conclude that decisions were very rapidly arrived at for most volunteers.

* * *

[ii]

*Daniel C. Martin, John D. Arnold,
T. F. Zimmerman, and Robert H. Richart
Human Subjects in Clinical Research**

* * *

[This] study attempted to determine why prisoners did or did not volunteer as subjects in a search for new antimalarial drugs and the extent to which they understood the element of

risk involved. Subjects of the motivation study were selected from inmates who had previously been asked to volunteer for the Malaria Project at the Jackson County Jail, Kansas City, Missouri.

The procedure originally used to enlist volunteers for the Malaria Project had been consistent with each prisoner. Inmates with sentences of one year or less were approached by a physician—one of the authors. He carefully explained the Malaria Project, the need for human subjects and the probable risks involved for the subjects. Each inmate was told that he would be paid for his participation but that he could expect no reduction of his sentence.

After the project had been explained in detail, inmates wishing to volunteer were examined to ascertain whether their current state of health permitted participation. Those determined to be in reasonably good physical and emotional health were given an "informed-consent" form to read. If they agreed to the conditions set forth in that document, they signed the consent form. To this point, all inmates who were approached had received the same initial explanation. However, those who volunteered continued to receive detailed information regarding the project, whereas nonvolunteers did not. During their extensive contact with the volunteers in the course of the project, the physicians continued to explain the element of objective risk (which was minimal). The process of the disease itself was explained in simple terms, and the discomfort that the volunteers would experience during the illness was carefully detailed.

In the present motivation study, two groups of inmates were interviewed. The inmates who served as volunteers in the Malaria Project (36 in number) comprised the first group. All had been ill with malaria and had been treated successfully. Inmates who could have volunteered for the project but did not (24 in number) made up the second group. The interviews and evaluations of the sample were carried out by behavioral scientists who were not involved in the clinical investigations of drugs and malaria.

The responses of these two groups (total of 60) were compared regarding their comprehension of the Malaria Project (that is, of the risks involved and the chances of being cured) and their reasons for volunteering or refusing.

The results of this pilot investigation pose more questions than they resolve. Inmates who had participated in the Malaria Project under-

* 279 *New England Journal of Medicine* 1426, 1427-1428 (1968). Reprinted by permission.

stood the nature of the disease and its probable threat to human life no better and no worse than those who had not volunteered. This occurred in spite of the fact that the volunteers had signed the "informed-consent" document and had continued to receive detailed information throughout the program. Although the physicians had repeatedly explained what the objective risks would be (and they were minimal), more than 60 per cent of the volunteers continued to describe the project in terms of "high risk."

The informed-consent procedure assumes that in reaching their decision, volunteers attempt to understand the information provided, consider the alternatives that have been explained and only then give free assent. The results of this short study indicate that the act of volunteering does not necessarily result from so logical a process. The volunteers' comprehension of the risks is little different from that of nonvolunteers, and, where it does vary, it is certainly not more accurate. Furthermore, very few in either group cited risk as a consideration in their decision. It becomes apparent that there are other issues involved in the decision to volunteer.

Both groups uniformly expressed belief in the importance of clinical research designed to discover new and better "cures" for disease. About half the participants gave "altruism," and the other half money, as the major reason for volunteering. One quarter of those who mentioned money gave "altruism" as a second reason. Nearly all the nonvolunteers believed that volunteering for such an enterprise was an "act of courage." Although nonparticipants gave a wide variety of personal reasons for not volunteering, they stated or implied respect for those who did volunteer.

The almost universal respect among nonvolunteers for those who did volunteer may offer some clue to the other group's reasons for volunteering. Although society at large regards prison life as having low status and few privileges, a system of privileges and status does operate within the prison itself. In a county jail, however, the opportunities to assert one's superiority are few, and those that do exist are open to a limited number of inmates. Projects like the malaria experiment provide many with a real chance to demonstrate their importance, not only to other inmates but to the "square Johns," and it is possible that this consideration takes precedence

over the weighing of risk and benefit implied by the informed-consent procedure.

* * *

NOTES

NOTE 1.

HOUSE OF DELEGATES OF THE AMERICAN
MEDICAL ASSOCIATION
RESOLUTION ON DISAPPROVAL OF
PARTICIPATION IN SCIENTIFIC EXPERIMENTS BY
INMATES OF PENAL INSTITUTIONS (1952) *

WHEREAS, During recent years, numerous medical and scientific experiments and research projects have been conducted partly or wholly in federal and state penal institutions; and

WHEREAS, Volunteers among the inmates of such institutions have been permitted to participate in scientific experimental work and to submit to the administration of untested and potentially dangerous drugs; and

WHEREAS, Some of the inmates who have so participated have not only received citations, but have in some instances been granted parole much sooner than would otherwise have occurred, including several individuals convicted of murder and sentenced to life imprisonment; and

WHEREAS, The Illinois State Medical Society's delegation to the American Medical Association's clinical session whole-heartedly supports research and progress in the fight against disease but does believe that persons convicted of vicious crimes should not qualify for pardon or early parole in this manner; now therefore be it

RESOLVED, That the House of Delegates of the American Medical Association express its disapproval of the participation in scientific experiments of persons convicted of murder, rape, arson, kidnapping, treason, or other heinous crimes, and also urges that individuals who have lost their citizenship by due process of law be considered ineligible for meritorious or commendatory citation; and be it further

RESOLVED, That copies of this resolution be transmitted to the Surgeons General of all federal services, the governors of all states, all officials of state and federal penal institutions and parole boards.

* *Digest of Official Actions*. Chicago: American Medical Association 617-618 (1959). Reprinted by permission.

NOTE 2.

ETHICAL COMMITTEE OF THE WORLD
MEDICAL ASSOCIATION
DRAFT CODE OF ETHICS ON
HUMAN EXPERIMENTATION (1961)*

* * *

Experiments not done for the benefit of the subject (whether healthy or ill) of the experiment, but solely for acquiring knowledge, should be conducted under the most stringent safeguards, as follows:

(a) The subject of the experiment should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

(b) No doctor should lightly experiment on a human being when the subject of the experiment is in a dependent relationship to the investigator, such as a medical student to his teacher, a patient to his doctor, a technician in a laboratory to the head of his department.

(c) Prisoners of war, military or civilian, should never be used as subjects of experiment.

(d) Civilians detained in any place as a result of military invasion or occupation, or for administrative or political reasons, should never be used for human experiment.

(e) Persons retained in prisons, penitentiaries, or reformatories—being "captive groups"—should not be used as subjects of experiment; nor persons incapable of giving consent because of age, mental incapacity, or of being in a position in which they are incapable of exercising the power of free choice.

(f) Persons retained in mental hospitals or hospitals for mental defectives should not be used for human experiment.

[iii]

Charles Black, Jr.

*Constitutional Problems in Compulsory
"National Service"*†

... Proposals for compulsory non-military service by young people show a considerable variety among themselves, and this variety gives to any constitutional discussion a tentative and very general character. But those proposals which I have seen would in some way require that those

young men, or perhaps even those young people, who are not selected for military service, enter, for a period of two or three years, some other kind of national, state or community training or service.

It may be needless to say that only the *compulsory* feature of these proposals raises serious constitutional issues. I cannot think that our Constitution inhibits us from tendering opportunities to our young people; the constitutional problems—and the very serious problems of policy—arise when we consider saying to these young people that they must accept one of the tendered opportunities or go to jail.

There is the Thirteenth Amendment. It seems, at first reading, that a distinction between "involuntary service," which is certainly the thing proposed, and "involuntary servitude," which the Thirteenth Amendment forbids, is too delicate to live in a constitutional atmosphere. . . .

To this principle there have been admitted, necessarily, exceptions based on history. The clearest and most important of these is the military draft. At this point I would suggest to you that the root-idea to which we ought to recur, in dealing with any suggested analogy from the draft, is that, in our public policy and in our constitutionalism, military service is and ought to be a striking, even a startling, exception, and not a thing which can readily be used for founding arguments by analogy. If one uses the military draft as an analogical basis for other invasions of personal freedom, then it seems evident that almost anything can be justified. Time forces me to make this point assertively, without briefing it, but I nevertheless emphasize it and commend it to your consideration. Either military service is an exception, a clearly delimited exception, from which analogical and *a fortiori* arguments may not be made, or there are few if any practical constitutional restraints in the government's dealing with our persons, whether we are 18, 8 or 80.

* * *

... In some manner or another, the military draft itself might be used to coerce, indirectly but effectively, participation in the National Service program. You can imagine the different ways in which this might be done—by holding up the military draft as a threatened alternative to entry, by drafting all who ceased to cooperate after

* 2 *British Medical Journal* 1119 (1962). Reprinted by permission.

† *Yale Law Report* 19–21 (Summer 1967). Reprinted by permission.

they had entered, and so on. It might even be suggested, though I hope it will not be, that Congress could provide for a universal draft, and then in effect parole those not needed in or really eligible for military service into civilian work groups.

Even this might not work. If the subterfuge were palpable enough (and anything so large-scale would be hard to conceal) the courts might not swallow it. But it is true that the Supreme Court ought to and traditionally does defer to Congress on the nature and size of the military establishment, and some use of the military draft to coerce non-military service might be devised, so sophisticated as to force the Court to go along with it.

I suggest to you that such a development would be most unfortunate. The use of mere fictions for supporting a course of action which very probably would violate the Thirteenth Amendment is a thing which it seems we ought to reject simply on hearing the issue stated. Or, at another and more realistic level, if it can reasonably be thought that this "National Service," standing in the open, would violate the Thirteenth Amendment, then the least Congress ought to do is to put it in the open, without protecting fictions, so that the processes of law may determine on the merits, unembarrassed by presumptions suitable only to real military determinations, whether the claim of unconstitutionality has substance.

* * *

b.

Deciding about Societal Interests and Priorities?

Jack Kevorkian
*Capital Punishment or Capital Gain**

Experimentation on human beings has, of necessity, been limited to volunteers during normal times whether it involves prisoners or others. However there is always a limit in such cases which curtails the means to any medical end, which detracts from the total of knowledge which might be obtained from the undertaking.

* 50 *Journal of Criminal Law, Criminology and Police Science* 50-51 (1959). Reprinted by special permission of the *Journal of Criminal Law, Criminology and Police Science* (Northwestern University School of Law). Copyright © 1959.

Capital punishment as it exists today offers a golden opportunity to break those limits by introducing into the situation an involuntary factor without destroying the necessary safeguard of consent. I propose that a prisoner condemned to death by due process of law be allowed to submit, by his own free choice, to medical experimentation under complete anesthesia (at the time appointed for administering the penalty) as a form of execution in lieu of conventional methods prescribed by law. After his choice has been made, let the condemned deliberate at his leisure, and have professional consultation at his request, and even let him reverse his decision within the week before the date set for execution.

The experiments should be very seriously outlined and should deal with questions that can be investigated under usual clinical circumstances on laboratory animals. They should be submitted from research scientists of many nations to an agency of the United States composed of reputable researchers who would select those deemed exceptionally promising. The same agency would then arrange for the research team to travel to the nation in which a prisoner has chosen to die under anesthesia. Thus the medical genius of all civilized nations can participate in a program of benefit to us all.

The medical, legal, and moral principles involved can best be discussed by considering the advantages and disadvantages to the parties concerned.

The disadvantages:

(1) For the condemned there is none. The choice is entirely his.

(2) For medicine, too, there is none. Physicians could not be executioners because their aim is not to kill but to learn. Ultimate death could be induced by an overdose of anesthetic given by a layman.

(3) For law one might say that the plan ostensibly tampers with the formality of law which stipulates executions in a prescribed manner. However, the plan simply offers a new form of execution which promises much more than the bleak aim of ending a criminal's life.

(4) For society it would mean tax dollars to run the agencies. But these costs need not be great, and a few human experiments would make allocations of funds for much animal work now in progress a complete waste of time and money.

The advantages:

(1) To the condemned it allows the dignity inherent in being permitted to decide how he

is to die. The only immediate rewards he can expect are the feeling of utility through death and the avoidance of a potentially harsh death (in contrast to non-condemned volunteers who usually anticipate special consideration at parole hearings). Furthermore, it would actually lengthen the condemned's life and create hitherto unthinkable "thirteenth" and even "fourteenth" hour chances of commutation.

(2) For medicine it would mean rapid progress in those fields where animal work cannot help (for one example, anatomy of the human brain). It also would make available a final and indispensable means of screening every new drug, device, or procedure before ultimate trial on sick patients.

(3) Law would acquire another beneficent aspect of enormous potential good to humanity. The plan would detract somewhat from the purely negative nature of capital punishment presently engendered by law.

(4) For society this proposed "judicial euthanasia" for the first time introduces the concept of recompensing into a matter now of pure vengeance. It offers a means of restoring some honor to the family of the condemned and of imparting positive significance to the death of his victim if he be a murderer. And it offers the ultimate means of assuring all of us and our descendants of improving health and lengthening life.

The plan differs markedly from the Nazi crimes of World War II which, in themselves, were wartime atrocities under the auspices of a demented government. The victims were unjustifiably condemned under makeshift "laws" on racial or political grounds; they were not asked for consent and were not anesthetized. The medical objectives were frivolous—the scientists sadistic.

The pros and cons of capital punishment are not at all involved in my proposal. My only contention is that so long as it is practiced, and wherever it is practiced, there is a far more humane, sensible, and profitable way to administer it. I have substantiated this through interviews with two men now facing electrocution, one of whom eloquently confirmed it in writing. Whether or not the plan is practicable on a worldwide basis remains to be seen. But it is feasible, and I hope that one of the states of our country which endorses capital punishment will legally allow a condemned man the choice and thereby set an example for the world to follow.

C.

Deciding about Harm?

Daniel C. Martin, John D. Arnold,
T. F. Zimmerman, and Robert H. Richart
*Human Subjects in Clinical Research**

* * *

The first phase of the study dealt with personal willingness to volunteer. Persons interviewed were arbitrarily drawn from fairly well defined groups that had been identified in terms of general socio-economic criteria. The subjects interviewed were clients of the Helping Hand (a Nazarene Mission) and other welfare recipients, maids and janitors, skilled maintenance men, policemen and firemen and professionals—that is, scientists, lawyers and educators. A sixth group, prisoners from the Kansas City Municipal Farm, was also included in the study. All subjects were interviewed privately and assured that their comments would be kept in confidence.

The study took the form of a simulated enlistment of volunteers for medical research. The subjects were aware that the experiments proposed were hypothetical. Each respondent was asked to volunteer for participation in each of four "experiments" investigating malaria, new-drug toxicity, the common cold and air pollution (poisons). In this last hypothetical procedure, the volunteer would exhale air into a machine that measured "enzyme efficiency."

These four "experiments" were selected because they presented the subject with different degrees of personal risk, different time demands, varying requirements for interrupting family or employment obligations and different degrees of social importance. It was expected that these differences would be apparent to the subjects.

The subjects were first asked to volunteer for participation in each of the four experiments in the sequence listed above. Little or no explanation was offered, but all questions were answered. After he had volunteered or refused to volunteer for each of the four, the subject was interviewed further. Regarding each experiment separately, the respondent was first asked what he knew about the disease. Those who had refused were also asked whether they would volunteer after receiving more detailed information, what they thought of those who were willing to volunteer and what inducements it would take to get

* 279 *New England Journal of Medicine* 1426, 1428-1429 (1968). Reprinted by permission.

TABLE 1
Willingness of Several Social Groups to Volunteer

Volunteer Group	TEST								Group Totals
	Malaria		Drugs		Cold		Air pol- lution		
	yes	no	yes	no	yes	no	yes	no	
Prisoners	40	20	44	16	49	11	50	10	60
Low income*	7	19	9	17	10	16	17	9	26
Fire & police	3	37	5	35	11	29	28	12	40
Professionals	0	28	1	27	2	26	26	2	28

* Welfare recipients & maintenance personnel.

them to volunteer. All respondents were then asked whether medical experimentation using human subjects was worthwhile, and where subjects should come from. . . .

Table 1 shows the frequency of volunteering for the various groups. Several groups have been merged because they gave similar reasons for volunteering or refusing to volunteer.

Table 1 clearly indicates that the hypothetical conditions elicit similar responses from all groups, in that each group shows least willingness to volunteer for the malaria experiment and a willingness that increases proceeding to "drugs" to "cold" and to "air pollution." It is inferred that the respondents perceive the four experiments in terms of differing degrees of risk or inconvenience or both. Even the prisoner group, generally inclined to volunteer for "everything," is least likely to volunteer for malaria and most likely to volunteer for the "air-pollution test," with gradations between. The evidence indicates that the four hypothetical experiments presented in the interview are responded to in low-to-high scalar fashion from malaria to air-pollution test.

Whereas all respondents are least likely to volunteer for malaria and most likely to volunteer for air-pollution tests, social groups having different socioeconomic characteristics are not equally willing to volunteer. It can be inferred from these data that people of lower socioeconomic circumstances show the greatest willingness to participate as subjects in clinical studies. In proceeding up the socioeconomic scale, willingness to participate greatly diminishes, except for the task (poison test) perceived as involving least risk or inconvenience.

The data were also organized along dimensions of age, sex, living conditions (with whom

do they live) and race. Examination of data by age and race shows no difference in any regard. When the prisoner group is extracted from the total, it appears that the sex of the respondent and the living arrangements do determine his willingness to volunteer.

* * *

In the tests that were perceived as having higher risk or discomfort, *women* demonstrate a significantly higher willingness to volunteer as human subjects. Both men and women perceive the requirements of the four tasks in scalar fashion. Experiments involving malaria are least likely, and air-pollution test most likely, to acquire volunteers, with gradations between.

* * *

In all experimental groups there is a significantly greater willingness to volunteer when the potential volunteer is not obligated to others. The closeness of that obligation seems to make a difference in willingness to volunteer. When subjects have only themselves to be concerned about, volunteering is relatively frequent. When they have obligations to others who are not "immediate" family, they demonstrate a lesser willingness. Willingness is lowest when the potential volunteer is responsible for spouse and children.

It should be noted at this point that all six groups uniformly agreed on the importance of human participation in medical research. For the most part, all groups indicated an understanding of the difficulties encountered in attempts to discover better ways to treat disease. They also spoke sensibly about the risks human subjects take in participating in such efforts. With the exception of the professional group, those inter-

viewed tended to emphasize what might be called the theme of "human responsibility."

* * *

2.

In Administering Research

a. Who Should Participate, within What Structure, in State Regulation?

[i]

*Committee Appointed by Governor
Dwight H. Green of Illinois
Ethics Governing the Service of Prisoners
as Subjects in Medical Experiments**

During the war the Governor of the state of Illinois and the Department of Public Safety permitted prisoners in one of the state penitentiaries in Illinois to serve voluntarily and without any prior promise of a pardon or a reduction of sentence in prison as subjects in medical experiments. These experiments were designed to find a better preventive and curative treatment of malaria. The question has arisen of giving a reduction of sentence in prison as a reward for such service in addition to that ordinarily allowed because of good conduct.

The expression "reduction of sentence in prison" is used to indicate that under the parole system the total sentence is not reduced since the prisoner is subject to the regulations of the Parole Board after parole, his activities are supervised and the board may return him to prison. A prisoner is not subject to parole or a reduction of sentence in prison until the minimum duration fixed by court has been served in the case of sentences for an indeterminate period (e.g., ten to twenty years) when the maximum is less than life and in the case of sentences for a definite term of years but not including life.

The committee was appointed by the Governor to advise the Department of Public Safety relative to the ethical principles governing the conditions under which prisoners may be (a) permitted to serve as subjects for medical experiments and (b) granted a reduction of sentence in prison as a reward for such service.

* * *

* A. C. Ivy, M.D., Chairman. 136 *Journal of the American Medical Association* 447-458, 461-465 (1948). Reprinted by permission.

It would appear likely that a reduction of sentence in prison as a recognition for service in a medical experiment is consonant with the statutory "good time," "merit time" and "industrial credits" provisions of the parole system.

Prisoners render meritorious services in prison, such as working in a barber shop, the kitchen, the shoe shop or furniture shop, and this service is rewarded. The rendering of such service is encouraged by the warden and his administrators, and service as a subject in a medical experiment may be similarly encouraged and rewarded.

Since one of the purposes of the parole system is reformatory, the reformatory value of serving as a subject in a medical experiment should be considered. Serving as a subject in a medical experiment is obviously an act of good conduct, is frequently unpleasant and occasionally hazardous and demonstrates a type of social consciousness of high order when performed primarily as a service to society. The extent to which the service of a prisoner in an experiment is motivated by good social consciousness on the one hand and by the desire for a reduction of sentence in prison on the other is a matter for consideration in the case of each prisoner.

Regardless of a prisoner's motives for volunteering for an experiment, a habitual criminal or a prisoner who has committed a notorious or heinous crime should not be considered an acceptable volunteer for a medical experiment.

The most important requirement for the ethical use of human beings as subjects in medical experiments is that they be volunteers. Volunteering exists when a person is able to say "yes" or "no" without fear of being punished or of being deprived of privileges due him in the ordinary course of events.

A reduction of sentence in prison, if excessive or drastic, can amount to undue influence. If the sole motive of the prisoner is to contribute to human welfare, any reduction in sentence would be a reward. If the sole motive of the prisoner is to obtain a reduction in sentence, an excessive reduction of sentence which would exercise undue influence in obtaining the consent of prisoners to serve as subjects would be inconsistent with the principle of voluntary participation.

It is not considered a function of this committee to determine where the reward becomes excessive. This is a matter to be considered in relation to each prisoner and the nature of the experiment.

Obviously no one may make representa-

tions to a prisoner concerning the extent and types of reward which may accrue as a result of his service as a subject in a medical experiment.

NOTE

RICHARD R. WILLEY
EXPERIENCE IN DESIGN, CONDUCT, AND
EVALUATION OF RESEARCH*

* * *

The motivation for prisoners' volunteering as subjects for research is also complex. I have heard Dr. Reuben Gustavson recount the days of the antimalarial testing at Joliet State Prison, in Illinois, about the time of World War II. He described the preparations that were made for the use of prisoners: the possible outcomes of the research were explained to them, the risks were explained, the possibility of sickness or death was explained. When the call went out for volunteers, a reasonable number responded. The research went along well until one prisoner died, obviously from the effects of the experimentation. The experimenters, at this point, expected the worst, anticipating that the volunteers would disappear. Much to their surprise, the number of volunteers increased markedly! It is rather interesting to reflect on why this might have occurred, what it was that was really motivating these men.

* * *

[ii]

Department of the Army Use of Volunteers as Subjects of Research†

1. *Purpose.* These regulations prescribe policies and procedures governing the use of volunteers as subjects in Department of the Army research, including research in nuclear, biological, and chemical warfare, wherein human beings are deliberately exposed to unusual or potentially hazardous conditions. These regulations are applicable world-wide, wherever volunteers are used as subjects in Department of the Army research.

2. *Definition.* For the purpose of these regulations, unusual and potentially hazardous conditions are those which may be reasonably expected to involve the risk, beyond the normal

call of duty, of privation, discomfort, distress, pain, damage to health, bodily harm, physical injury, or death.

3. *Exemptions.* The following categories of activities and investigative programs are exempt from the provisions of these regulations:

- a. Research and nonresearch programs, tasks, and tests which may involve inherent occupational hazards to health or exposure of personnel to potentially hazardous situations encountered as part of training or other normal duties, e.g., flight training, jump training, fire drills, gas drills, and handling of explosives.
- b. That portion of human factors research which involves normal training or other military duties as part of an experiment, wherein disclosure of experimental conditions to participating personnel would reveal the artificial nature of such conditions and defeat the purpose of the investigation.
- c. Ethical medical and clinical investigations involving the basic disease process or new treatment procedures conducted by the Army Medical Service for the benefit of patients.

4. *Basic Principles.* Certain basic principles must be observed to satisfy moral, ethical, and legal concepts. These are—

- a. Voluntary consent is absolutely essential.

* * *

- b. The number of volunteers used will be kept at a minimum. . .
- c. The experiment must be such as to contribute significantly to approved research and have reasonable prospects of yielding militarily important results essential to an Army research program which are not obtainable by other methods or means of study.
- d. The experiment will be conducted so as to avoid all unnecessary physical and mental suffering and injury.
- e. No experiment will be conducted if there is any reason inherent to the nature of the experiment to believe that death or disabling injury will occur.
- f. The degree of risk to be taken will never exceed that determined to be required by the urgency or importance of the Army program for which the experiment is necessary.

* 169 *Annals of the New York Academy of Sciences* 509 (1970). © The New York Academy of Sciences, 1970. Reprinted by permission.

† Army Regulation No. 70-25 (1962).

- g. Proper preparations will be made and adequate facilities provided to protect the volunteer against all foreseeable possibilities of injury, disability, or death.
- h. The experiment will be conducted only by scientifically qualified persons. . . .
- i. The volunteer will be informed that at any time during the course of the experiment he will have the right to revoke his consent and withdraw from the experiment, without prejudice to himself.
- j. Volunteers will have no physical or mental diseases which will make the proposed experiment more hazardous for them than for normal healthy persons. This determination will be made by the project leader with, if necessary, competent medical advice.
- k. The scientist in charge will be prepared to terminate the experiment at any stage if he has probable cause to believe, in the exercise of good faith, superior skill, and careful judgment required of him, that continuation is likely to result in injury, disability, or death to the volunteer.
- l. Prisoners of war will not be used under any circumstances.

5. *Additional safeguards.* As added protection for volunteers, the following safeguards will be provided:

- a. A physician approved by the Surgeon General will be responsible for the medical care of volunteers. The physician may or may not be the project leader but will have authority to terminate the experiment at any time that he believes death, injury, or bodily harm is likely to result.
- b. All apparatus and instruments necessary to deal with likely emergency situations will be available.
- c. Required medical treatment and hospitalization will be provided for all casualties.
- d. The physician in charge will have consultants available to him on short notice throughout the experiment who are competent to advise or assist with complications which can be anticipated.

6. *Approval to conduct experiment.* It is the responsibility of the head of each major command and other agency to submit to the Surgeon General a written proposal for studies which

come within the purview of this directive. The proposal will include for each study the name of the person to be in charge, name of the proposed attending physician, and the detailed plan of the experiment. The Surgeon General will review the proposal and forward it with his comments and recommendations on medical aspects to the Chief of Research and Development for approval. When a proposal pertains to research with nuclear, biological, or chemical agents, the Chief of Research and Development will submit the proposal, together with the Surgeon General's review, to the Secretary of the Army for approval. No research with nuclear, biological, or chemical agents using volunteers will be undertaken without the consent of the Secretary of the Army.

7. *Civilian employees.* When civilian employees of the Department of the Army volunteer under this program, the following instructions will be observed:

- a. Any duty as a volunteer performed during the employee's regularly scheduled tour of duty will be considered as constructive duty for which straight time rates are payable. Time spent in connection with an experiment outside the employee's regularly scheduled tour will be considered as voluntary overtime for which no payment may be made nor compensatory time granted. The employee will be so informed before acceptance of his volunteer services.
- b. Claims [are authorized to be] submitted to the Bureau of Employees' Compensation, U.S. Department of Labor, because of disability or death resulting from an employee's voluntary participation in experiments. . . .

* * *

b.

Who Should Participate, within What Structure, in Professional Regulation?

[i]

*Robert E. Hodges and William B. Bean
The Use of Prisoners for Medical Research**

* * *

. . . Because we needed [volunteers] urgently, we held a conference with officials of both pris-

* 202 *Journal of the American Medical Association* 513, 514-515 (1967). Copyright 1967 by the American Medical Association. Reprinted by permission.

ons, members of the Board of Control which governs these institutions, and physicians from several departments of the College of Medicine and the university hospitals. As a result of this conference, a working arrangement was agreed upon verbally. The physician who wished volunteers was to send a written request to the warden who would then ask for those inmates who wished to participate in a particular project. We knew that this procedure was not specifically permitted by law but neither was it specifically prohibited. But the law did permit the hospitalization of prisoners at the university hospitals for treatment of medical illness.

For a time things went well. As a result of this arrangement, we were able to conduct and complete many useful investigations. As time went by, new state officials were puzzled about this arrangement. On one occasion, the state attorney general was asked to rule upon the legality of our operation. In his judgment, it was not legal for us to accept prison volunteers for medical research. Accordingly, we discontinued use of prisoners for research purposes for two years. During this time, we sought and obtained enactment of a specific law permitting the use of prisoners for medical research at the university hospitals. This law states:

The Board of Control may send to the hospital of the medical college of the state university inmates of the Iowa state penitentiary and the men's reformatory for medical research at the hospital. Before any inmate is sent to the medical college, he must volunteer his services in writing. An inmate may withdraw his consent at any time.

Since enactment of this law, we have availed ourselves of this valuable opportunity to conduct clinical investigation in healthy volunteers under ideal investigative conditions.

One of the chief advantages of this arrangement is that it permits selection of men of any given age, height, and weight. By screening, the investigator can select persons who have a specific disorder, such as diabetes mellitus or hypertension. He can select subjects with any characteristic that might commonly be found within a prison population. These subjects can then be hospitalized in the metabolic ward under combined prison and research discipline or in the clinical research center under similar supervision for the time necessary to complete an experiment.

* * *

Once a faculty member has decided upon a

project, he presents his proposal to a research committee of the College of Medicine. Following the committee's evaluation and approval, the dean sends a note of approval to the investigator who establishes liaison with the prison authorities by calling or writing the director of penal institutions in the Board of Control and sends a copy of the message to the warden of the prison. . . . After the proposal has been approved by the Board of Control, the warden is authorized to present to the men a simple explanation of the type of study to be conducted and to provide an opportunity for volunteers to make themselves known. From these volunteers, the prison authorities select a suitable group of men who are not emotionally ill, nor habitually unreliable, nor otherwise unsuited for the project. Usually the authorities provide a select group of volunteers which is about double the number requested by the investigator. The investigators, along with the head nurse of the metabolic ward and other authorized personnel, then visit the prison for the purpose of explaining in detailed yet simple language the nature of the investigation, the risks involved, and the manner in which the study will be conducted. The volunteers are then given an opportunity to withdraw or to ask additional questions before accepting. After the final selection is made, the men are transported by prison authorities to the university hospitals where they are hospitalized either on the metabolic ward or on the clinical research ward. In no instance are prison research subjects housed on the open wards. After they arrive at the hospital, they are given an additional detailed briefing and an opportunity to ask additional questions. Then they sign a consent form and undergo the customary detailed history and physical examination followed by appropriate laboratory tests.

. . . For their participation in research activities, they receive no reduction of their sentences nor any favoritism regarding paroles. We do, however, send a letter to the warden at the termination of each experiment expressing our appreciation for the inmate's participation in the study. It is possible that this letter in the prisoners' file may favorably influence the parole board.

Since our first patient, who was an unofficial volunteer, we have accepted a total of 224 prisoners for medical research at university hospitals. Only a few of these represent "repeaters" since we try to avoid selecting a man more than once. . . . Of the total, ten have escaped. Most of the escapees were subjects for the medical experiment who had been selected rather hastily at the

insistence of an investigator; hence prison officials had not been given ample opportunity to make their usual careful selection.

The level of compliance by prisoners with research rules and regulations has been surprisingly high. They have eaten strange diets, swallowed tubes, submitted to repeated venipunctures, and participated in a wide variety of physiological tests with a commendable degree of good humor and cheerfulness. Although any man may leave the study to return to the prison if he so desires, this has happened in very few instances. . . . We feel that the use of prison volunteers for medical research is justified and highly desirable for the investigator, for the subjects, and for society. It not only permits the conduct of human investigation under ideal circumstances, but it enables the participants to feel that they are serving a useful function as indeed they are.

* * *

NOTE

THOMAS E. STARZL
ETHICAL PROBLEMS IN ORGAN
TRANSPLANTATION—A CLINICIAN'S POINT
OF VIEW*

* * *

[P]enal volunteers [for organ donation] had been accepted in our Colorado hospitals under conditions that it was thought would fully insure the protection of their individual rights and permit their complete freedom of choice, objectives that in principle may have been less realistic than with the identical twin minors. In any event, there is every reason to believe that this practice, however equitably handled in a local situation, would inevitably lead to abuse if accepted as a reasonable precedent and applied broadly. For these reasons, and because the donor motivation that characterizes proper intrafamilial transplantation could not be said to exist except in the most idealized and universal sense, the acceptance of criminal volunteers was permanently discontinued at the University of Colorado 1½ years ago.

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* 67 *Annals of Internal Medicine* (Supplement No. 7) 32, 35 (1967). Copyright 1967. Reprinted by permission.

[ii]

*Community Research Review Committee Requirements for Research Involving the Black Community**

PREAMBLE

In a time when the research findings of social and biological scientists are being used increasingly to justify political and legal decision-making, it is imperative that all parties responsible for research projects that may involve such extra-theoretical and -methodological uses pay careful attention to these issues in the planning, conduct and reporting of their research.

Since the major consequences of political and legal decisions of a social nature descend upon members of this country's black communities, the need for vigilance in the conduct of research in black communities is most acute.

Members of the black community do not believe that a large majority of social science investigators who conduct research projects in black communities are sensitive to the many extra-theoretical or -methodological issues that their research necessarily entails. More than that, members of the black community do not believe that most of these investigators are sensitive to cultural nuance which is a necessary input to any well-conceived and conducted research in the black community.

If an investigator obtains results that for one reason or another are inaccurate, or if the results of his investigations are used by people in powerful positions to effect abhorrent policies, the investigator may find his professional reputation tarnished, but the people who are recipients of the false conclusions or abhorrent policies may find their lives, psychologically and physically, in extreme danger.

"Academic freedom," "scientific objectivity" are ivory tower terms that are applicable to ivory tower activities. But, when these ivory tower practitioners step out into the world of people and begin to deal with human lives, they must accept a *pronounced* shift in the balance sheet of "Rights and Responsibilities"—away from the former and toward the latter.

When investigators use human beings in their research, they are *required* to provide assurances of ethical and moral treatment for these subjects. Furthermore, these investigators are re-

* Boston: Black United Front (1971). Reprinted by permission.

quired to abide by all Civil Rights statutes as they may apply in the conduct of their research. Members of the black community feel we need such assurances also. We further feel that we need to have a working, first hand relationship with all research conducted in our community to insure the faithful, steadfast adherence to our interest in self-preservation.

However, all research conducted in the black community is not academic. A vast amount of money directly from political sources is spent on projects and programs in the black community. These programs themselves are often not research in the sense of data gathering and analysis. However, funding sources like to know how well or productive their grant or program dollars are spent. Evaluation is the inevitable consequence.

The black community can no longer allow foreign parties uncontrolled access rights. Every viable institution or entity in this country maintains the right of ultimate control. We of the black community feel that such control is critical to our collective survival, and further, to our ability to formulate the concepts and experiences which will move us toward a collectively liberated future.

Pursuant to the issues raised above, we have organized and adopted the following set of principles as guidelines for the conduct of all research in the black communities of the greater Boston areas.

Guidelines

1. A Committee composed of Black agencies, organizations, professional groups, and individuals from the Black Community, representing 25,000 Black people, was established by the Boston Black United Front as the Community Research Review Committee (CRRC). The CRRC's function is to review research being conducted or proposed in the Black Community, and to determine whether, in its judgment, such research and/or its implications will be in the best interests of the Black Community.
2. All research grant proposals that intend to use Black subjects and/or facilities in the Black Community are subject to review and approval by the CRRC *before* any such research may begin, and are subject to continuing approval by this Committee.
3. All research conducted in the Black Community must involve Black personnel at significant positions of authority. The role of such Black staff would, of course, vary with different

kinds of projects and investigations, but must include significant involvement in the *design and development* of the study. Generally, the primary role would be to protect the interests of the Black Community.

* * *

5. Those research projects approved for operation in the Black Community will necessitate monitoring of all project activities for their duration.

- a. Approved Black staff, as well as consultants, must be involved in all aspects of the study including:
 - (1) design and development of the study
 - (2) implementation of the study
 - (3) monitoring of the study
 - (4) analysis and interpretation of the results
 - (5) preparation and publication of reports, papers, talks, etc., based on the research data.
- b. Copies of all data, subsequent analyses, and relevant materials must be available for deposit with the CRRC as these become available. The confidentiality of such materials will be maintained by the CRRC.

* * *

d. After analyzing the data, summarizing the results, and preparing a preliminary final report, but *before* disseminating any such information to the funding source, or to the professional or lay public, the principal investigator must:

- (1) circulate a copy of the proposed report to the CRRC for review and comment, criticism, and, if necessary, rebuttal. If the principal investigator has the report independently reviewed of his own initiative, such reviews must be included with the report when it is sent to the CRRC.
- (2) agree to include (under separate authorship) *as part of the final report and as part of any subsequent publication of the findings*, a critical presentation of any alternative interpretations of major findings which cannot be reconciled with the principal investigator's main finding.

6. The monitoring activities imposed on the CRRC by the operation of a project in the Black Community are substantial. Therefore, the expenses of the monitoring are to be borne by each project in question. These expenses, not to

exceed ten percent (10%) of the total project funds, are calculated on a project by project basis.

* * *

[iii]

*Harvard Medical School
Rules Governing the Participation of
Medical Students as Experimental Subjects**

The participation of medical students as experimental subjects in research studies has raised practical and philosophical problems difficult to resolve. Misunderstandings have arisen, owing in part to inadequate communication and in part to the complex nature of the issues involved.

In discussing this situation, the principles that should govern the employment of human beings as research subjects, the motivations of medical students in volunteering, the educational implications, the matter of financial remuneration, the protection of health, the conflict with scheduled studies, the moral and legal responsibilities of the investigator and of the Medical School, and the advisability of the centralization of all pertinent records, have all been considered by the Administrative Board and the Faculty of Medicine.

After extensive study of these points, the University Health Services and the Dean's Office formulated the following policies and procedures, which have been unanimously approved by the Administrative Board and supported by the Faculty of Medicine.

Statement of Policy

1. The guiding principle in considering the participation of medical students as subjects in experiments is the belief that no student should be exposed to risk as far as his health and well-being are concerned.
2. A student's time should not be invaded to the extent of creating conflicts with his scheduled work.
3. Inasmuch as motivation should stem from an opportunity to learn and to contribute, rather than from a financial inducement *per se*, payment should not ordinarily be made to the student for participating as a subject in an experiment. This does not preclude remuneration for collaborating in a research project nor for participation in programs in which a student may be employed during vacation

periods, or under special circumstances at other times during the academic year, or as a Student Research Fellow.

4. The contact between investigator and student is recognized as an excellent opportunity for the investigator to demonstrate to the student both his personal responsibility for the student's health and safety and an active interest in furthering the student's education.

Procedure

In order to simplify and to standardize the participation of medical students as experimental subjects, the following administrative procedure has been established for the mutual benefit of the student, the investigator, and the Medical School.

1. Each project must be approved by the head of the department, of which the investigator is a member. This provision specifically shall include approval of the desirability of the proposed study, the details of the experimental protocol, and the use of medical students as subjects. It shall imply, in addition, the assumption of responsibility for any medical expenses that the student may incur as a consequence of participation.
2. Subsequent to such approval, a detailed protocol must be submitted to the Director of the Medical Area Health Service and to the Dean's Office. In experiments involving the use of radioactive materials, a copy of the protocol shall be submitted also to the Secretary of the Committee on Medical Research in Biophysics.
3. Following review and commentary by these parties, the protocol must be presented to the Administrative Board for discussion and for approval or disapproval of student participation.
4. If approved, the investigator must explain the details of the project to the medical student in advance, and must refer him to the Health Service for medical clearance before beginning the experiment. The result of the Health Service's examination shall be sent in writing to the investigator.
5. The Health Service must maintain records of the research projects in which medical students participate. These records shall include dosages of drugs or radioisotopes used on each individual and the total body irradiation received. In addition, the investigator must report to the Health Service concerning any significant medical observations that are made during the course of a given experiment.

* Memorandum from George Packer Berry, M.D., Dean (1968). Reprinted by permission.

c.

Should Research Design and Scientific Merits Be Evaluated?

Norval Morris
*Impediments to Penal Reform**

* * *

It has recently become fashionable to stress our lack of knowledge of the relative efficacy of our various treatment methods and I do not wish on this occasion to retrace that melancholy story. The central question eludes us: which treatment methods are effective for which types of offenders and for how long should they be applied for optimum effect? . . . At last, however, there is widespread verbal agreement (if not action) that we must critically test our developing armamentarium of prevention and treatment methods, and that to do so requires testing by means of controlled clinical trials. Follow-up studies, association analysis, predictive attributes analysis—no matter how sophisticated other research techniques we apply, we cannot escape the need for direct evaluative research by means of clinical trials. And this leads me to the next impediment to penal reform—clinical trials themselves raise important ethical issues that demand consideration.

* * *

There is . . . a respectable and reasonable ethical argument against clinical trials of correctional treatment methods which must not be buried in our enthusiasm for the acquisition of knowledge. It runs like this: Terrestrially speaking man is an end in himself; he must never be sacrificed to some self-appointed superman's belief that knowledge about man's behavior is of greater value than respect for his human rights. This is particularly true if the sacrifice is made without his uncoerced and fully informed choice. The explorer may, choosing thus freely, risk his life in the pursuit of knowledge. The citizen may, under certain controlled conditions, risk his life and physical well-being in furtherance of medical experiments. But when hint of coercion, or restraining or unduly influencing pressures appear, it is (choose your epithet) sinful, unethical, socially unwise, to permit such sacrifice of the individual to the supposed collective good. The argument shifts, of course, in wartime; but then

the threat to the collectivity is seen as the overwhelming value.

Put in less pretentious terms, the proposition is: given that our knowledge is exiguous, nevertheless, we must at all times act in the way that within that knowledge is thought best for the individual we are treating. When the problem of his treatment raises (as it does generally in relation to criminal sanctions) the issue of the proper balance between the community's need for protection from him and people like him, and his treatment needs if he is to be reestablished as a member of society, conforming sufficiently to avoid criminal conduct, the same principle holds true; we are never justified in applying other than our best judgment concerning that balance for the sake of experimentation aimed at expediting the acquisition of knowledge of how to handle like cases in the future.

It is my view that the ethical argument against clinical trials is not convincing and that, given certain safeguards, it is entirely appropriate, indeed essential, for evaluative research projects of this type to be built into all new correctional developments. The two safeguards that I have in mind may not in perpetuity solve the problem, but they do at least provide sufficient protection of human rights for many decades of correctional research.

First, we do not have to apply such research techniques at the stage of judicial sentencing; they can well operate within the sentence that the judge has determined to be the just and appropriate sentence. Secondly, by applying a principle which might be called the principle of "less severity," abuse of human rights can be minimized.

Experiment at the judicial stage is not necessary since correctional sanctions already include wide diversities of treatment within the judicially imposed sentence. A defined term of imprisonment may in any one state involve a commitment to possibly extremely different types of institutions having substantially different reformatory processes and with appreciably different degrees of social isolation. And given the operation of discretionary release procedures, including parole, most prison sentences permit widely differing periods of incarceration. Likewise, a sentence of probation can lead to a close personal supervision or to the most perfunctory experience of occasional reporting. The range of subtreatments within each correctional treatment is thus very wide; so wide that ample room for evaluative clinical research into these

* 33 *University of Chicago Law Review* 627, 646-653 (1969). Reprinted by permission.

subtreatments exists without interference with judicial processes. Of course, as information relevant to sentencing emerges from such administratively created clinical trials, it will be fed back into the judicial process and will then create new opportunities for further evaluative research. And knowledge will grow without experimentation at the judicial level.

"Less severity" is the other safeguard. By this I mean that the new treatment being studied should not be one that is regarded in the mind of the criminal subjected to it, or of the people imposing the new punishment, or of the community at large, as more severe than the traditional treatment against which it is being compared. To take a group of criminals who otherwise would be put on probation and to select some at random for institutional treatment would be unjust; conversely, to select at random a group who would otherwise be incarcerated and to treat them on probation or in a probation hostel would seem to be no abuse of human rights. Applying this principle it is possible to pursue many decades of valuable evaluative research.

There are many methodological problems in evaluative research. I do not wish to deal with them now, but rather to continue to focus on these ethical issues. Have these two principles of administrative rather than judicial experimentation and "less severity" sufficiently disposed of the ethical problems? Let us probe this question by the classroom method of a hypothetical case. Last night this problem was on my mind when I went to sleep and I had a dream which still troubles me. I dreamt that I observed and heard a conversation between a furious burglar sitting in his cell and a garrulous social scientist. Physically, each was a Lombrosian stereotype, and their speech too was a caricature of what one would expect from their widely different backgrounds and experiences. I cannot precisely recall their words, and perhaps it is a mercy that neither the sociologese nor the scatological blasphemy have remained in my mind. I can, however, describe the situation in which they found themselves and, later, in less colorful terms than theirs, tell you the substance of their conversation.

In my dream I saw the furious burglar sitting in his cell. He was part of our control group. The experiment had been impeccably and carefully designed. We desired to test the wisdom of releasing a defined group of offenders some three months earlier than they would otherwise be re-

leased by sending them to a recently established halfway house where daily they would go out to work and where their evenings and leisure time would be devoted to guided group interaction, using the most modern techniques, and to other processes designed for their easier and more effective resettlement into the community. This relatively new type of facility had been legislatively and administratively established as an "experiment" which, as you know, is the name of all new penal developments. This experiment differed from the usual experiment in that the social scientists were allowed to make it an experiment.

The group of offenders thought suitable for this new type of treatment had been carefully delineated in terms of their personalities and background. Since the halfway house could accommodate only twenty people it became necessary to discover how many such offenders would be found in the prison system. A careful assessment of the prison population and cautious predictions of its likely future shape led to the view that there were at any one time forty prisoners precisely matching the criteria for selection for this new treatment facility. It was therefore decided that the diagnostic center would be responsible for the selection of the prisoners who fell and might fall within this category; that they would be given a code number; and that chance would be allowed to condition whether a man fell within the T group, and would go to the new halfway house, or the C group, and would be treated just as he would have been had the facility not been built. It was, of course, early and necessarily decided that the C group must never know this had happened and that the T group must never know that they were part of a controlled experiment—though, of course, it would be clear to them that new opportunities were being given to them. They must believe that they were given these opportunities because the staff of the diagnostic center had convinced the parole board of their peculiar suitability for the halfway house. They might prefer to believe that they had conned the diagnostic center and the parole board, this being an even better belief, experimentally speaking. My furious burglar fell within the C group. My social scientist had been garrulous indeed, and a series of indiscretions had led to his revealing this fact to the burglar. That is why the burglar was furious.

FB (Furious Burglar): You mean you're holding me here because of some . . . experiment!

GSS (Garrulous Social Scientist): Yes.

FB: Why didn't you tell me?

GSS: It would spoil the experiment . . . the Hawthorne effect, you know.

FB: Habeas corpus? What chance?

GSS: That is a somewhat difficult question. I am told that it has some constitutional aspects to it. To my knowledge the matter had never been tested. You should ask our Legal Aid Division.

FB: Wasn't it tested in the Nuremburg Trial?

GSS: Everyone knows that was different.

FB: How different?

GSS: Well, you see, the Nazi experimentation met our criterion that the decision must be administrative and not judicial but it did not meet the important and to my mind determinative criterion; that is, the new treatment we are testing must be, in our eyes, and in your eyes, and in the eyes of all right-minded members of the community, a lesser infringement on freedom, a lesser suffering, than the traditional punishment against which it is being tested and which would otherwise be applied to everyone. You have not lost anything; twenty people just like you have gained, but you have not lost. And think what good you do for others. We will learn how to develop better release procedures; earlier release for some is a likely result; crime will be diminished. You should be thanking me, not complaining.

FB: I'm complaining. Obfuscate it as you will, because of your . . . experiment, I'm here. Have I an action in false imprisonment against you, or the warden, or the governor?

GSS: That too is a matter for our Legal Aid Division but I don't think you do. We have not increased the maximum of your legally prescribed punishment in any way. Why are you complaining? You had a fifty per cent chance of getting out three months ago; we were quite fair; without us you would have had no chance.

FB: You lie. The halfway house would have been set up whether you had anything to do with it or not. The prison administrators are not conned by you social scientists; that's just the way they get federal subsidies. I know and you know that I am peculiarly suited to release to a halfway house and that I can talk well to the parole board and that if you had kept your white coat out of it I would have had at least an eighty per cent chance of being sent to that halfway house. By grouping me with those other thirty-nine and tossing coins, you reduced my chances to fifty per cent. Surely it must be clear to you that it is

thirty per cent likely that I am here because of your . . . experiment.

GSS: All of us must suffer in the cause of science, you know. Your error lies in failing to appreciate that men must fall into categories for purposes of social research, they cannot be seen entirely as individuals, and we treated you fairly as part of your appropriate category.

And then the garrulous social scientist stalked out of the cell mumbling, "How else will we ever learn?" and slammed the cell door shut behind him, which awakened me. The dream continues to trouble me. I think there were one or two more things that the garrulous social scientist should have said in his own defense, but I am not sure that they are finally convincing. He should have pointed out the randomness of the whole edifice of correctional sanctions. He might well have stressed that repeated studies over the past forty years have beyond a doubt established the gross irrational variations in sentencing practice, even within the same courthouse, and should have tried to persuade the burglar that this type of experimentation was one effective way of acquiring knowledge relevant to the elimination of such unjust disparities. He might have more strenuously argued that the need to devise treatments suitable to categories of individuals sometimes of necessity involves an insufficiently fine balancing of differences between them, and that the burglar's differences from the other thirty-nine in the punishment control group were so slight as to be immeasurable in the macrocosm of the sentencing and punishing jungle. I think he should have tried more diligently to persuade the burglar of the need for such groupings of individuals, if knowledge of rational treatment methods is ever to be acquired. I doubt that he would have succeeded, and I am convinced that it is unwise to employ a garrulous social scientist.

Some have suggested that one way of avoiding this dilemma is, in an experiment of this type, to have arranged that both the treatment and the control groups obtained an advantage over the traditional punishment. That is, that in the previously considered experiment, twenty should be sent to the halfway house three months before their otherwise planned release and twenty should be completely released at the earlier time. Though this minimizes the ethical problem, it does not eliminate it. Now the furious burglar who is complaining is to be found in the halfway house bemoaning the fact that he is under the de-

gree of control that he is there. And also, it becomes a different experiment, and it will be necessary if effective knowledge is to be gained from the experiment to compare both our freely released group and our halfway house group with some control group still in the institution if the maximum knowledge is to be gained from the experiment—and they have cause for complaint.

* * *

In conclusion, let me say that it is my position that the ethical difficulties in empirical evaluation research are so slight as not to constitute a serious impediment to it. I confess that I feel happier when such projects test differences of practice within existing treatments, so that no burglar will bother to be furious, but I know that is no answer. My final reason for not being persuaded by the furious burglar, even in his precise situation, is this: the whole system of sanctions, from suspicion to arrest to trial to sentence, punishment, and release is now so full of irrational and unfair disparities that marginal arguments of the type the furious burglar produces are to me lost in the sea of injustice from which in the long run we can only be saved by these means. Yet I remain on his side to the extent that I abhor experimental design which is not anxiously perceptive of these ethical problems and does not do its utmost to minimize them.

* * *

d.

Should Consent Be Supervised?

[i]

Louis Jaffe

*Law as a System of Control**

* * *

There appears to have crept into the thinking of some people the notion that the motivation of a consenting subject should be disinterested, that he should be acting for the benefit of mankind. There is a disposition, for example, to scrutinize closely the motivation of prisoners and to exclude their use because their presumptive motive is self-interest. This line of thinking seems to me to reflect an excessive ethical fastidiousness. (It may also possibly proceed from a subcon-

scious impulse to glorify the enterprise—which, it is thought, might be sullied by the participation of unworthy persons.) But assuming that the experiment otherwise satisfies professional standards, the only requirement, in my opinion, is that no “undue” advantage be taken of the subject. A prisoner, even a patient, may be under pressures to consent not present in the situation of a citizen at large or a stranger. But those pressures should not be accounted an undue advantage. A prisoner, for example, may consent in order to give meaning to his life or because he hopes (though no promise has been given) to receive favorable treatment. A stranger may consent because he is paid, because he seeks excitement, or because he has a problem. Indeed, the motivation of consent is so complex, so various, and so obscure that it defies determination.

From the point of view of the experiment, the motivation of the subject is irrelevant unless his psychology is a factor in the experiment. From the subject's point of view, there is no lack of respect in allowing him to decide to participate for what seem to him to be sufficient reasons. He must be treated fairly, and the touchstone of fairness is, for the most part, what in retrospect will seem fair to him. Indeed fairness is at the heart of the whole consent problem, at least from the point of view of the subject or the patient.

... Assuming that the subject has the requisite minimum of intelligence, presumptively what he thinks is fair suffices to justify the experimental action. Both law and morals disapprove of the use of certain tactics in securing consent—such as falsification, failure to state crucial facts, and undue pressure. What is “undue” is a function of the situation. We can decide (as, for the most part, we have) that to seek the consent of a prisoner is not undue despite the presence of pressures absent in the case of the citizen at large. He must not, however, be threatened with adverse consequences if he refuses, and for this reason his refusal should not be of record. Let us admit that problems arise in part because there are disturbing contradictions in the prison situation itself. But that statement characterizes almost any life situation, and for that reason it may be the path of wisdom to focus on the simplicities. Experimentation on prisoners offers advantages to the experimenter, to the prisoner, and to the public. It offends, I believe, only a very few persons. . . .

* * *

* 98 *Daedalus* 406, 423–425 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

[ii]

Edmond Cahn

*Drug Experiments and the Public Conscience**

* * *

Reasonable compensations for serving as subjects are entirely warranted provided they do not operate to purchase or coerce an unwilling consent, particularly from those who are poor or in hospital wards or derelict. It is clearly wrong to purchase the consents of prisoners by offering them a release or parole or any equivalent inducement that exercises a coercive effect. There is not much to say for a society that sends a burglar to prison for ten years and gives him to understand that he can be free in five if he subjects himself to medical experiments.

* * *

3.

In Reviewing Decisions and Consequencesa. **Through Public and Professional Scrutiny?**

[i]

*Drug Investigation Committee of the
Medical Association of the State of Alabama
The Use of Prisoners for Drug
Trials in Alabama†*

* * *

It appears that the Southern Food and Drug Research, Inc. has been operating a research program in the Alabama Prison System since 1962 with the approval of Commissioner Frank Lee and the Alabama Board of Corrections. The president of Southern Food and Drug Research . . . is Dr. Austin R. Stough who is a graduate of the University of Oklahoma and of the Medical College of the University of Tennessee. He conducted research programs in the Oklahoma prison system before coming to Alabama. Dr. Irl Long who was previously in general practice in Montgomery and who is still prison physician for Kilby Prison is associated with Dr. Stough

in providing medical direction for Southern Food and Drug Research.

The original emphasis for Southern Food and Drug Research was on a plasmapheresis program but this was discontinued in 1964 following an outbreak of hepatitis which involved 376 prisoner participants with three deaths. (A Public Health Service investigation showed that the outbreak was definitely linked with the plasmapheresis program and a significant break in aseptic technique was found which accounted for this.) In 1963, however, the Food and Drug Administration set for the various drug houses much stricter standards for drug testing and these included a greatly increased demand for Phase I testing (Phase I testing is that done on healthy humans after completion of the animal experimental work). As a result, proficient investigators with adequate facilities were in considerable demand and Southern Food and Drug Research then concentrated its attention in this area.

Over the years since then, the drug houses seem to have been generally satisfied with what was done in Alabama and the Food and Drug Administration has had no specific complaints although they queried the number of investigations being done at any one time as being perhaps too many for adequate medical supervision by the limited medical staff of Southern Food and Drug Research. Internal control over the program by the Board of Corrections and its officers appears to have been limited in amount with the medical member of the board (Dr. McLaughlin) briefly reviewing the protocols for each new drug trial and occasionally mentioning them to members of the Board.

Membership on the Board of Corrections is not a full-time position. With their primary interest to attend to, it could not be expected that members of this board be completely and constantly aware of every transaction affecting the prison system at a given time. A busy physician could not devote the time required to properly evaluate the protocols without neglecting his private patients.

The Commissioner and his wardens apparently gave Dr. Stough and his group ready cooperation with very few questions being openly asked. The prison physicians for the other two prisons involved in the drug testing program (Dr. Edwards at Tutwiler and Dr. Mracek at Draper) generally required that they be kept advised of new drug-testing programs in their own prisons when they were initiated.

* * *

* Paul Talalay, ed.: *Drugs in Our Society*. Baltimore: The Johns Hopkins Press 225, 263 (1964). Reprinted by permission.

† Tinsley R. Harrison, M.D., Chairman (1969). Reprinted by permission.

In January, 1969, the *Montgomery Advertiser-Journal*, over the byline of Mr. Harold E. Martin (Editor and Publisher), launched a series of attacks at the drug-testing program being conducted in Alabama prisons. In addition to hinting at excessive profits being made at the expense of the health of the prisoners by Southern Food and Drug Research, certain additional medically oriented accusations were made:

1. Although the inmates signed a waiver they were not told of the possible effects of tests while the prisoners' strong need for extra money largely invalidated the requirement of informed consent.
2. Physical examinations were not being performed before each program as required in some protocols.
3. A doctor was not present during many of the potentially critical periods of reaction.
4. Some of the experiments left the men too sick to perform their regular duties.
5. Prison inmates drew blood and performed other technical procedures.
6. The contrast between the facilities for the private concern's testing program and the extremely inadequate facilities available for treating sick prisoners was shocking.
7. A number of quite serious reactions had occurred among prisoners but these had received little attention.
8. The administration of the program, with prisoners sometimes giving false histories and not taking the medicine provided for them, made the results of the testing program somewhat unreliable.

The newspaper articles were not entirely negative and they did point out that needed research was carried out, inmates did receive money to buy cigarettes and other needs, and the Prison Welfare Fund received some monies which could be used for programs that the state did not provide. (At Kilby and Draper twenty percent of the money paid to the prisoners went to the Prison Welfare Fund.) The newspaper suggested that the entire program be placed under the authority and supervision of the University of Alabama Medical School, that the participants be properly remunerated, that profits from the program should go for improvements in the prison system, that the testing program be so scheduled as not to interfere with the work or training at the prison, that the participants be clearly informed of possible dangers involved in the program, that the controls over the program provide for good scientific evaluation and that

good medical supervision be exercised at all times.

Following this adverse publicity which carried distinct connotations of laxity on the part of the Board of Corrections and possible dishonesty on the part of certain of their senior employees, the Board of Corrections adopted the following resolution:

That the Chairman be authorized to appoint a committee of two or more persons qualified to determine from a medical standpoint, and not connected with the Board of Corrections, to investigate any drug-testing programs conducted in the state prisons, to determine whether the programs are properly supervised to protect the health of the participants, both in testing and in the event of any aftereffects of the testing, to determine whether any prisoners are being abused in any way, and to report to the board their findings.

Upon receipt of this request, this committee was appointed by the governing body of the medical association. This report constitutes our findings.

* * *

1. Prison Testing Facilities

* * *

At Kilby Prison a list was seen of prisoners who had been selected by Southern Food and Drug Research from their records as being suitable subjects for a new test which was being started that morning. No person in the prison system had any hand in selecting this initial list. From about 60 names which had been submitted, the warden had deleted about ten because, so he advised us, these persons could not be spared by their division heads from their official prison occupation. Most of the remaining 50 prisoners had been called into the testing room in the prison that morning in groups of about six persons. While blood was being taken from them (apparently for laboratory testing) they had received a rapid explanation of the purpose of the test (there was considerable variation in the understanding of what had been said), with the statement that the drug being tested was safe and, should the laboratory tests be satisfactory, they would be asked to sign a waiver-consent form. All this had seemingly been done by technicians with no physician being present as far as could be determined. Two of the four prisoners who were interviewed indicated that they had never been examined by a physician while they were in the prison although they had been on

several drug trials. One of these prisoners told of tests with an anti-hypertensive drug which had had to be discontinued after three weeks (the trial was supposed to run for four weeks) because of severe reactions among those taking the pills. He himself had hung on to the end although he had been feeling very ill and had not complained of this illness, because it would have meant his losing the pay which he was hoping to receive for his participation. The majority of the prisoners interviewed indicated that the only reason they participated in the drug trials was because of the money which they were paid.

* * *

Conditions in the so-called hospital at Kilby were appallingly bad and would not have been acceptable fifty years ago, let alone today. One felt that a little extra effort and a little additional money would have made a tremendous difference if only the drive had been there. The importance of this hospital at Kilby is that it turned out later that persons having severe reactions to any of the drug trials in any of the prisons were transferred to this hospital for more intensive care.

* * *

The situation in Draper was similar to that which had been found at Kilby, though not as bad. The difference was probably related to the dedication of the prison physician and to the strong sense of responsibility of the warden. There was no question here but that inmates had been used as technicians until very recently, while severe drug reactions were not being given the attention (medical or experimental) which their condition deserved. Supervision for patients who had been "stopped up" in the special room constructed by Southern Food and Drug Research appeared to be almost entirely non-medical in nature and no really adequate provision had been made for any serious, unexpected, severe reaction. Once again, it appeared that most of the prisoners were volunteering purely for monetary reasons and were staying on the tests even after disturbing reactions had occurred simply to be paid more. . . .

Your committee believes that, by and large, the research studies completed and published in highly respected journals by staff members of Southern Food and Drug Corporation represent creditable, useful, and practical contributions to medical science. However, this good should not be permitted to hide the manifest defects in the present system.

The Board of Corrections with its physician member has naturally assumed that any doctor conducting experimental studies on human subjects would take the utmost precautions to safeguard the health of such subjects. Their confidence has been gravely abused.

* * *

This committee was confronted with a seeming conflict of interest when it viewed the dual role of Dr. Irl Long serving as both senior prison physician and as an officer of Southern Food and Drug Research. Even Dr. Long readily acknowledged that a potential conflict of interest could exist. This unconscionable situation, regardless of reason, should never have been permitted to come into existence. This situation places all persons concerned in an untenable position exemplified by the necessity for the investigation.

* * *

3. *Drug-House Relationships*

Reputable drug firms are concerned with developing and producing effective, safe medications. Their record in carrying out this function is unassailable. In their search for new therapeutic agents they maintain an impressive laboratory operation with a competent, highly trained research staff. . . .

* * *

In the present instance there is no reason to believe that the pharmaceutical firms failed to act in good faith or failed to discharge their responsibility to the general public to develop safe effective therapeutic agents. They contracted with approved clinical investigators to carry out approved research projects. However, there are some points for possible criticism: (1) There may have been a too superficial monitoring of the clinical work which they support. (2) They demonstrated some lack of discretion in selection of their Phase I investigator. Thus, there was a need to consider the number of projects to which the prospective investigator was already committed. (3) Their initial conference sessions may not have provided for adequate grounding of the investigator in all the significant basic properties of the test material, a particularly important point when the limited training in basic pharmacology of both clinical investigators (Drs. Stough and Long) is considered.

That the drug manufacturers are interested in conducting and supporting research programs of quality is confirmed by a consideration of two

clinical programs established and operated by two of the major firms, the Upjohn Company and Parke-Davis at the Southern Michigan State Prison. These programs involved an initial expenditure of perhaps one half million dollars for facilities and are generally believed to be first class, both in providing for optimum safety and welfare of the human subjects and in providing dependable clinical data.

There is no reason to doubt that excellent programs are desired by the drug manufacturers or that they would support such programs. Despite this, both the drug firms and FDA have given tacit approval to the research in Alabama prisons, and approval based on their confidence in the reliability of data so obtained. It should be noted, however, that neither is primarily concerned with the rights and welfare of the institutionalized research subject. There is within the body of the law some provision for protecting the welfare and rights of prisoners used as research subjects, but in the absence of sufficient funds and some watchdog mechanism, these rights may be abused. There is the justifiable view that the drug manufacturer is not abandoning any moral or ethical responsibility in assuming that the welfare of institutionalized human subjects used in testing its products will be adequately underwritten by the administrators of the institutions or by other state agencies, boards, or commissions charged with that responsibility. . . .

* * *

Implications

Our investigations have shown substantial defects in the drug-testing program as administered at present in Alabama prisons. This does not, however, change our opinion that drug trials using prisoners can and do serve an essential purpose. They benefit the nation and provide the prisoner with an opportunity to contribute something back to society, to earn some extra needed money and to improve living conditions in the prisons through a well-developed welfare fund. In addition, a well-conducted drug-testing program would provide extra medical coverage for prisoners with the possibility of the early diagnosis and treatment of disease and better diagnostic facilities than might otherwise be available. Actually this has frequently happened in Alabama.

Considering the present situation we regard it as being distinctly unsatisfactory. The pris-

oners' welfare is not being adequately safeguarded and the validity of the drug trials themselves must occasionally be seriously in doubt. The chief deficiencies are undoubtedly the lack of an adequately trained staff, the lack of sufficient interest in the prisoner as a patient, the lack of medical supervision, the unique pressure toward signing a "consent form" because of the need for money, unsatisfactory conditions for the treatment of those prisoners who do fall ill and the lack of any adequate peer review of protocols which are submitted. For the staff and facilities which are available, there is no question but that far too many trials are being conducted at the same time. Thus, at the time of our visit it appeared that no fewer than seven separate trials were being conducted in the three prisons we visited.

. . . The work of Dr. Stough and, to some extent, Dr. Long, is bluntly unacceptable. Others seem to have been involved more through innocent acceptance than through anything else. In retrospect it is easy to see that a request to the State Health Officer for an adequate control inspection might have saved a lot of grief, but this overlooks reality.

It is only right that prisoners, as wards of the state, should in the absence of a drug-testing program, receive medical care of the same general quality as that received by the average citizen of the state.

We believe that with very little help from the state, a sincere attempt has been made at Attmore prison to give this level of medical care. The dedicated physician providing this care has paid not only with time and at the probable price of his own health but, in part, out of his own pocket. It is totally wrong that a physician should, because of his dedication be forced to meet an obligation that should rest firmly on the shoulders of the tax payers of Alabama.

Where there is a drug-testing program the obligation is different. Here the responsibility is to provide the quality of care that a volunteer ordinarily receives at a first-class research institution. The fact that the volunteer is a prisoner does not alter this. . . .

* * *

Alternatives

[W]e are faced with the dilemma of "right" versus "right." It is certainly "right" that new drugs should be evaluated before release to the general public; it is "right" that this evaluation

should be meaningful—that is, it should be done in a thorough, scientific manner by competent individuals. It is “right” that the individual who is to participate in the trial (whether he is a prisoner or not) should do it purely on voluntary basis with full knowledge of the hazards involved.

In this area we are to be guided by the principles outlined in the Nuremberg Code, the Declaration of Helsinki, and the American Medical Association’s Ethical Guidelines for Clinical Investigation. . . . It is “right” that the prisoner with few rights of any kind should receive at least the average medical care available to free citizens, and be protected from those who might abuse his position and sometimes his ignorance to the detriment of his health for experimental purposes. It is certainly good if not right that prisoners be given a chance to earn some money (especially considering the pittance they receive otherwise in the Alabama Prison System). It is also good that prisoners so motivated may enhance their self-esteem by making a positive contribution to the general public welfare by participating in a medical research program. . . .

If there is so much right and good about the program, it is also right that [it] should be regulated and be well run by reputable free enterprise (such as ethical drug firms presumably do in Michigan) or by nonprofit research organizations as long as the research is monitored adequately by the officially designated commission or regulatory board. . . .

A foundation established by a state institution such as a major university could serve as a functional unit with laboratories and other necessary fixed facilities and with clerical and administrative staff directed by a clinical pharmacologist qualified to conduct human drug research. This foundation would be under control of a board of appointees qualified in medico-legal aspects of human experimentation, with the foundation director serving as permanent chairman. The controlling board would be charged with the responsibility of reviewing all protocols from pharmaceutical firms, or others submitting clinical research projects, assessing hazards inherent in the projects and critically evaluating the safeguards to be provided. The controlling board would also be responsible for seeing that all research subjects were aware of hazards and entered the programs voluntarily.

To protect themselves from any possible imputation of a “conflict of interest,” the control-

ling board of the responsible foundation might advantageously appoint a Prison Experimental Review Committee to advise them on any potential risk to the health of the prisoners. The members of this committee should not be related to the research foundation and might include a competent practicing physician appointed by the Board of Censors, a lawyer nominated by the Attorney General, and a designee of the State Health Officer. Since our suggestion does not envisage a monopoly for the responsible foundation (though the bulk of research investigations would be channeled through them) the proposed committee could also advise with regard to other groups which wish to conduct their own research in the Alabama prison system.

* * *

Summary

It is the unanimous opinion of this committee that the drug-testing program is almost essential and should be continued for the benefit of the prisoners and society in general. However, as presently conducted the program does not provide adequate safeguards for the health of the prisoners and leaves something to be desired in quality of results obtained. . . .

Early in our report, we likened our task to that of observing and commenting upon a “play” in a theater. Perhaps it is not inappropriate to pursue that analogy.

It has been our privilege to sit on the front row. We have observed a drama that has displayed certain minor aspects of comedy and many features of melodrama. But the major impact has been that of tragedy. There has appeared, over and over again, conflict between right and right.

From our posts of vantage we have watched the entrances and the exits of the characters and the unfolding of the plot of this drama, we have constantly asked ourselves one question: “Who if anyone, is the villain in the play?”

From time to time we have made tentative judgments as indicated earlier in this report, but our final judgment indicates that our search has been successful and that the greatest villain has been identified. At times, he brazenly occupied the spotlight; at others he has been seen flitting in the shadows. More often his presence has been felt even while he remained hidden in the wings. That villain is human nature. The same character is also the knight in shining armour, the hero of the play.

[ii]

Walter Rugaber
*Prison Drug and Plasma Projects
 Leave Fatal Trail**

The Federal Government has watched without interference while many people sickened and some died in an extended series of drug tests and blood plasma projects.

The profits generated by these activities have gone to an enterprising contractor for the nation's biggest pharmaceutical manufacturers.

The immediate damage has been done in the penitentiary systems of three states. Hundreds of inmates in voluntary programs have been stricken with illness and serious disease. An undetermined number of the victims have died.

In a broader sense, countless millions of American consumers have been involved.

Potentially fatal new compounds have been tested on prisoners with little or no direct medical observation of the results.

Prisoners failed to swallow pills, failed to report serious reactions to those they did swallow, and failed to receive careful laboratory tests.

These studies have generated data that have in turn been used to justify the sale of drugs at prescription counters across the country.

This forbidding trail has been marked out by an Oklahoma-born physician named Austin R. Stough and corporations in which he owns a substantial interest. Despite his importance in two vital fields, he is practically unregulated in either.

As a general practitioner who reports no formal training or education in pharmacology, he is said to have conducted between 25 per cent and 50 per cent of the initial drug tests in the United States.

The 59-year-old doctor, whose companies have been blamed for the repeated use of dangerous methods and inadequate equipment, is estimated to have produced the plasma for about a fourth of an important byproduct that is widely used to protect people exposed to infectious diseases.

These prison-based enterprises have regularly incurred local disfavor. Dr. Stough was evicted from one prison by the Oklahoma authorities in 1964. He was forced out of an Arkansas prison by officials there in 1967. One of

his corporations is now under orders to close down prison operations in Alabama.

But Dr. Stough (rhymes with HOW) is said to retain financial interests in some private blood banks in Birmingham and Dallas, and he is known to be seeking connections with prison systems in new areas.

He can do so freely. He has incurred no penalties, and dissatisfaction with his performance in one state has not prevented a repetition of it in another.

The Federal Government and the pharmaceutical industry—the two forces with enough broad power to compel safe practices from state to state—have maintained a general indifference at every turn.

Several agencies within the Department of Health, Education, and Welfare have known the details of Dr. Stough's plasma collections and drug tests for years. They have not curtailed them.

* * *

The Division of Biologics Standards, a unit of the National Institutes of Health that is responsible for the regulation of blood products, recently asserted that the safety of plasma donors was not its concern.

Several major pharmaceutical manufacturers have recognized that some of the methods employed by Dr. Stough were extremely dangerous. They continued to support him with large sums of money.

An executive of Cutter Laboratories once acknowledged, for instance, that gross contamination was apparent in the areas where the largest blood plasma operations were conducted. The rooms were "sloppy," he observed.

When a Government doctor asked why Cutter continued to reward such an enterprise with hundreds of thousands of dollars' worth of business, the executive explained that the Stough group enjoyed crucial "contacts" with well-placed officials.

These contacts involved, among other things, the payment of sizable retainers to influential lawyer-legislators and the establishment of "partnerships" for a number of prison physicians who remained on the public payrolls.

* * *

On March 25, 1962, the inmates at McAlester began lining up to participate in a medical procedure called plasmapheresis. Under it, a unit of whole blood is drawn and the plasma, a fluid

* *The New York Times* 1, col. 5; 20, col. 1 (July 29, 1969). © 1969 by The New York Times Company. Reprinted by permission.

that makes up about 55 per cent of the blood, is taken out.

The remaining cells are reinjected. That was the critical step on Sept. 19, 1962, when one of Dr. Stough's technicians processed an inmate named Tommy Lee Knott, 47, an illiterate prisoner with a long criminal record.

Knott's blood type was O-positive, but he subsequently charged in a lawsuit that after the plasma had been drawn off, the technician pumped another man's cells, which happened to be A-negative, back into his veins.

Unfortunately for Knott, his liver, lungs, brain, kidneys and other organs were injured, his nervous system underwent shock, and his weight dropped 58 pounds in 17 days.

In suing Dr. Stough and two associates for \$270,000 in damages, Knott also reported that the incompatible blood had caused a double hernia, permanent secondary anemia and a 10 per cent reduction in life expectancy.

The defendants managed to settle out of court for \$2,000 after Knott, who had been removed from the penitentiary for treatment, went off on a crime spree that landed him in a small-town jail.

Only three months after this inauspicious episode, Dr. Stough embarked on an ambitious expansion effort. The financial rewards inherent in his initial plasmapheresis program would now be greatly multiplied.

He brought his plasma operation to Kilby Prison, a drab institution near Montgomery, Ala., in December, 1962, and in the following year he began drawing blood in two more of the state's prisons, Draper and Atmore.

* * *

As a measure of his grip on the market at about this time, a Government source calculated that Dr. Stough's plasma would produce 193,970 cubic centimeters of hyperimmune gamma globulin solution monthly.

Since only about 800,000 cubic centimeters of this type of plasma product were distributed each month throughout the United States, Dr. Stough's output was the source of practically a fourth of the entire national supply.

"With demand exceeding supply," a Government doctor wrote of the boom, "inquiries were made in other states concerning the possibility of opening plasmapheresis centers in other . . . prisons."

A certain style had developed. In Oklahoma, Dr. Stough himself was the prison physi-

cian. The salary of \$13,200 a year was inconsequential by his standards, but the standing it gave him within the prison was invaluable.

So, in Alabama, he awarded Dr. Irl R. Long, the senior prison physician, a financial interest in the program. Until a few weeks ago, Dr. Long simultaneously received a salary of \$942 a month from the state.

A committee of the Alabama Medical Association remarked in a report issued earlier this year that "this unconscionable situation, regardless of reason, should never have been permitted to come into existence."

The prison physician in Arkansas, Dr. Gwyn Atnip, was paid \$20,000 a year for his work in the plasma program there. As a desperately needed doctor among the inmates, he received \$8,000 annually from the state.

Dr. Stough also lined up political support outside the prisons, a tactic that demonstrated its importance when members of the Oklahoma Legislature began to ask whether his penitentiary operations were sanctioned by law.

One of Dr. Stough's most vehement opponents was Gene Stipe, then a State Senator. But early in 1963 Senator Stipe changed sides and successfully pushed a bill that firmly established the physician's standing in the prison.

Later it was discovered that at about the time this change of direction occurred and the saving law was enacted, Mr. Stipe, a lawyer, began to receive a \$1,000-a-month retainer from the concern headed by Dr. Stough.

A spokesman for the organization asserted that the money was for legal services only. Mr. Stipe agreed. Henry Bellmon, then Governor, expressed displeasure but noted that the state had no applicable conflict-of-interest law.

* * *

The factors pertinent to Dr. Stough's activities included a lack of medical attention (it bordered on the nonexistent in Arkansas), an absence of records, and an atmosphere of isolation and secrecy.

Still, Dr. Stough's trail remains vivid at each significant turn, and its progress behind the high walls of Kilby Prison serves to illustrate the type of infection that was spread through four other institutions.

By April, 1963, five months after Dr. Stough had opened his plasmapheresis center at Kilby, the incidence of viral hepatitis, an often fatal disease of the liver, was climbing sharply.

From none or one or two cases a month,

the disease now rose to more than 20 in a single period. Moreover, the outbreaks held generally firm between 10 and 15 a month through the following November.

The rates then soared again. There were 29 cases in December, 22 in January, 1964, 23 in February, 27 in March, and 27 in April. A tenth of the prison population had been admitted to the Kilby hospital.

Joe Willie Tifton, 46, died on March 18. Emzie B. Hasty, 42, died on April 14. Charlie C. Chandler Jr., 31, died on April 16. David McCloud, 27, died on May 22. Each death was attributed to infectious hepatitis.

Little bits and pieces then began to leak to the outside world. A penciled note from one inmate said, "They're dropping like flies out here."

But a prison spokesman said:

"The doctors are quite confident that there is no connection between the plasma program and the cause of hepatitis and jaundice."

* * *

The exact number of hepatitis cases in the five prisons was never established and is never likely to be. Too many medical histories vanished, too many were never completed, and too many were improperly kept by "inmate doctors."

Some 544 cases were firmly established, and that conservative figure is the one most often used. But the communicable disease center records also contain estimates of more than 800 and evidence that the figure could run to more than 1,000.

The number of deaths is similarly undetermined. In addition to at least the four in Alabama, there were reports of at least one in Arkansas and at least one in Oklahoma.

The dimensions of the disease were more clearly and precisely stated in sets of percentages, or "attack rates," that measured the incidence of hepatitis among those who gave plasma and those who did not.

At Kilby, for example, 28 per cent of the men who participated in Dr. Stough's program came down with the disease. For those who did not take part, the rate was only 1 per cent.

The rate for participants in one of the barracks at Kilby was 39.1 per cent. At the four other centers, the illness struck between 20 per cent and 26 per cent of the donors and from 0.9 per cent to 1.8 per cent of the nondonors.

The Federal investigators, reflecting scientific caution, initially referred to the prison cases as "illnesses associated with jaundice". . .

* * *

The single physician employed by the Food and Drug Administration to investigate drug tests throughout the United States has visited Dr. Stough's operations twice, an agency spokesman said.

Some citizens tend to think of the agency as an eternally vigilant organization, and in his dealings with local officials and newspapermen Dr. Stough has turned this misapprehension to advantage.

"They [F.D.A. officials] love to close people down," he said in the brief telephone conversation in which he refused to grant an interview. "So if I was off-color, they'd be on me like a hawk."

"That's one of the reasons the [Alabama Corrections] Board wasn't concerned," explained Frank Lee, the state's commissioner. "We knew they [F.D.A. officials] came in here and looked into the operation."

Dr. Herbert L. Ley, Jr., the F.D.A. Commissioner, branded Dr. Stough's assertion "a non sequitur."

The Food and Drug Administration's lone medical inspector is alert to "flagrant" dishonesty, and there have been men who tested drugs on nonexistent people and who produced imaginary results.

But an inspection is limited mostly to checking data that have been submitted to the sponsoring drug company to insure that it agrees with data sent to the agency. There is little or no effort to look behind the figures.

"Our responsibility is not the direct supervision of the [drug] investigators," Dr. Ley said in an interview. "Our responsibility is to evaluate the data that come in to us. We can't be omnipotent or omniscient."

While the agency has never found occasion to reprimand Dr. Stough, its inspector, Dr. Alan B. Lisook, did make some "suggestions" earlier this year about "the lack of medical supervision of patients."

"We told him we thought there should be more supervision," Dr. Lisook said, "and he admitted there was not as much as he would like because of the volume of drugs being tested."

This was virtually an acknowledgement by Dr. Stough that more tests had been undertaken than could be adequately overseen, but the F.D.A. did not require change.

The agency "frowns" on insufficient supervision, Dr. Ley said, but under present policies there are no specific minimum standards. In the gray area that results, frowning is about the limit.

Since between 25 per cent and 50 per cent

of the phase one studies have been concentrated in Dr. Stough's hands, Dr. Ley was asked whether volume alone—quality aside—concerned his agency.

"It's a red flag; there's no question about that," he replied. But the commissioner explained that neither law nor regulation permitted the agency to force a cutback in the number of studies assigned to a single man.

There is no step short of outright disqualification for obvious misconduct, Dr. Ley said. That is an action the F.D.A. has taken no more than a dozen times in its history.

The drug companies contend there is a shortage of investigators, and Dr. Ley said that while he believed there were enough to study the "really new drugs," he wanted to avoid charges that the agency blocked progress.

"It's harder to get a driver's license in the United States than it is to get fatal drugs," complained Dr. William M. O'Brien, an associate professor of preventive and internal medicine at the University of Virginia. He added:

"To get a driver's license you have to take tests, show you know how to drive, and so on. For drugs, you just walk in the door and say, 'I'm an M.D. I want to test drugs.' It's fantastic. It's unbelievable."

It is difficult to measure the precise sums of money that the pharmaceutical industry has poured into Dr. Stough's operations, but a number of reliable clues are available.

Operating within at least nine separate corporations, the major one of which is Southern Food and Drug Research, Inc., Dr. Stough has a gross income in a good year probably approaching \$1-million.

He has not carried a high overhead. His net income in Alabama in 1967 was nearly \$300,000 (on a \$500,000 gross), and his profit before taxes in Arkansas in 1966 was about \$150,000.

* * *

NOTE

WALTER RUGABER

F.D.A. WILL REQUIRE DRUG TEST REVIEW*

... A Federal agency said today that it would move to halt abuses in tests of new drugs. It announced that it would impose requirements for the direct review of studies within prisons and other institutions.

* *The New York Times* 1, col. 2; 32, col. 3 (August 13, 1969). © 1969 by The New York Times Company. Reprinted by permission.

Dr. Herbert L. Ley, Jr., Commissioner of the Food and Drug Administration, disclosed the plans for stricter controls and other enforcement measures during testimony before a Senate monopoly subcommittee.

He said the agency would soon publish formal proposals to establish committees that would examine preliminary plans for drug tests and monitor the evaluation work itself.

These groups will be made up of physicians, lawyers, clergymen and other professionals, Dr. Ley said, and will be appointed by institutions where much of the initial testing is carried out.

The committee will be expected to have no connection with the pharmaceutical manufacturer seeking to have the drug approved for sale and no connection with the evaluator paid to conduct the tests, he said.

* * *

The local review committees that Dr. Ley suggested would fit somewhere between the present system and a more extensive reform advocated by Senator Gaylord Nelson, the subcommittee chairman. Senator Nelson, a Wisconsin Democrat, recently introduced legislation to take the management of drug testings away from the manufacturers and give it to the Federal Government.

Senator Nelson asked, as an example, how the "peer group" provision could have prevented a case of gross fraud reported by Dr. Ley today. An unidentified doctor in upstate New York falsified data in drug tests.

The Commissioner conceded that the proposed arrangement would not cover individuals operating on their own and that this represented a "remaining loophole." The review committees would not be "a sole cure," he said.

He also acknowledged under questioning that it was "unusual" for 14 pharmaceutical concerns to have sought out "a general practitioner in a small New York State community" to conduct tests on 45 drugs.

[iii]

*The Editors of the New England Journal
of Medicine
Typhoid in Volunteers**

* * *

Reported in this issue are the values of amino acids in the serums of patients in whom

* 278 *New England Journal of Medicine* 332-333 (1968). Reprinted by permission.

typhoid fever was induced. [The subjects were seventeen healthy inmates of the Maryland House of Corrections.] . . . The primary overall aim of the studies was to appraise the efficacy of typhoid vaccine for use in our military personnel. . . .

* * *

In 1948 field trials, involving volunteers who exposed themselves in endemic areas, demonstrated that antibiotics would prevent scrub typhus fever. Basic immunologic principles were firmly established. . . .

Carefully designed studies conducted during the past 10 years have defined the human dose of *Salmonella typhosa* needed to produce disease and have shown that typhoid vaccines are of low protective value. The cooperation of more than 400 healthy volunteers has provided the data regarding typhoid vaccine; the infected men recovered promptly, and there have been no important complications or sequelae, nor has the carrier state developed. Volunteers have been infected only when testing of animals, including primates, failed to yield meaningful data.

Field trials can yield interpretable results if properly conducted. They place heavy demands, however, on resources and health manpower. Limitations also include lack of information about the size of the infecting dose, its relation to host resistance and natural variations in virulence. Volunteer trials with induction of typhoid fever have permitted the following goals over and above those attainable by field trials: measurement of duration of vaccine protection; evaluation of immunity in nonendemic areas; appraisal of effect of various antigenic fractions in small numbers of vaccines; measurement of the effect of combinations of vaccines and of booster doses; evaluation of the protection against varying doses of the infecting bacilli; simultaneous appraisal of the physiologic and biochemical abnormalities of the blood and intestinal tract that help to clarify pathogenesis; analysis of the immune response and its influence on the presence of typhoid bacilli in the feces and blood; information on the nature of the protective antibodies; and reduction in the time and costs of vaccine evaluation. In addition to these considerable benefits, experience derived from volunteer studies provides invaluable guidance for better planning of field trials and interpretation of the results.

NOTE

LAWRENCE A. KOHN
EXPERIMENTAL TYPHOID IN MAN*

The apologetic editorial in the February 8 issue fails to relieve the *Journal* of the onus of having published the article on "Whole-Blood Amino Acids in Experimentally Induced Typhoid Fever in Man." It is unfortunate that this type of study is conducted, but even more so that the *Journal* should announce the results, which incidentally are of limited value since the food intake of the subjects was not apparently standardized. Even with available drug treatment, typhoid fever is not free of immediate or delayed risks. The paper in itself gives no assurance that there were no ill effects; the editorial comment must have been based on generalizations or on data not presented.

Other responses to infection might be studied experimentally in man: the dyspnea of lobar pneumonia, the chemical changes in the spinal fluid in meningitis; and the nature of the natural defenses against poliomyelitis and how to modify them. These analogies are farfetched, but the principles outlined in the editorial do not convince one that this study was either more justified or more necessary. The *Journal* could well have refused it space.

b.

By Action of Subject?

*The People ex. rel. Blunt v. Narcotic
Addiction Control Commission*
58 Misc. 2d 57, 295 N.Y.S. 2d 276, aff'd.,
251 App. Div. 456, 296 N.Y.S. 2d 533 (1968).

HYMAN KORN, J.: The relator Rudolph Blunt, by way of a writ of habeas corpus, seeks his release from Rikers Island on the grounds that the New York State Narcotic Addiction Control Commission, hereinafter referred to as NACC, has failed to provide rehabilitative treatment for his drug addiction.

A hearing was held pursuant to a direction of this Court and extensive testimony was adduced with respect to the issue raised by the relator.

Relator was convicted of a misdemeanor on October 17, 1967. Though such violation would ordinarily have subjected him to punishment for no more than one year at the penitentiary, as a

* 278 *New England Journal of Medicine* 739 (1968). Reprinted by permission.

convicted addict, he was committed to the custody of the NACC for an indefinite period not to exceed 36 months (Mental Hygiene Law, §208). He is presently at Rikers Island in the custody of the Addiction Service Agency, hereinafter referred to as ASA. This agency administers the narcotics program in the City of New York for criminal addicts under a contract entered into between the State of New York and City of New York.

Specifically it is relator's contention that he is being treated in no different manner than the other nonaddict inmates at the prison. Testimony offered by the relator was to the effect that he and the other committed criminal addicts live and work with nonaddict prisoners and are subject to the same prison routine and regulations as their nonaddict cellmates. However, where the nonaddict cellmates are released within one year, relator and other criminal addicts may be held for a period of 36 months.

* * *

The respondent seriously contests relator's claim and asserts that there is presently on Rikers Island a bona fide and meaningful program under which effective rehabilitative treatment is afforded to the committed criminal addict.

* * *

There is no question that confinement of relator for a period in excess of that provided for in the Penal Law could not be based purely on his status as an addict. Justification for holding him in custody for a maximum period of three years may be predicated solely on the basis that such additional term is required to effect treatment for his addiction. Absent such rehabilitative treatment, his continued confinement became purely custodial and is legally untenable.

At the outset, it should be noted that it is not for this court to determine the nature of the treatment to be given nor the facilities to be furnished. The commission, with its expertise in the field, ought to be left to determine the method of care and treatment best suited for achieving its established purpose. It is only where the court finds that the treatment offered is so meaningless, that as a matter of law it is really no treatment or where the claim of treatment is a mere pretext to keep an addict in custody, that the court is under a duty to intercede on the addict's behalf. . . .

Upon a review of the facts in this case, the

court is not prepared to find that the narcotic program presently offered by the ASA is totally without merit. However, the evidence adduced does show serious flaws in the present approach to the problem. Though millions have been spent in setting up this program, the results have not been too encouraging. To date, only 20 to 25 criminal addicts have been provisionally designated as rehabilitated. A critical problem which seriously threatens the program's success is the refusal by the committed addicts to participate. [O]ver 50 per cent of the addicts presently in custody by their own choice do not take part in its rehabilitative plan and receive no other treatment or therapy. [T]here is little, if any, professional attention given during the initial motivational phase of the agency's program. Major responsibility for making the very vital first phase work is placed upon addict-group leaders who themselves are in the same program. They in turn are supervised by a director and assistant director who are former addicts. Well-meaning as they may be, these persons have little, if any, formal education. Except for some scientific jargon they may have gleaned during their own treatment, they seem to operate to a large extent on their own intuition. . . .

* * *

[W]hatever its present shortcomings, New York State's new and revolutionary approach to drug addiction and crime should be given every chance to succeed. Some addicts are participating in the city program and some progress has been shown. The experimental nature of this program is obvious, and trial and error must be permitted if an effective and efficient program is to be evolved. The courts should not thwart the legislative purpose in enacting article 9 of the Mental Hygiene Law by prematurely interfering in its mechanics. For the reasons stated, relator's writ is dismissed.

NOTE

SKINNER V. OKLAHOMA
316 U.S. 535 (1942)

MR. JUSTICE DOUGLAS delivered the opinion of the Court:

* * *

The statute involved is Oklahoma's Habitual Criminal Sterilization Act. That Act defines an "habitual criminal" as a person who, having

been convicted two or more times for crimes "amounting to felonies involving moral turpitude" either in an Oklahoma court or in a court of any other state, is thereafter convicted of such a felony in Oklahoma and is sentenced to a term of imprisonment in an Oklahoma penal institution. Machinery is provided for the institution by the Attorney General of a proceeding against such a person in the Oklahoma courts for a judgment that such person shall be rendered sexually sterile. . . .

* * *

[T]he instant legislation runs afoul of the equal protection clause, though we give Oklahoma . . . large deference. . . . We are dealing here with legislation which involves one of the basic civil rights of man. Marriage and procreation are fundamental to the very existence and survival of the race. The power to sterilize, if exercised, may have subtle, far-reaching and devastating effects. In evil or reckless hands it can cause races or types which are inimical to the dominant group to wither and disappear. There is no redemption for the individual whom the law touches. Any experiment which the state conducts is to his irreparable injury. He is forever deprived of a basic liberty. . . . When the law lays an unequal hand on those who have committed intrinsically the same quality of offense and sterilizes one and not the other, it has made as invidious a discrimination as if it had selected a particular race or nationality for oppressive treatment. . . . Sterilization of those who have thrice committed grand larceny, with immunity for those who are embezzlers, is a clear, pointed, unmistakable discrimination. Oklahoma makes no attempt to say that he who commits larceny by trespass or trick or fraud has biologically inheritable traits which he who commits embezzlement lacks. . . . In terms of fines and imprisonment, the crimes of larceny and embezzlement rate the same under the Oklahoma code. Only when it comes to sterilization are the pains and penalties of the law different. The equal protection clause would indeed be a formula of empty words if such conspicuously artificial lines could be drawn. . . .

* * *

Reversed.

MR. CHIEF JUSTICE STONE, concurring:

* * *

Science has found and the law has recognized that there are certain types of mental deficiency associated with delinquency which are inheritable. But the state does not contend—nor can there be any pretense—that either common knowledge or experience, or scientific investigation, has given assurance that the criminal tendencies of any class of habitual offenders are universally or even generally inheritable. In such circumstances, inquiry whether such is the fact in the case of any particular individual cannot rightly be dispensed with. Whether the procedure by which a statute carries its mandate into execution satisfies due process is a matter of judicial cognizance. A law which condemns, without hearing, all the individuals of a class to so harsh a measure as the present because some or even many merit condemnation is lacking in the first principles of due process. . . .

MR. JUSTICE JACKSON, concurring:

* * *

I . . . think the present plan to sterilize the individual in pursuit of a eugenic plan to eliminate from the race characteristics that are only vaguely identified and which in our present state of knowledge are uncertain as to transmissibility presents other constitutional questions of gravity. This Court has sustained such an experiment with respect to an imbecile, a person with definite and observable characteristics, where the condition had persisted through three generations and afforded grounds for the belief that it was transmissible and would continue to manifest itself in generations to come. *Buck v. Bell*, 274 U.S. 200.

There are limits to the extent to which a legislatively represented majority may conduct biological experiments at the expense of the dignity and personality and natural powers of a minority—even those who have been guilty of what the majority define as crimes. But this Act falls down before reaching this problem, which I mention only to avoid the implication that such a question may not exist because not discussed. On it I would also reserve judgment.

CHAPTER FOURTEEN

Experimentation with Dying Subjects

The decision to use dying patients as research subjects is one of the most controversial an investigator can make. Persons suffering from terminal illness present many of the same problems as those encountered in the previous two chapters—like children, their ability to make informed decisions is often either impaired or disregarded, and, like soldiers and prisoners, they are not really free but are the “captives” of their disease, their physicians and hospital, and their enforced isolation. It is therefore not surprising that some commentators flatly oppose the use of the dying as subjects. On the other hand, investigators argue that meaningful research on some fatal diseases can be conducted only on those suffering from these diseases, that terminally ill patients are often eager to receive innovative treatment, and that participation in research may make their final period of life worthwhile.

The issues raised in this chapter have of late taken on added significance because organ transplantation usually involves dying patients, both as recipients and as donors. Moreover, experimental organ surgery has raised a host of troublesome new questions revolving around the criteria and procedures for determining death as well as for choosing potential recipients and donors.

In studying these materials, consider the following questions:

1. Should research on dying persons be permitted?
2. If research is permitted, who ought to set its limits and balance the risks against the potential benefits to the patient and to society?
3. Since the prolongation or termination of life has social, legal, moral, psychological,

and religious ramifications, what considerations enter into the choice of adopting firm standards or of allowing decisions to be made on a case-by-case basis?

4. Since the length of life can increasingly be extended by a variety of experimental means, how, to what extent, and to whom should opportunities be provided to terminate such experiments?

A.

Case Studies of the Dying as Research Subjects and Organ Donors

1.

**James A. Helmsworth, Johnson McGuire,
and Benjamin Felson**
**Arteriography of the Aorta and Its Branches
by Means of the Polyethylene Catheter***

As the scope of vascular and thoracic surgery is extended, detailed information concerning abnormal morphology of the major vessels is of more than academic interest. For example, knowledge of the length of the constricted segment in aortic coarctation and of the exact relations of the vessels in arteriovenous aneurysm in the neck enables the surgeon to plan accurately an effective operative procedure. Similarly, the differentiation between a mediastinal tumor and an aneurysm may be the determining factor for exploration of the chest.

* * *

The catheter was the most important item of equipment used in this method. A standard woven ureteral catheter was used in several of the early cases but the advantage of its radiopacity was outweighed by the disadvantage of the thickness of its wall. Catheters made of polyethylene tubing were employed because of the experience of others and proved more satisfactory. Lengths of from 50 to 75 cm. were prepared. . . .

* * *

The arteries selected for this study were the brachial and the ulnar collateral at the level of the transverse crease of the elbow, and the femoral in the middle third of the thigh below the origin of the profunda.

After preparation of the skin, anesthesia was produced by local infiltration. The artery

was exposed through a small incision and a 2 cm. segment mobilized by ligation and division of the fine branches. It was essential that the field be entirely free of ooze and that the vessel segment be without hematoma in the adventitia. After a looped sling of ligature silk had been placed about the proximal and distal extremities of the segment, the artery was opened by a transverse incision estimated to be slightly longer than the diameter of the catheter to be inserted. The catheter, filled with heparinsaline solution (70 mg. of heparin to 1 liter of physiological saline) and free of bubbles, was then inserted and advanced toward the heart as tension on the proximal looped sling was relaxed. To prevent the formation of a thrombus within the catheter or about its tip, it was necessary to keep a stream of heparin solution flowing slowly through the catheter. The catheter was advanced until its tip was estimated to be near the desired site of injection. Under roentgenoscopic control the opaque medium, diodrast or neo-iopax, was injected slowly into the catheter until it opacified the tip. The catheter was then advanced or withdrawn to the site of injection. The patient was placed in the position best suited for roentgenographic demonstration of the artery. A fraction of a cubic centimeter of the contrast substance was then injected as a test for sensitivity.

The injection of the contrast medium was made as rapidly as possible with the 50 cc. syringe. This step was carefully timed and usually required from 0.7 to 1.8 seconds. The volume injected varied from 8 to 30 cc. and the Potter-Bucky roentgenogram was usually made as the last cubic centimeter was ejected from the syringe. . . .

During withdrawal of the catheter the artery was irrigated with a liberal quantity of heparin solution. When it had been determined that no thrombus was present proximal or distal to the incised segment the artery was repaired. . . . In several instances repair of the brachial artery was

* 64 *American Journal of Roentgenology* 196-200, 210-212 (1950). Reprinted by permission.

impossible, and ligation and division of this artery was carried out. A simple approximation of the skin margins completed closure of the wound. Anticoagulant was administered only during the examination, as described above. With this method visualization of the aorta and its major branches was undertaken.

* * *

In the present attempt at coronary arteriography preliminary experiments were carried out on 5 unselected mongrel dogs. . . .

Attempts at coronary arteriography were then made on 6 patients. In 4, no filling was obtained. Visualization of some of the circulation was obtained in the other 2 cases, which follow.

CASE I. B. K., a white female, aged eighty-eight, was admitted on February 23, 1949, in coma following a cerebral accident. A history of coronary occlusion one year earlier was obtained from the family. The patient remained deeply comatose throughout her stay in the hospital. On March 10, under local anesthesia, catheter No. 2 was inserted through the left brachial artery into the proximal portion of the ascending aorta. With the patient in the left posterior oblique position 12 cc. of 70 per cent diodrast was injected in 0.5 second. A Potter-Bucky film was obtained at the end of the injection. The procedure was repeated five times. Immediately following the last injection the patient suddenly developed an arrhythmia and, despite emergency treatment, died. Autopsy showed marked cerebral softening, marked arteriosclerosis of the coronary arteries, and an old thrombosis of an anterior coronary branch near the cardiac apex. The coronaries were otherwise patent. There was no evidence that the catheter had traumatized the ascending aorta and no anatomic cause of the sudden death was apparent.

Review of the roentgenograms . . . showed the tip of the catheter in the ascending aorta at the level of the aortic valve. Two of the five films revealed filling of the right coronary artery and its branches, but no filling of the left.

CASE II. L. Z., a white male, aged seventy-four, was admitted on February 19, 1949, in a stuporous condition. A diagnosis of multiple myeloma was established. On March 3, with the patient obviously moribund and deeply comatose, catheter No. 2 was inserted through the right brachial artery into the proximal ascending aorta. Ten cubic centimeters of 75 per cent neo-iopax was injected in about 0.7 second with the patient in the left posterior oblique position. The roentgen exposure was made as the injection was completed. The procedure was repeated six times using between 5 and 10 cc. of the contrast substance with each injection. The catheter was re-

moved and the artery repaired. The patient's condition did not appear to change immediately following the procedure but he died six hours later. Autopsy revealed multiple myeloma and lobular pneumonia. The coronary vessels and aorta showed arteriosclerosis of a moderate degree. The coronary ostia were not narrowed. Again, evidence of trauma to the aorta was lacking.

* * *

Although Cases I and II died following the procedure, it should be noted that in both instances the patients were already moribund, and that multiple injections of contrast agent were administered. In Case I the death must be attributed to the arteriography, but in Case II the procedure was probably not at fault. Failure to visualize the coronaries occurred in a number of the attempts in these 2 patients. It is possible that the failures were due to the relatively small quantity of the agent used. Further studies of this problem are being made.

* * *

The most important consideration in a procedure of this type is its effect upon the patient. One death, in a woman aged eighty-eight who was already moribund, was directly attributable to the procedure. Another patient developed convulsions immediately after the injection of contrast medium, but recovered. A third patient, who was semicomatose at the time of the procedure, became excited for a brief period following the injection.

Experience with this method has yielded certain information concerning these reactions. In the first place, there have been no serious symptoms attributable to the procedure of catheterization itself. In some of the earlier attempts vasospasm, unaccompanied by pain, occurred in the extremity and continued up to thirty-six hours. In every instance this followed the use of a catheter which was too large. In later studies, in which smaller catheters were used, this complication was not encountered, even though repeating the injections sometimes meant that the catheter remained in the artery from thirty to ninety minutes. Thrombosis of the incised artery did not occur when the artery was sutured and even when ligation of the brachial [artery] was performed no sequelae developed. In one patient the right brachial artery was catheterized on two occasions six days apart, using the same incision. The radial pulse remained normal after both procedures and no complications arose. Bleeding was never a problem since the contraction of the

artery sealed the opening of the vessel around the catheter.

* * *

The one fatality occurred after the injection of 70 per cent diodrast while the other 2 cases developed symptoms following the use of 75 per cent neo-iopax. In all 3 instances concentrated medium might have entered the cerebral circulation and, as noted by Broman and Olson, cerebral damage might well have been responsible for the reactions. . . .

It is imperative to weigh the dangers of the procedure against the value of the information obtained. Although the present study was basically experimental, the resulting information was often important in the management of the patient and could not have been obtained by completely safe conventional methods. If its dangers can be reduced or eliminated, as by improving the contrast medium, arteriography may prove of value in the elucidation of diseases of the aorta and its major branches.

* * *

2.

**Howard R. Bierman, Earl R. Miller,
Ralph L. Byron, Jr., Kenneth S. Dod,
Keith H. Kelly, and Daniel H. Black**
**Intra-Arterial Catheterization of Viscera
in Man***

The afferent artery from which a neoplasm obtains its blood supply represents a route of attack on such growth, with diagnostic and possibly therapeutic implications. . . .

* * *

If the major artery leading to a specific organ could be isolated to the exclusion of other viscera, not only could that specific organ be visualized roentgenographically, but also various chemotherapeutic agents could be administered in high concentration directly to neoplastic lesions involving this organ. Furthermore, such an isolation of the arterial supply of such an organ in vivo would enable the employment of this method for many pharmacological and

physiological studies. In the search for clinical methods by means of which the afferent artery to deep-seated neoplasms could be reached, the feasibility of intra-arterial catheterization of viscera was explored. This communication reports the development of the method.

Materials and Methods

The investigations were carried out by a team of a surgeon, radiologist, internist and anesthetist. Radiopaque, intracardiac catheters, 100 to 150 cm. long, No. 6 to No. 9F with a fixed curve at the tip, were used.

The technique was first tried on cadavers. . . .

Twenty-eight arterial catheterizations were then performed on 24 patients with metastases from various neoplastic diseases. The procedure in its entirety, including the hazards, risk and experimental nature, was explained fully to each patient and an unqualified agreement was obtained in all cases.

Catheterization technique. The procedure in adults is carried out under routine preoperative medication and local procaine anesthesia. The 3 children in this series had a general anesthetic; the 2 eldest had nitrous oxide and the fourteen-month-old received ether. The artery is exposed in the supraclavicular area and loops of thin, flexible rubber tubing or rubber bands are placed around the vessel above and below the site for the opening of the artery. . . . A 2 mm. longitudinal incision is made through the wall of the artery with a small scalpel and the tip of the catheter is inserted. . . . The catheter is filled with saline containing 2 mg. per 100 cc. of heparin before insertion, and this solution is kept running slowly through the catheter during the procedure. . . .

After insertion into the artery, the catheter is guided by roentgenoscopy. . . . The catheter is advanced into the aortic arch via the innominate artery . . . and into the descending aorta. . . .

To enter the celiac artery, the tip of the catheter is pointed anteriorly as it descends to the aortic hiatus at the level of the diaphragm. . . . The injection of 5 cc. of 70 per cent . . . diodrast visualizes the vascular pattern of the hepatic, left gastric, and splenic arteries and their branches. . . .

The superior mesenteric, inferior mesenteric, renal . . . middle sacral, iliac, hypogastric, and gluteal vessels . . . have been similarly catheterized. . . .

* 66 *American Journal of Roentgenology* 555-567 (1951). Reprinted by permission.

Tumor masses in the neck may prevent satisfactory exposure of the carotid arteries. To reach the carotids, subclavians, and their branches under these circumstances, the brachial, ulnar, and femoral arteries have been employed. . . .

After completion of the procedures with the catheter in place, the catheter is withdrawn under roentgenoscopic control and the arterial incision is closed with arterial silk suture after milking the artery from both ends to remove any thrombi that may be present. The wound is closed in routine fashion.

* * *

Complications

Four complications have been encountered. There was a wound infection in one case . . . with subsequent hemorrhage three weeks after catheterization. In this case the exposure of the carotid artery had to be performed through a large lesion of mycosis fungoides which, despite rigorous cleansing, probably was not completely sterile. The erosion in the artery was sutured, but was followed within thirty-six hours by a left hemiplegia, with later recovery of motion in the face and lower extremity. Approximately eight weeks later hemorrhage again ensued and the carotid was ligated without significant change in the patient.

The second complication during the procedure occurred in a male, aged sixty-five with carcinoma of the larynx, metastatic to the neck with a hypertension of 170/110, arteriosclerotic heart disease, and chronic nephritis (non-protein nitrogen 59 mg. per cent). The patient developed a left hemiplegia five minutes after the procedure started and after the injection of only 11 cc. of 35 per cent diodrast. He died four days later. The right cerebral hemisphere was found to be infarcted, probably due to the marked arteriosclerosis of the right carotid artery together with compression of the artery by the tumor mass, as the head was moved to the left during the procedure, and perhaps aided by arterial spasm from the diodrast.

In a third case . . . the physician holding the rubber bands about the artery became confused in the dark of the roentgenoscopic room and somehow switched the clamps so that tension was exerted downward on the upper tubing and upward on the lower tubing, resulting in twisting the artery into a knot and completely shutting off the blood flow through the right

common carotid. Complete left hemiplegia appeared twelve hours later.

The fourth complication occurred in a moribund male, aged fifty-six, with marked arteriosclerosis, syphilitic aortitis, aortic insufficiency and widespread metastatic adenocarcinoma. The blood pressure in the right arm was 90/0 and 160/70 in the left. The catheter was inserted into the left brachial artery at the mid-humeral level. Twelve hours later the forearm and hand were cyanotic, cold and cadaveric. The patient continued to fail progressively and died forty-eight hours after nitrogen mustard was administered into the aortic arch and a thrombus was found just above the cut-down site.

* * *

Discussion

The technique of intra-arterial catheterization has proved to be a feasible procedure. However, it must be undertaken with a calculated risk. . . .

The injection of a 70 per cent diodrast solution usually, but not always, causes the patients to complain of a burning sensation along the course of the vessels with somatic reference. The position of the catheter may often be confirmed in this manner.

While four serious complications in a group of 24 patients would appear to give a high incidence, it is not prohibitively high considering the initial effort in this direction, mostly on critically ill patients with far advanced neoplastic illnesses. The complications of wound infection (Case I) and surgical error (Case III) are avoidable and have been corrected. From our further experience it is now almost certain that the complication in Case II was in all likelihood due to a diodrast reaction which together with the marked arteriosclerosis and large metastatic tumor was sufficient to cause cerebral anoxia. The fourth complication occurred before we instituted the milking of the artery from both ends to remove any thrombi that may have occurred during the procedure. Since that time no further complications of this sort have been noted.

New techniques encounter difficulties until they are perfected. Since the complications noted were all amenable to improvement, as has been shown in the later catheterizations, it would appear that this procedure has some value for the purpose stated.

* * *

3.

**R. H. Johnson, A. C. Smith, and
J. M. K. Spalding**
**Oxygen Consumption of
Paralysed Men Exposed to Cold***

When a mammal is exposed to a cold environment its metabolism increases and there may be a progressive increase in activity of skeletal muscle . . . leading eventually to shivering. In small mammals metabolism also increases in tissues other than skeletal muscles . . . but it is uncertain whether this is so in larger mammals including man. . . . The oxygen consumption of five subjects whose skin was cooled for 80–210 min was measured. Two subjects were healthy men, one had almost complete paralysis of skeletal muscle due to poliomyelitis and two were unconscious and were studied before and after receiving a muscle relaxant.

Subjects. Subjects R. H. J. (28 years; 69 kg; 175 cm) and A. C. S. (45 years; 64 kg; 163 cm) were healthy men. Subject G. W., male, 34 years, had had poliomyelitis 2½ years before and was completely paralysed below the neck except that he was capable of slight movement of the right toes. He was entirely dependent upon intermittent positive pressure respiration (IPPR) which he received from a Radcliffe Respiration Pump . . . through a cuffed tracheostomy tube . . . which provided an air-tight seal in the trachea. His autonomic nervous system was intact as judged clinically and by the response of the arterial blood pressure to Valsalva's manoeuvre and by observations on central venous pressure and venous distensibility. He received no drugs.

Subject E. H., male 68 years, had been unconscious for 3 months after hypotension and anoxia associated with an abdominal operation elsewhere. He had been emphysematous for several years and after the operation could not breathe adequately. He received artificial respiration in the same way as subject G. W. His autonomic nervous system was imperfect, for the response of the arterial blood pressure to Valsalva's manoeuvre showed little evidence of reflex vasoconstriction. The following autonomic responses, however, were normal: he did not have postural hypotension; on cooling one arm there was vasoconstriction in the opposite hand, as indicated by a reduction in heat flow from the pulp of the finger, measured with heat-flow

disks; when his trunk was heated with a radiant-heat cradle there was normal vasodilatation in his hands measured in the same way, and sweating tested with Quinizarin was normal. His metabolic rate was first examined without his having received any drugs, and then whilst receiving paralysing doses of D-tubocurarine. (Heights and weights are not available for the patients receiving IPPR.)

Subject M. M., male (17 years; 54 kg; 170 cm) had been unconscious for 12 months after a severe closed head injury. He normally breathed spontaneously. The same tests of the autonomic nervous system were performed as in subject E. H. Sweating was slightly greater on the right than the left side of the body, but other tests gave normal results. In particular the response of the arterial blood pressure to Valsalva's manoeuvre, to changes of posture and to noise were normal.

* * *

Skin temperature was measured at one point on the abdomen with a thermocouple. Body temperature was measured in subject R. H. J. with a mercury thermometer in the mouth, in A. C. S. with a thermocouple in the rectum, and in G. W., E. H., and M. M. with a thermocouple in the oesophagus. Oesophageal temperature reflects changes in arterial blood temperature. Temperatures of room air and of the gas in the Benedict Roth spirometer were measured with mercury thermometers.

Procedure. Observations were made over a 10-min cycle which was repeated continuously throughout the experiment. Minute 1 (approximately); the subject breathed oxygen through the closed circuit. Minutes 2 and 3; he breathed the oxygen-air mixture through the open circuit. . . .

Minutes 4–6; the subject's oxygen consumption was measured with the closed circuit. . . . Minutes 7–10; the subject breathed the oxygen-air mixture. The skin, body and room temperatures were measured.

In each subject this cycle of observations was continued for 40–80 min while the subject was recumbent and covered with blankets. The blankets were then removed and fans played cool air on the subject for 80–210 min and the observations were continued. The subject was then covered with blankets or warmed with a heat cradle and further observations were made during the recovery period.

When the normal subjects R. H. J. and

* 169 *Journal of Physiology* 584–587, 590 (1963). Reprinted by permission.

A. C. S. were cooled there was pilo-erection and sporadic shivering. "Skin" temperature fell to 24–26° C, deep temperature rose slightly and O₂ consumption and CO₂ output increased. When the subjects were warmed these changes were reversed. When subject G. W. (who had had poliomyelitis) was cooled, there was pilo-erection and his teeth chattered. "Skin" temperature fell to a minimum of 17.6° C. Oesophageal temperature fell by 1.5–1.8° C and O₂ consumption and CO₂ output did not rise and may have fallen. . . . When subjects E. H. and M. M. (who were unconscious) were cooled without receiving any drugs there were pilo-erection and sporadic shivering, and O₂ uptake and CO₂ output increased. When they received paralysing doses of muscle relaxants (D-tubocurarine, E. H.; gallamine, M. M.) there was no shivering and no rise in O₂ consumption or CO₂ output.

These findings indicate that, under the conditions of our observations, an increase in O₂ uptake and CO₂ output occurred when men with active skeletal muscles were cooled. It did not, however, occur in men whose skeletal muscles were paralysed. This was true whether the paralysis was due to poliomyelitis or muscle relaxants (D-tubocurarine or gallamine).

* * *

. . . Our results are consistent with the view that in man the increase in metabolism on cooling for periods up to 3½ hr occurs solely in skeletal muscles.

4.

**Renato Cavaliere, Enrico C. Ciocatto,
Beppino C. Giovanella, Charles Heidelberger,
Robert O. Johnson, Mario Margottini,
Bruno Mondovi, Guido Moricca, and
Alessandro Rossi-Fanelli**

Selective Heat Sensitivity of Cancer Cells*

Numerous laboratory and clinical reports scattered throughout the literature strongly suggest a remarkably selective destructive effect of heat against cancer cells that could be systematically exploited for therapeutic purposes.

* * *

Patients with large, recurrent or single meta-

* 20 *Cancer* 1351, 1360–1361, 1364–1369, 1373 (1967). Reprinted by permission of the American Cancer Society.

static cancers localized in an extremity offer an excellent opportunity to study the effect of localized high temperature treatment because of the availability of amputation as an alternative form of therapy if the disease were not well controlled or the limb irreparably damaged. Isolation perfusion with extracorporeal circulation for localized high-dose chemotherapy of tumors of the extremities has become an established technique, which has been adopted for the present study; however, in this case no drugs were perfused and the perfusate fluid was heated. Studies on the isolated dog hind limb have indicated that a temperature of 42 to 44° C (107 to 111° F) for two hours can be tolerated without major damage.

* * *

We are reporting on the first 25 high-temperature perfusions that were performed in 22 patients at the Regina Elena Institute, of which 18 were done via the iliac, six via the axillary and one via the brachial vessels. . . . The total perfusion times ranged between 2 hours, 7 min to 8 hours, 5 min, with the duration of adequate temperatures (above 40° C) in the tumor from 50 minutes to 6 hours, 50 min.

The tumors in this series included 12 sarcomas, seven melanomas, two squamous cell carcinomas of the skin and one metastatic leiomyosarcoma from the uterus. . . .

* * *

Intensive postoperative care was required, especially during the first 5 days. The patients required multiple transfusions of whole blood, plasma, fluids, electrolytes, hydrocortisone, mannitol, cardiac supportive therapy, antibiotics, multiple vitamins and physiotherapy. Operative interventions were required in a few patients. These procedures included tracheotomy, amputation, vascular repair, incision and drainage, debridement, skin grafting and embolectomy.

Complications: Eight of the 25 perfusions were accomplished without complications, which were often multiple. Second degree burns occurred in six patients, one of which was serious. Death occurred in six patients within 15 days postoperatively: One died of a myocardial infarction at 12 hours; one patient died of shock one day after perfusion at a tumor temperature of 49° C due to a thermometer failure (subsequently, two independent thermometer systems were always used); one died at 3 days from a transfusion reaction; another at three days from septicemia; one at 5 days from a "crushed limb

syndrome" from kidney failure probably caused by the total regression of a massive tumor; and one from an embolus on the fifteenth day. . . .

Response: . . . A complete gross disappearance of the tumor was obtained in 10 of the 22 patients; a 20 to 80 per cent decrease in tumor volume was observed in five patients (good response), no response was seen in three patients (of which two received inadequate temperatures) and in four cases the response could not be evaluated for various reasons. Microscopically, a total necrosis of the tumor with no viable cells visible in any of the sections examined was obtained in eight patients; seven of these patients are alive and free of disease at the present time and one died of the "crushed limb syndrome."

Histologically an excellent response as indicated by a very massive necrosis, but no visible nests of viable tumor cells, was observed in eight patients; all of these had recurrences of their tumors. Microscopically no response was observed in three patients and the response could not be evaluated in three. In the present series malignant melanomas appear to be the most responsive to high temperature perfusion.

Most of these patients had a poor prognosis since 14 of 22 had recurrent disease prior to high-temperature perfusion. At present, 12 of the 22 patients are alive and free of the disease over intervals ranging from 3 to 28 months after perfusion; however, in this group eight had other forms of therapy subsequent to the perfusion, including two amputations that were required by the loss of a functional limb due to total destruction of bone and total regression of the osteogenic sarcoma; four amputations due to tumor recurrence; one recurrence that was amputated and followed by x-ray therapy and one recurrence that was treated with x-ray therapy. One patient is currently alive with disease and two have been lost to follow-up. In spite of the advanced status of their diseases, only one of the patients that responded to the perfusion has died of metastatic disease.

* * *

The method of high-temperature perfusion of advanced cancers of the extremities has demonstrated the clinical feasibility of heat treatment. Nevertheless, the procedure is far from ideal. It is hazardous and there were numerous complications which have declined with experience. . . .

The incidence of therapeutic effects of high-

temperature perfusion and degree of response to it was considerably greater than those produced by the conventional regional perfusions with short-acting chemotherapeutic agents; however, in many cases it was necessary to amputate the limb after treatment (only in case 1 as a complication of the perfusion) because of the destruction of the tumor and consequent loss of a functional limb or because of recurrences when a second high-temperature perfusion was impractical or refused. In the three patients that received a second perfusion one tumor disappeared totally and has not recurred 17 months after the second perfusion and two patients had recurrences 2 months after the second treatment.

Of the 25 high-temperature perfusions in 22 patients there were 10 total gross disappearances of tumor and eight microscopic total necroses. It seems rather unlikely that the mechanical act of perfusion or the supportive therapy, i.e., cortisone and transfusions, contributed appreciably to the therapeutic results but these possibilities cannot be ignored.

Deaths from complications occurred rather early in the series but with experience and more aggressive post-perfusion supportive therapy the mortality was diminished. Local complications were also diminished by the early abandonment of tourniquets and infrared heating. The death of patient 8 from a "crushed limb syndrome" following total regression of a massive tumor suggests that large tumors should be reduced surgically before high-temperature perfusion is carried out. The possibility of combining high-temperature perfusion with chemotherapy obviously deserves exploration. The present study and its current extension to additional cases will serve as a baseline for the evaluation of such combined treatments.

* * *

This method of high-temperature treatment obviously has limitations and at present is indicated in patients with primary or recurrent malignant tumors of the limbs for whom the only alternative therapy would be amputation, which often does not prevent metastases. The fatal risks and complications encountered in the earlier cases have been gradually overcome but this method should be attempted only by highly qualified and experienced clinicians. The selective destructive effect of high temperature on neoplastic cells suggests the possibility of combining this treatment with a local excision of the

tumor when this is feasible. It is evident that future progress in this field will come from total-body high-temperature treatment. We are now in the process of developing techniques towards this end. . . .

5.

Eric Kast LSD and the Dying Patient*

* * *

While observing patients during the final months of life, one can see certain defense mechanisms developing in an attempt either to structure death and subsequent "existence" or to deny all possibility of death and assume an eerie positivism which seems surrealistic in character. The usual approach to death is by a combination of both, and it seems to take an extraordinary toll in a person's ability to relate to his environment and communicate with his family. He becomes isolated and is deprived, to a large extent, of his ability to realistically and deeply experience these last months or weeks of greatest importance in his life. Therefore, interference seems justified if it enables the patient to see and feel with greater intensity. Of course, such medicinal interference must not tamper with the patient's religious ideas and must have the latitude to permit any philosophic interpretation. This study attempts to explore LSD as a means of increasing the perceptive powers of the dying patient. Lysergic acid diethylamide (LSD) has been reported to enhance the depth of feeling without structuring the individual's interpretation of these increased feelings. Increased communication lessens suffering and isolation and there is always the possibility that increased perception may enable the patient to penetrate, to some extent, the mysteries of cessation of existence.

To explore the means of making the last months of a patient less distressful is the second purpose of this study. . . .

* * *

Eighty patients suffering from terminal malignant disease with an estimate life expectancy of weeks or months were selected. Only patients who had been informed of their diagnosis were included. An interview was conducted in

which the patient's condition and prognosis were discussed, and he was invited to participate in this investigation. It was emphasized that there was no curative value in LSD.

* * *

No placebo control was used because of the obvious and immediate differentiation of LSD from placebo by the patient as well as the observer. After the interview we gave 100 meg of LSD hypodermically to insure uniformity of absorption. A trained observer was at the patient's bedside until the termination of the experiment. Upon the appearance of fear, panic, or the desire to rest, the patient was given 100 mg. of chlorpromazine intramuscularly which induced sleep within 30 minutes. The patients were interviewed daily for the subsequent three weeks. . . .

As expected, the overall improvement rate of gravely ill patients after 100 meg of LSD administration was considerable during the first eight or ten hours. About half of the patients became upset around six hours after administration, and the experience was terminated with chlorpromazine at that time. Only ten patients were able to tolerate the experience for more than ten hours without having some frightening image that necessitated termination. However, contrary to our previous experience only 10 per cent or eight patients did not wish to repeat the administration, compared to 33 per cent in our previous study in which the experience was not terminated and the patients were permitted to experience the whole gamut of feelings, even when the frightening images made their appearance. The relatively high percentage of patients whose experience was terminated can be accounted for by the fact that these were debilitated patients who tired easily.

Thus it seems that an avoidance of the tiring and, at times, the frightening images can add to the patient's willingness to repeat the experience.

Seventy-two patients gained a special type of insight from this experience: This "insight" was a greater lucidity and tridimensionality with which they viewed events in and around themselves. Through this insight, communication was greatly facilitated, both between observer and patient and among the patients themselves. It also created a sense of cohesion and community among patients, excluding those who did not "know" the experience. This greatly enhanced the morale and self-respect of the patients involved.

* 26 *Chicago Medical School Quarterly* 80-82, 86 (Summer 1966). Reprinted by permission.

Only seven patients felt that the experience in some way interfered with the privacy of their religious and philosophical ideas. These were the patients who experienced strong hallucinatory or frightening images, and whose experience had to be terminated early. It is interesting to note that the unstructured question, "did it go too far?" was universally understood. The 12 patients responding positively were among those with frightening images whose experience had to be terminated early.

While the depression returned to a certain extent, a definite lifting of the mood was noted for approximately two weeks. . . .

* * *

During and after LSD administration, acceptance and surrender to the inevitable loss of control were noted; and this control is anxiously maintained and fought for in non-drugged patients. LSD administration apparently eases the blow which impending death deals to the fantasy of infant omnipotence, not necessarily by augmenting the infantile process, but by relieving the mental apparatus of the compelling need to maintain the infantile fantasy. Parallel to the general improvement in the patient's feelings, mood and conflict situation, sleep patterns improved for approximately 12-14 days.

The results of this study seem to indicate that LSD is capable not only of improving the lot of pre-terminal patients by making them more responsive to their environment and family, but it also enhances their ability to appreciate the subtle and aesthetic nuances of experience. . . .

* * *

6.

**James D. Hardy, Carlos M. Chavez,
Fred D. Kurrus, William A. Neely,
Sadan Eraslan, M. Don Turner,
Leonard W. Fabian, and Thaddeus D. Labecki**
Heart Transplantation in Man*

Heart transplanation has interested many investigators. [I]n the spring of 1963, Webb and the senior author considered that the laboratory and clinical heart work justified a planned ap-

proach directed toward eventual heart transplantation in man. This objective, a natural outgrowth of transplantation research, was cleared with the administrative officials of the University Medical Center.

* * *

As the laboratory work continued and animal heart transplants came to exceed 200 in number, considerable reflection was devoted to a definition of the clinical circumstances under which heart transplantation might be ethically carried out. . . .

* * *

During the last weeks of December, 1963, a number of patients considered by their physicians to be in absolutely terminal heart failure were admitted and served to sharpen the orientation of the surgical group. . . .

. . . One patient was admitted to the emergency room "moribund" from acute myocardial infarction, but he recovered. Another patient admitted in deep shock from myocardial infarction improved considerably, only to die abruptly. No time would have been afforded in which to make the most meager preparations for cardiopulmonary bypass using a disposable bag oxygenator, even had a suitable donor been available. Still other similar instances made it clear that the recipient must be dying of long-standing heart disease, in which the downward course had been progressive and inexorable to a clearly discernible terminal collapse. In such a situation, the transplant would offer some possibility of life prolongation, as opposed to certain death otherwise.

As with clinical lung transplantation previously performed, specific written protocols had been drawn up for the donor team and for the recipient team, and these had been distributed as confidential information to all personnel who might be immediately involved in a transplant.

* * *

By this stage of the program it had become abundantly clear that unless one were willing to halt mechanical support of respiration in a potential donor, it would be exceedingly unlikely that a potential recipient would die during the time a patient dying of myocardial insufficiency and shock could be kept on the pump oxygenator. Since we were not willing to stop the ventilator, we had concluded that a situation might arise in which the only heart available for trans-

* 188 *Journal of the American Medical Association* 1132-1139 (1964). Reprinted by permission.

plantation would be that of a lower primate. Following a visit to New Orleans to examine at first hand the surprising but remarkable results achieved in maintaining survival of functioning primate heterotransplants using immunosuppressive drugs, we had purchased two large chimpanzees for possible use as kidney donors when no human donor kidney was available. Routine studies of these animals performed using anesthesia had included chest x-ray, ECG, blood grouping and chemistries, blood volume, and cardiac output. . . .

* * *

On Jan. 21, 1964, a 68-year-old white man was referred to the surgical service with gangrene of the lower portion of the left leg. He had had hypertensive cardiovascular disease for many years for which he had been taking digitalis and diuretics. Two nights earlier he had been admitted to his community hospital in a comatose state and with no detectable blood pressure. At that time rapid atrial fibrillation had been recorded, and vasopressor drugs in high dosage had been required to elevate the blood pressure to a systolic level of 100 mm Hg. By the following morning, however, it was possible to maintain his blood pressure level with minimal vasopressor drug therapy. The sensorium had cleared slightly, but it was not determined whether his impaired mental state was secondary to previous shock with hypoxia imposed upon an already atherosclerotic cerebral vascular bed, or to an intracranial vascular accident, or to the fact that the blood pressure level remained abnormally low for this previously hypertensive patient. He was able to move all four extremities, but such motion was limited. The bifurcation of the left common femoral artery had been explored while using local anesthesia in an attempt to restore blood flow in the left lower leg and a clot suggestive of an embolus had been removed, but without improvement in blood flow.

When his condition had stabilized, he was referred to the University Hospital for amputation of the gangrenous left lower leg and further management.

Examination revealed a large man of approximately the stated age of 68 years who was in a stuporous or semicomatose condition and who responded only to painful stimuli. The grossly irregular cardiac rhythm was again identified by an ECG as atrial fibrillation and the blood pressure in this previously hypertensive individual fluctuated at a systolic level of be-

tween 90 and 110 mm Hg. It was uncertain how much digitalis he had received, but the medical consultant now initiated all the usual measures available for support of the heart, whose failing capacity was reflected in the marked arrhythmia, cardiomegaly, relative hypotension, and dependent edema. Since the respiratory effort was inadequate in depth and irregular, a tracheostomy was performed and mechanical ventilatory assistance was initiated. This reduced the degree of cyanosis and appeared to somewhat improve his general condition.

The following day his total clinical condition was essentially unchanged, although the rate of urine secretion had increased. Use of vasopressor drugs had been required intermittently to support the blood pressure at a systolic level of 100 mm Hg. Meanwhile, the condition of the gangrenous portion of the left lower leg had further deteriorated, and it was decided to perform brisk amputation of this portion of the extremity under analgesia achieved through minimal anesthesia administered through the tracheostomy tube. This amputation was quickly completed without detectable effect on the patient's general condition.

Cardiac Evaluation.—By noon of Jan. 23 the formal report of the cardiologist was available. . . .

The conclusions of the cardiologist were as follows: "From the cardiovascular standpoint, the situation is unequivocally critical due to myocardial failure and apparent multiple emboli arising from the left atrium or ventricle. By all rules, life expectancy can be measured in the case in hours only."

In view of this opinion, which was concurred in by members of the transplant team, the possibility of heart transplantation was raised. There was in the recovery ward a young man near death from irreversible brain damage who might serve as a suitable donor, and the responsible relatives of the heart patient were apprised of the situation. They were well aware that death was imminent and were willing to have heart transplantation performed in the event of a terminal collapse. The written permission stated that the undersigned understood that, although many hearts had been transplanted in animals in our laboratory and elsewhere, no heart had ever been transplanted in man. The factors weighing against long-term success of the transplant were acknowledged. Furthermore, at this point the possibility of using a lower primate heart, raised at the time of the operation on the previous pa-

tient one week earlier, was made a part of the permission that was to be signed. It was not expected that this need come to pass, but experience with the previous case had underscored the fact that, for a homotransplant to succeed, the donor and the recipient must "die" at almost the same time; although this might occur, the chances that both prospective donor and prospective recipient would enter fatal collapse simultaneously were very slim. The properly signed permission was witnessed by three persons who were not members of the transplant team.

* * *

At approximately 6 PM the prospective recipient went into terminal shock, with a systolic blood pressure of 70 mm Hg and virtual apnea without the continued use of mechanical ventilation through the cuffed tracheostomy tube. Death was clearly imminent, and it was obvious that if heart transplantation were to be performed it must be done at once. Meanwhile, the condition of the prospective donor was not such that death appeared to be immediately imminent. At this time a tranquilizing drug was given to the larger of the two chimpanzees. This animal weighed 96 lb., considerably less than the heart patient, but his cardiac output had been measured at 4.25 liters per minute. . . . The cardiac output of the prospective recipient had been measured at 3.6 liters per minute prior to the terminal collapse; this output was certainly not at a normal level for a man of his size, but it had been sufficient to sustain a systolic blood pressure level of from 90 to 110 mm Hg. Should the primate heart be used, the artificial ventricular pacemaker could be employed to produce a relatively rapid rate in order to increase the minute output of the large venous return.

The patient was moved to the operating room while being maintained on ventilation by the anesthesiologist. . . . He was quickly prepared and draped, and at approximately 7:30 PM the heart was exposed through the usual median sternotomy incision; a femoral artery was simultaneously exposed to receive the arterial return catheter. . . . By this time, approximately 20 minutes of operating time had elapsed, and the blood pressure afforded by the extremely rapid and irregular heart beat was intermittently obtainable at only 40 mm Hg systolic despite all supportive measures employed by the anesthesiologist. The caval catheters were inserted through purse-string sutures in the lateral wall of

the right atrium. Effective heart action ceased at about this time, not to be resumed even as the blood pressure was raised to a level of 100/60 mm Hg by the extracorporeal circuit. . . .

The Decision.—The decision that the work in animals should lead eventually to clinical exploration had been made almost a year before and this posed no problem, although the clinical occasion had developed sooner than had been anticipated. But now a second, and in many ways a far more difficult, decision of critical importance had to be faced. The patient was on cardiopulmonary bypass and the prospective human donor lingered on in the recovery ward. The larger chimpanzee had already been anesthetized in an adjacent operating room. The decision had to be made either to discontinue cardiopulmonary bypass and allow the patient to die, or to transplant the primate heart. At this point both teams were assembled in the main operating room to consider the matter. The major factors weighed in the decision were essentially three: (1) The senior author had been impressed at first hand by the surprising degree of at least early clinical success that had been achieved with chimpanzee kidney transplants, and certainly a vigorous organ for transplantation would be available if the chimpanzee heart were used. In contrast, failure of a cadaver heart to beat following transplantation might be due to antemortem changes, a failure which could not be properly assessed. (2) Clinical transplantation of another nonpaired organ, the liver, under otherwise hopeless conditions, had been accepted as justifiable by us and apparently by many other physicians. (3) An extracorporeal apparatus for extended cardiac support had justifiably been used in a heart patient in a terminal condition. The fact that total success could hardly have been expected with this less than final model of such equipment was no reason that such a beginning should not have been made under the circumstances.

Nevertheless, regardless of the positive factors in favor of proceeding with the heterotransplant, it was appreciated that psychological problems were involved. The clinical transplantation of a human heart might prompt controversy, and the clinical transplantation of the primate heart was even more likely to arouse controversy. Even so, it was felt that to perform this transplant, under the specific set of circumstances which existed at that instant, was well within ethical and moral boundaries. Thus, the five primary team members were individually polled and their

votes made a matter of record. Four voted to proceed and the fifth abstained. The first author believed that the circumstances justified the heterotransplant, and from this point on the transplantation proceeded smoothly.

Donor Preparation.—Thoracotomy was quickly performed under sterile conditions and the heart of the primate was exposed. His body temperature had drifted downward to 32 C (89.6 F) and he was now heparinized. . . . The heart was briefly perfused with a cold, heparinized Ringer's lactate solution through which oxygen had been bubbled to increase the pO_2 . After the primate blood had been removed, the perfusion fluid was changed to cold oxygenated blood, administered by gravity flow, with the heart remaining submerged in cold Ringer's lactate solution. A slow and satisfactory ventricular fibrillation developed.

The Recipient.—Meanwhile, the still heart of the recipient was excised. . . . The total body perfusion was proceeding smoothly, the blood pressure was satisfactory, and the patient's pupils were not unduly dilated, indicating that irreversible brain damage did not necessarily exist.

The continuously perfused donor heart was sutured in place. . . .

The coronary sinus perfusion catheter was removed and the aorta was unclamped approximately 45 minutes from the beginning of the actual insertion of the donor organ. The time was now 9 PM, and the patient had been on total bypass for slightly more than one hour. The blood from the pump oxygenator quickly rewarmed the transplanted heart, and a strong ventricular fibrillation was developed and recorded by camera. A single shock with the pulse defibrillator produced complete cardiac arrest, which was followed by a regular and forceful beat at a rate of approximately 80 per minute. This was a most gratifying development, since it had been agreed that this must represent the minimal acceptable degree of success.

* * *

It was soon apparent that the smaller heart would not be able to handle the large venous return, unless its rate was increased. For this reason, and to prevent problems referable to heart block postoperatively, the electrodes of a ventricular pacemaker were sutured to the left ventricle. Just at this stage, 0.5 mg of digoxin (Lanoxin) was given intravenously, producing a pulsus bigeminus which was broken by turning up the amplitude of the pacemaker which had

been set at a rate of 100 beats per minute. Meanwhile, the left ventricular vent had been removed and the bypass support greatly reduced. At 9:45 PM all perfusion catheters were removed. . . .

The primate heart paced at a rate of 100 beats per minute was able to maintain a blood pressure ranging from 60 to 90 mm Hg. Unfortunately, as time passed, the heart became increasingly unable to handle the large venous return. By 11 PM, approximately one hour after the removal of the bypass catheters, the heart was judged incapable of accepting the large venous return without intermittent decompression by manual cardiac massage. Further support was abandoned, even though a weak and regular beat continued. The azathioprine that was to be injected intravenously at the close of the operation to suppress the immune response had not been given.

What Was Accomplished.—First, it was found that the heart could be effectively preserved for one hour while being transplanted into man. . . . Second, the suture techniques widely employed for heart transplantation in experimental laboratories were adequate and otherwise acceptable. Third, a regular and forceful beat was promptly restored following defibrillation with a single weak shock of the pulse defibrillator. . . . Fourth, the transplanted heart reacted immediately to intravenously administered digoxin, as reflected in relative heart block with pulsus bigeminus. The cardiac pacemaker readily broke through this arrhythmia when the current was increased.

It was also apparent that the heart of the lower primate, at least at the chimpanzee level, is not quite large enough to support the circulatory load of the adult human being.

* * *

Public Announcement.—[B]y the time the operation was over, almost 25 persons, many of them physicians, had gained entrance to the operating suite on one pretext or another, despite the fact that a doorkeeper had been placed at the only unlocked entrance. Clearly, the news would shortly be disseminated and, to announce the bare facts accurately, the director of public information decided to release a short statement. In accord with usual Medical Center policy, no member of the transplant team was to grant any interview, release any illustrative material, or be photographed, except under the formal auspices of national medical meetings. This was strictly adhered to.

Unfortunately, the first release resulted inadvertently in the need to permit another. The initial announcement did not specify that a chimpanzee heart had been used; this was to be divulged at the Sixth International Transplantation Conference a few days later. However, when it was announced in a distant city that the donor heart had been taken from a living human being, the situation had to be clarified. At this point, the university officials decided to halt piecemeal news leaks by one final announcement which included the membership of the transplant team.

* * *

The general discussion which the heart transplant stimulated has had, with other factors, a penetrating influence on and within the transplantation movement. Many are reassessing their positions, reappraising their guidelines. We ourselves underestimated the extent and the vigor of the debate which was to center around the use of clinical transplants—especially the use of lower primate organs. We believed then and we believe at this writing that the insertion of the chimpanzee heart, under the conditions which existed at that moment, was well within the bounds of medical ethics and morality. While the transplant did not function for as long a period as we had hoped, a great deal was learned, and this will render continuing laboratory studies more meaningful.

NOTES

NOTE 1.

OPERATIVE PERMIT*

I hereby give full permission for left leg amputation and heart surgery on Boyd Rush. I understand that any clots present will be removed from the heart to stop them from going to still more arteries of his body. I further understand that his heart is in extremely poor condition. If for any unanticipated reason the heart should fail completely during either operation and it should be impossible to start it, I agree to the insertion of a suitable heart transplant if such should be available at that time.† I further understand that

* James D. Hardy and Carlos M. Chavez: "The First Heart Transplant in Man—Historical Reexamination of the 1964 Case in the Light of Current Clinical Experience," 1 *Transplantation Proceedings* 717, 721 (1969). Reprinted by permission.

† "The possibility of using a lower primate heart was acknowledged in discussion with the recipient's relatives, should the anticipated death of the patient with massive brain injury not occur." *Ibid.*

hundreds of heart transplants have been performed in laboratories throughout the world but that any heart transplant would represent the initial transplant in man.

Signed (for family) Mrs. J. H. Thompson
(sister)

* * *

NOTE 2.

SURGEONS CHEER RISING TRANSPLANT SCORE*

At the second International Congress of the Transplantation Society, the atmosphere was pervaded by the sweet smell of success. . . . The big news of the conference, said Nobelist Peter B. Medawar, was that kidney transplants are no longer news. He predicted that heart grafts would reach the same point before the next transplant congress two years from now.

The bulk of the program dealt with experimental work and basic research, but the tenor of the meeting reflected what Dr. Medawar called "the year of the surgeon." For many, the high point of the conference came when Dr. Denton Cooley presented his patient Louis John Fierro, who four months before had been near death with repeated bouts of congestive heart failure. With a teen-age heart beating in his 54-year-old chest, the chunky used-car salesman strode up the four steps to the stage, shook his surgeon's hand, and gave a triumphant wave in response to the congress audience's applause.

Exactly a week later, Dr. Cooley would perform his 11th human heart transplant—an operation that has catapulted transplant surgery into the era of multiple organ preparation grafts. He and his colleagues at St. Luke's Hospital in Houston transplanted a heart-lung preparation, including both whole lungs, from a dead anencephalic child into a two-month-old recipient, a girl, who had a persistent A-V shunt and defective mitral and aortic valves. She was near to death's door with congestive heart failure and severe pulmonary vascular disease.

Because of this combination of defects, a hospital spokesman said, Dr. Cooley decided that "a heart transplant alone would not suffice. So the heart and attached lung were transplanted."

Breathing with the aid of a respirator, the child regained consciousness following the operation, then quickly lapsed into coma. She died of cardiac arrest 14 hours after surgery.

* *Medical World News* 26-27 (September 27, 1968). Copyright 1968, McGraw-Hill, Inc. Reprinted by permission.

Another participant was Dr. James Hardy of the University of Mississippi, who suffered severe censure when he transplanted a chimpanzee heart into a man in 1964.

Dr. Hardy reclaimed his place as the world's first cardiac transplant by showing his heretofore self-suppressed filmed record of that historic occasion. But in the light of acute failure in that case and two subsequent ones elsewhere, Dr. Hardy and the other panelists agreed that, at least for the time being, heart xenografts are unworkable.

* * *

Several of the surgeons expressed the fear that delayed rejection would place the now surviving heart patients in jeopardy in the not too distant future. This dismal outlook is based in part on experience with kidney transplants. According to the tissue-typing pioneer Paul Terasaki of UCLA, who did all the histocompatibility studies for the Houston heart transplants, recipients of mismatched kidney grafts do well for a year or so but tend to die off two or three years later at a more rapid rate than those who are well matched. All but one of the Texas heart recipients turned out to have been poorly matched. Oddly enough, rejection occurred in the well-matched exception and killed the patient.

In bridging the antigen gap, antilymphocyte globulin (ALG) has established itself—at least for the next few years—as an important part of the immunosuppressive armamentarium. By a show of hands, the heart transplant panelists indicated that they all use it. But Dr. Thomas Starzl, who has achieved excellent results in kidney and liver transplants at the University of Colorado, reported that a trial with refined ALG on 13 kidney patients had resulted in three deaths and five rejections. Like Dr. Michael DeBakey, he is now attempting a "blitzkrieg approach" of giving larger doses of ALG at the outset, with the hope of avoiding long-term use of the agent.

* * *

NOTE 3.

BLAIBERG—VICTORY OR DEFEAT?*

The death of Dr. Philip Blaiberg on August 17 in Cape Town, South Africa, fixes the longest survival of a heart-transplant recipient at 593 days—19½ months. The 60-year-old retired dentist had been kept alive by the heart of a 24-year-

old factory worker since Jan. 2, 1968, when Dr. Christiaan Barnard performed the transplant, his second and history's third.

* * *

"The autopsy report isn't complete yet," [Dr. Christiaan Barnard] told MWN, "but I think that the cause of death is quite clear. It's extensive myocardial damage due to acute and chronic rejection."

* * *

[H]is condition had come full cycle. By the time of his final admission to the hospital, he was carrying a heart more than two thirds destroyed by the relentless rejection process. "He was back to the point where he was before we did the transplant," Dr. Barnard said. "I think that in Dr. Blaiberg we were unfortunate to have two acute rejection episodes. When this happens, even if you reverse the episode, there's a certain amount of permanent damage."

During the more severe bout with rejection in July 1968, a second transplant was considered and Dr. Blaiberg consented to having it done if necessary. But with the final illness, Dr. Barnard felt the opportunity no longer existed. "By the time he really needed it, his renal function had deteriorated and he had very bad arteriosclerosis, marked weakness in the legs, and muscle wasting. The autopsy showed that one renal artery and both femoral arteries were occluded. He also had a patch of pneumonia in his right lung."

* * *

Dr. Barnard is completely satisfied with the original operation and subsequent course taken. "We are sad that it is all over now, but we did far better than we expected."

Other heart surgeons and immunologists are not so certain. The frequency of heart transplants has dropped off sharply from a peak of 26 last November; since April, no more than four have been done in any month. The total number of heart transplants recorded by the American College of Surgeons is 143 in 141 recipients, of whom 29 are living, 21 of them surviving more than six months. Of the total, U.S. surgeons have performed 84 in 82 recipients, of whom 19 survive, 13 for more than six months.

A number of surgeons have said that with the death of the longest-surviving patient and with a continuing decline in the percentage of survivors, it is time for a reappraisal of heart transplantation. The Montreal Institute of Cardiology team headed by Dr. Pierre Grondin,

* *Medical World News* 14-15 (September 5, 1969). Copyright 1969, McGraw-Hill, Inc. Reprinted by permission.

which has done nine of the 15 Canadian heart transplants, suspended its work early this year to study such factors as the importance of tissue matching and immunosuppressive regimens and has not yet resumed transplant operations. Of the 56 teams that have done heart transplants, no more than ten are still active.

Dr. Barnard strongly disagrees about the need for reassessment now. "I can't understand why Dr. Blaiberg's death should make any difference," he says. "Dr. Blaiberg did much better than we anticipated, or than anybody anticipated. People were predicting that he wouldn't last 14 days, 17 days, two months, three months, a year."

Far more significant, he feels, is that the total survival time of his five transplant patients, of whom two are still alive, is 1,101 days. "That means that the average survival time of these patients is 220 days. Now Dr. Norman Shumway has figured that the average life expectancy of patients at the same stage of illness who don't get transplants is 30 days, so there's more than a 700 per cent improvement already."

* * *

Dr. [C. Walton] Lillehei adds: "Though I'm more encouraged than ever, I'm sure potential recipients have become discouraged. The problem now is not so much a lack of donors but recipients. We've been turned down about six to eight times in the past three months."

Dr. Lillehei also blames the transplant slowdown in part on "some surgeons who jumped on the bandwagon without the background or psychological make-up to do developmental work in this area. Those who get discouraged easily have dropped out, though."

Dr. Adrian Kantrowitz of Maimonides Medical Center in Brooklyn concurs. "Those who've viewed heart transplants as experimental all along and have anticipated the problems are going on with it," he says. He and his team expect to perform more transplants, but their tissue-matching standards will be more stringent. "We'll want at least a B-minus match," he declares.

NOTE 4.

TESTIMONY OF DR. CHRISTIAAN BARNARD—
MARCH 8, 1968*

SENATOR CURTIS: [T]he young lady whose heart was transplanted into Mr. Washkansky's body received artificial respiration.

DR. BARNARD: Yes, sir.

* * *

SENATOR CURTIS: Who made the decision to discontinue the use of the machine?

DR. BARNARD: The neurosurgeons and neurologist. Those are a group of four doctors—

SENATOR CURTIS: Now, that coincided with the time you were ready to begin the surgery?

DR. BARNARD: Yes, sir; that is correct.

SENATOR CURTIS: It did not necessarily coincide with the time they made the decision that she was going to die?

DR. BARNARD: This was a few hours later.

SENATOR CURTIS: So the machine was continued and stopped, not in relation to the time that the knowledge was available that she would not live, but it was continued to a time and stopped at a time to fit in with the schedule of the heart transplant to another person?

DR. BARNARD: That is correct.

SENATOR CURTIS: And her surgeons made that decision?

DR. BARNARD: The doctors who were caring for her, as she was a patient who had severe brain damage, and therefore was cared for by the neurologist and the neurosurgeons.

SENATOR CURTIS: Did they represent the recipient of the heart?

DR. BARNARD: No; they were only representing the donor. Their names are not on this team that you see published as the transplant team.

* * *

* *National Commission on Health Science and Society—Hearings on S.J. Res. 145 before the Subcommittee on Government Research of the Senate Committee on Government Operations, 90th Congress, 2d Session 74-75 (1968).*

B.

Appraising the Role of the Participants*

1.

In Formulating Policy

a.

Deciding about Societal Interests and Priorities?

What Price Transplanted Organs?†

The last desperate 16 days of heart transplant recipient Mike Kasperak's life at the Palo Alto-Stanford Hospital cost \$28,845.83. Care for Everett C. Thomas, one of the six patients to survive more than four weeks among the world's first 21 heart recipients, is expected to cost \$25,000 by the time he is discharged from St. Luke's Hospital in Houston.

Cardiovascular surgeons tend to agree, says Dr. Theodore Cooper, director of the National Heart Institute, "that it costs \$20,000 for the care of cardiac transplant patients in the immediate intraoperative period until the cardiovascular status is stabilized. Thereafter, it takes another several hundred dollars a day to manage the patient and deal with the immune phenomenon."

Such sums are astronomic to the average American. Multiplied by the estimated 5,000 potential transplant recipients a year, the total bill for new hearts would come to a staggering \$100 million annually. . . .

* * *

Where does the money for transplants come from in the U.S., where the government does not generally pay a citizen's medical bills? In the initial stages of a new procedure, funds stem mostly from grants made by the National Institutes of Health or private foundations.

Over the past five years, for example, the NIH has contributed about \$2 million for the cardiac assist and transplant research carried out by Dr. Adrian Kantrowitz at Brooklyn's Maimonides Medical Center. And since 1959, the American Heart Association has given

* This appraisal section focuses on dying subjects. For a fuller exposition of the factors requiring appraisal, consult section D of Chapter Eleven, beginning at p. 818 *supra*.

† *Medical World News* 28-29 (June 28, 1968). Copyright 1968, McGraw-Hill, Inc. Reprinted by permission.

\$437,960 to Dr. Norman E. Shumway and his research team at Stanford University.

* * *

Some of the same factors—enormous amounts of lab work, heavy drug costs, and intensive care—go into the high costs of transplanting other organs. At the University of California Medical Center in San Francisco, the average kidney transplant costs \$11,753, plus another \$2,000 to \$3,000 for the hospital care of live donors. And in Denver, at the University of Colorado Medical Center, the prices of five recent kidney transplants ranged from \$3,057 to \$31,663, with an average of \$12,070.

* * *

None of the figures from university medical centers includes professional fees. Like Colorado's Dr. Thomas E. Starzl, most surgeons transplanting kidneys in a university setting are full-time, salaried faculty members. And even though they may charge fees for other types of surgery—such money usually goes into a fund for educational and other uses—the university men generally have waived professional charges in kidney operations up to now.

"Kidney transplantation is a research procedure," says Dr. Samuel L. Kountz, associate professor of surgery and chief of transplant surgery at the University of California's San Francisco medical center. If the men who do the transplants were to be compensated on a fee-for-service basis, he estimates, "it would probably add \$2,000 or \$3,000 to the cost—if you could find doctors willing to work that hard."

* * *

A bill now in Congress would provide up to \$30 million a year in federal aid for the establishment and operation of new, badly needed kidney centers. Although it is part of a \$1-billion program proposed last year by a White House-appointed committee, the bill lacks Administration support. PHS Surgeon General William H. Stewart told a Senate subcommittee in March that such a program would require "drastic curtailment or abandonment of many other health programs."

A massive kidney care campaign would have to compete for dollars with the federal program

for artificial heart research and development. About \$8 million in National Heart Institute money was spent on this project in fiscal 1967. But Dr. Frank W. Hastings, chief of the artificial heart program, estimates that a fully implantable artificial heart is at least five years away from clinical trials. Meanwhile, Congress is threatening to wield an ax on federal research funds in general.

[A]nother problem confronting the prospective kidney program is the controversy over medical priorities. Is it more important to improve the quality of specialized care for the few or to deliver more general care to the many? Sen. Walter F. Mondale (D-Minn.), who is proposing a national commission to study the issues involved in transplants, puts it this way: "A public commitment of \$1 billion could buy enough kidney dialysis centers to serve 25,000 persons in the next decade—or it could provide ambulatory care of a general nature for 1.2 million poor people."

NOTES

NOTE 1.

HENRY K. BEECHER

ETHICAL PROBLEMS CREATED BY THE
HOPELESSLY UNCONSCIOUS PATIENT*

... Inevitably, with more and more bold and venturesome and commendable attempts to rescue the dying, more and more patients will accumulate in the hospitals of the land—patients who can be kept "alive" only by extraordinary means, in whom there is no hope of recovery of consciousness, let alone recovery to a functioning, pleasurable existence, and all this at a cost of \$25,000 to \$30,000 per patient per year. Burdensome as this cost is, it is the lesser of two. Another cost: if the average hospital stay is two weeks, the irretrievably unconscious patient then occupies space that could have been used by 26 others in a year's time. There are today great delays in hospital admissions owing to bed shortages, even of patients with cancer. A life could be lost owing to delay in getting definitive hospital care—lost because a bed was occupied by a hopeless patient.

It seems clear that the time has come to re-examine this situation. Money is human life; so

are available hospital beds. The money spent to maintain unconscious and hopelessly damaged persons could be used to restore those who are salvageable. What are our privileges and responsibilities in this confusing situation? What decisions must we make about this "striving officiously to keep alive"? It must be borne in mind that "hopeless" when established by a killing disease is often not the same thing as "hopeless" resulting from a recent accident. Astonishing recoveries have occurred in the latter case. A five-year-old boy, for example, was submerged for 22 minutes in a Norwegian river at a temperature of -10°C and still recovered.

It must be remembered that such advances as were employed in this case are sometimes the result of intensive, even desperate efforts to alleviate the condition of the hopelessly ill. There is profit for mankind sometimes in the prolongation of dying, justified as it can be by concern for the specific sick man. The rights of the individual and the rights of society are interrelated.

NOTE 2.

LEON R. KASS

CAVEAT ON TRANSPLANTS*

* * *

The development of borrowed and artificial vital organs presents a new instance of an old problem: how to distribute scarce resources justly. Medical care is a scarce resource; quality care, especially so. Is large-scale transplantation the best use of these limited resources?

Is it just that 30 doctors perform a heart transplant while the ordinary medical problems of the indigent go untended because of a shortage of physicians? The treatment of a child's streptococcal sore throat is less spectacular than the replacement of the heart, but the former can prevent the development of rheumatic heart disease and thereby obviate the possible need for a future transplant.

I am not suggesting that Drs. Barnard, Kantrowitz and their colleagues give up their surgical virtuosity for a career in pediatrics or public health. But I am arguing that the public planning and expenditures for medical development be guided by a concern for the health of the entire community. Decent health for the majority of

* 278 *New England Journal of Medicine* 1425, 1429 (1968). Reprinted by permission.

* *The Washington Post* B-1, col. 5 (January 14, 1968). © 1968, *The Washington Post*. Reprinted by permission.

our people should not be sacrificed to our infatuation with technological progress.

* * *

b.

Deciding about the Ambit of Experimentation?

Hans Jonas

*Philosophical Reflections on
Experimenting with Human Subjects**

* * *

[P]atients should be experimented upon, if at all, *only* with reference to *their* disease. Never should there be added to the gratuitousness of the experiment as such the gratuitousness of service to an unrelated cause. This follows simply from what we have found to be the *only* excuse for infracting the special exemption of the sick at all—namely, that the scientific war on disease cannot accomplish its goal without drawing the sufferers from disease into the investigative process. If under this excuse they become subjects of experiment, they do so *because*, and only because, of *their* disease.

Experiment as part of therapy—that is, directed toward helping the subject himself—is a different matter altogether and raises its own problems, but hardly philosophical ones. As long as a doctor can say, even if only in his own thought: “There is no known cure for your condition (or: You have responded to none); but there is promise in a new treatment still under investigation, not quite tested yet as to effectiveness and safety; you will be taking a chance, but, all things considered, I judge it in your best interest to let me try it on you”—as long as he can speak thus, he speaks as the patient’s physician and may err, but does not transform the patient into a subject of experimentation. Introduction of an untried therapy into the treatment where the tried ones have failed is not “experimentation on the patient.”

Generally, there is something “experimental” (because tentative) about every individual treatment, beginning with the diagnosis itself; and he would be a poor doctor who would not learn from every case for the benefit of future cases, and a poor member of the profession who

would not make any new insights gained from his treatments available to the profession at large. Thus, knowledge may be advanced in the treatment of any patient, and the interest of the medical art and all sufferers from the same affliction as well as the patient may be served if something happens to be learned from his case. But this gain to knowledge and future therapy is incidental to the bona fide service to the present patient. He has the right to expect that the doctor does nothing to him just in order to learn.

In that case, the doctor’s imaginary speech would run, for instance, like this: “There is nothing more I can do for you. But you can do something for me. Speaking no longer as your physician but on behalf of medical science, we could learn a great deal about future cases of this kind if you would permit me to perform certain experiments on you. It is understood that you yourself would not benefit from any knowledge we might gain; but future patients would.” This statement would express the purely experimental situation, assumedly here with the subject’s concurrence and with all cards on the table. In Alexander Bickel’s words: “It is a different situation when the doctor is no longer trying to make [the patient] well, but is trying to find out how to make others well in the future.”

But even in the second case of the nontherapeutic experiment where the patient does not benefit, the patient’s own disease is enlisted in the cause of fighting that disease, even if only in others. It is yet another thing to say or think: “Since you are here—in the hospital with its facilities—under our care and observation, away from your job (or, perhaps, doomed), we wish to profit from your being available for some other research of great interest we are presently engaged in.” From the standpoint of merely medical ethics, which has only to consider risk, consent, and the worth of the objective, there may be no cardinal difference between this case and the last one. I hope that my medical audience will not think I am making too fine a point when I say that from the standpoint of the subject and his dignity there is a cardinal difference that crosses the line between the permissible and the impermissible, [under the] principle of “identification”. . . . Whatever the rights and wrongs of any experimentation on any patient—in the one case, at least that residue of identification is left him that it is his own affliction by which he can contribute to the conquest of that affliction, his own kind of suffering which he helps to alleviate in

* 98 *Daedalus* 219, 241–243 (1969). Reprinted by permission of *Daedalus*, Journal of the American Academy of Arts and Sciences, Boston, Massachusetts.

others; and so in a sense it is his own cause. It is totally indefensible to rob the unfortunate of this intimacy with the purpose and make his misfortune a convenience for the furtherance of alien concerns. The observance of this rule is essential, I think, to attenuate at least the wrong that non-therapeutic experimenting on patients commits in any case.

NOTE

HENRY K. BEECHER
RESEARCH AND THE INDIVIDUAL—
HUMAN STUDIES*

* * *

The remarkably increased average length of life indicates that the time of dying has been greatly postponed. Even the characteristics of dying often differ from those of earlier years. The changes have been brought about by a variety of factors: antibiotics, potent drugs, intravenous fluids, transfusions, pain suppression, and artificial and transplanted organs. Sometimes the ancient prerogatives of the patient—his right to be let alone and to die in comfort and dignity—seem to be overlooked. Individuals who may die suddenly or who seem to be in imminent danger of death should not, under ordinary circumstances, be chosen as subjects for experimentation, however harmless the planned procedure may be. Obviously, if death occurs during such an experiment, it could cast a shadow over a potentially valuable agent or useful technique, not to mention placing the investigator in an unhappy predicament where, although innocent, he may have the appearance of guilt.

* * *

[T]hose who are in imminent danger of death should not ordinarily be subjected to experimentation, except as part of a therapeutic effort to save their lives. An exception to this can be found in the irreversibly comatose individual who may be used as an organ donor under certain rigid circumstances. Occasionally one encounters reports wherein the term *hopelessly incurable* seems to be used to justify dangerous experimentation. It is not the physician's prerogative to make or to profit from such dubious judgments. . . .

* * *

* Boston: Little, Brown and Co. 44, 85 (1970). Reprinted by permission.

c.

Deciding about Choice of Subjects?

[i]

Henry K. Beecher
*Ethical Problems Created by the Hopelessly
Unconscious Patient**

* * *

Starzl has spoken of "the declining curve of life," implying that as the end approaches there is less and less life in the individual, and that a quantitative factor is present—a sort of death by inches. To a certain point this is supportable in that all organ and nerve centers do not become irreversibly damaged simultaneously; consciousness as a brain function is often irretrievably destroyed months before the respiratory and vasomotor centers fail. At the same time one can share Schreiner's discontent and insist that "a coordinating vital principle exists which is either there or not there." The moment of death can only be approximated.

From ancient times down to the recent past it was perfectly clear when the respiration and heart stopped that the brain would die in a few minutes, so that the obvious criterion of a heart in standstill as synonymous with death was accurate enough. This is no longer the case when modern resuscitative and supportive measures are involved. These improved activities can now restore "life" as judged by the ancient standards of persistent respiration and continuing heartbeat, even when there is not the remotest possibility that consciousness will be recovered after massive brain damage. In other situations "life" can be maintained only by means of artificial respiration and electrical stimulation of the heartbeat, in temporary bypass of the heart or, in conjunction with these things, reducing with cold the body's oxygen requirement.

* * *

. . . When is death, what is death, what is life? It is self-evident that there is no simple answer to what life is. One can submit that life is the ability to communicate with others. If this ability is lost in permanent unconsciousness, the future will surely confirm that that man is dead. One can make a considerable case that if a physician judges his patient's ability to communicate as lost beyond retrieval through permanent un-

* 278 *New England Journal of Medicine* 1425-1427 (1968). Reprinted by permission.

consciousness, he not only may, but *must*, declare the man dead.

When is death? The traditional compulsive urge to know and record the exact moment of death is not useful, except sometimes for legal purposes. What usually matters is not the time of death, but the time when a physician undertook to declare the patient dead.

So much for general comments; now we come to specifics in an attempt to decide how death is exhibited. As mentioned, there is the incontrovertible fact that when the circulation ceases the brain dies within five minutes under ordinary circumstances. Various workers have striven to go beyond this basic situation. For example, according to Schreiner, "Some biologists (unrealistically) accept one minute of E.E.G. silence as incontrovertible proof of death. Others accept three minutes or five minutes." Alexandre states that a flat electroencephalogram alone is not an adequate criterion of death, and he does "[not] think five minutes would be enough anyway." Hamburger reports that "at least two cases in Paris were observed to have a flat E.E.G. for several hours, followed by complete recovery; in both cases the coma was due to severe barbiturate poisoning." Alexandre states that air embolism during heart surgery can lead to a flat encephalogram with recovery. Murray asks if a flat electroencephalogram for four to six hours along with the other conditions set down by Alexandre (enumerated below) would be enough to indicate incontrovertible evidence of death. Alexandre objects that one cannot wait six hours if the object is kidney transplantation, for falling blood pressure would have led to conventional death and an unsatisfactory kidney for transplantation. Starzl doubts if any member of his transplantation team would accept a person as dead as long as there was a heartbeat. If there was a mistake in evaluating the "living cadaver," he continues, removal of a kidney should not necessarily lead to death. The taking of single organs such as the liver is a different matter. He asks if any physician would be willing to remove an unimpaired organ before the circulation had stopped. In transplantation of a kidney one's reliance would depend on a kind of "statistical morality": the severity of the operation itself in such desperately injured persons would doubtless have an appreciable death rate—if the subjects were alive. Alexandre, in Belgium, has in nine cases used unconscious patients with head injuries, whose hearts had not stopped, as kidney donors

for transplantation. "Five conditions were always met in these nine cases: (1) complete bilateral mydriasis; (2) complete absence of reflexes, both natural and in response to profound pain; (3) complete absence of spontaneous respiration, five minutes after mechanical respiration had been stopped; (4) falling blood pressure, necessitating increasing amount of vasopressive drugs; (5) a flat E.E.G." Some have spoken of taking organs from a dying person. "I would like to make it clear [says Alexandre] that, in my opinion, there has never been and never will be any question of taking organs from a dying person who has 'no reasonable chance of getting better or resuming consciousness.' The question is of taking organs from a dead person, and the point is that I do not accept the cessation of heart beats as the indication of death". . . .

Revillard looks for Alexandre's five signs and adds two others: interruption of blood flow in the brain as judged by angiography (he assumes that this is a better sign of death than a flat electroencephalogram); and ("of less value") the absence of reaction to atropine. He does not agree with Alexandre that the blood pressure inevitably falls at once. He finds that it sometimes stabilizes at a satisfactory level for transplantation for several hours.

Calne states bluntly that Alexandre was "in fact removing kidneys from live donors." He believes that "Any modification of the means of diagnosing death to facilitate transplantation will cause the whole procedure to fall in disrepute with the entire profession."

Alexandre and Calne agree that two separate teams should be involved in deciding these matters, one concerned with resuscitating the patient and the other with an interest in donor possibilities. Schreiner differs; he does "[not] believe that mechanical separation of two teams and the problems of the surgeon's disrepute are really germane to the philosophical problem. . . . The moral problem can't be settled on the basis of what might happen to a reputation. . . . This question of deciding death transcends the problems of transplantation." Schreiner concedes that, if cadaver transplants become available by "updating" death and do as well or nearly as well as organs from live donors, the morality of continuing to use transplants from live, unrelated donors is open to question.

These matters have been presented in some detail to show the differences of opinion and uncertainty among experts who have given much

thought to the as yet unresolved question of what is truly death.

* * *

[iif]

*Ad Hoc Committee of the
Harvard Medical School
A Definition of Irreversible Coma**

Our primary purpose is to define irreversible coma as a new criterion for death. There are two reasons why there is need for a definition: (1) Improvements in resuscitative and supportive measures have led to increased efforts to save those who are desperately injured. Sometimes these efforts have only partial success so that the result is an individual whose heart continues to beat but whose brain is irreversibly damaged. The burden is great on patients who suffer permanent loss of intellect, on their families, on the hospitals, and on those in need of hospital beds already occupied by these comatose patients. (2) Obsolete criteria for the definition of death can lead to controversy in obtaining organs for transplantation.

Irreversible coma has many causes, but we are concerned here only with those comatose individuals who have no discernible central nervous system activity. If the characteristics can be defined in satisfactory terms, translatable into action—and we believe this is possible—then several problems will either disappear or will become more readily soluble.

More than medical problems are present. There are moral, ethical, religious, and legal issues. Adequate definition here will prepare the way for better insight into all of these matters as well as for better law than is currently applicable.

An organ, brain or other, that no longer functions and has no possibility of functioning again is for all practical purposes dead. Our first problem is to determine the characteristics of a permanently nonfunctioning brain.

A patient in this state appears to be in deep coma. The condition can be satisfactorily diagnosed by points 1, 2, and 3 to follow. The electroencephalogram (point 4) provides confirmatory data, and when available it should be utilized. In

situations where for one reason or another electroencephalographic monitoring is not available, the absence of cerebral function has to be determined by purely clinical signs, to be described, or by absence of circulation as judged by standstill of blood in the retinal vessels, or by absence of cardiac activity.

1. *Unreceptivity and unresponsivity.*—There is a total unawareness to externally applied stimuli and inner need and complete unresponsiveness—our definition of irreversible coma. Even the most intensely painful stimuli evoke no vocal or other response, not even a groan, withdrawal of a limb, or quickening of respiration.

2. *No Movements or Breathing.*—Observations covering a period of at least one hour by physicians are adequate to satisfy the criteria of no spontaneous muscular movements or spontaneous respiration or response to stimuli such as pain, touch, sound, or light. After the patient is on a mechanical respirator, the total absence of spontaneous breathing may be established by turning off the respirator for three minutes and observing whether there is any effort on the part of the subject to breathe spontaneously. (The respirator may be turned off for this time provided that at the start of the trial period the patient's carbon dioxide tension is within the normal range, and provided also that the patient had been breathing room air for at least 10 minutes prior to the trial.)

3. *No reflexes.*—Irreversible coma with abolition of central nervous system activity is evidenced in part by the absence of elicitable reflexes. The pupil will be fixed and dilated and will not respond to a direct source of bright light. Since the establishment of a fixed, dilated pupil is clear-cut in clinical practice, there should be no uncertainty as to its presence. Ocular movement (to head turning and to irrigation of the ears with ice water) and blinking are absent. There is no evidence of postural activity (decerebrate or other). Swallowing, yawning, vocalization are in abeyance. Corneal and pharyngeal reflexes are absent.

As a rule the stretch of tendon reflexes cannot be elicited; i.e., tapping the tendons of the biceps, triceps, and pronator muscles, quadriceps and gastrocnemius muscles with the reflex hammer elicits no contraction of the respective muscles. Plantar or noxious stimulation gives no response.

4. *Flat Electroencephalogram.*—Of great confirmatory value is the flat or isoelectric EEG.

* Henry K. Beecher, M.D., Chairman. 205 *Journal of the American Medical Association* 337-339 (1968). Reprinted by permission. [The committee, all members of the faculty of Harvard University, included ten physicians, one theologian, one historian, and one lawyer.]

We must assume that the electrodes have been properly applied, that the apparatus is functioning normally, and that the personnel in charge is competent. We consider it prudent to have one channel of the apparatus used for an electrocardiogram. This channel will monitor the ECG so that, if it appears in the electroencephalographic leads because of high resistance, it can be readily identified. It also establishes the presence of the active heart in the absence of the EEG. We recommend that another channel be used for a noncephalic lead. This will pick up space-borne or vibration-borne artifacts and identify them. The simplest form of such a monitoring noncephalic electrode has two leads over the dorsum of the hand, preferably the right hand, so the ECG will be minimal or absent. Since one of the requirements of this state is that there be no muscle activity, these two dorsal hand electrodes will not be bothered by muscle artifact. The apparatus should be run at standard gains $10\mu\text{V}/\text{mm}$, $50\mu\text{V}/5\text{mm}$. Also it should be isoelectric at double this standard gain which is $5\mu\text{V}/\text{mm}$ or $25\mu\text{V}/5\text{mm}$. At least ten full minutes of recording are desirable, but twice that would be better.

It is also suggested that the gains at some point be opened to their full amplitude for a brief period (5 to 100 seconds) to see what is going on. Usually in an intensive care unit artifacts will dominate the picture, but these are readily identifiable. There shall be no electroencephalographic response to noise or to pitch.

All of the above tests shall be repeated at least 24 hours later with no change.

The validity of such data as indications of irreversible cerebral damage depends on the exclusion of two conditions: hypothermia (temperature below 90°F [32.2°C]) or central nervous system depressants, such as barbiturates.

The patient's condition can be determined only by a physician. When the patient is hopelessly damaged as defined above, the family and all colleagues who have participated in major decisions concerning the patient, and all nurses involved, should be so informed. Death is to be declared and *then* the respirator turned off. The decision to do this and the responsibility for it are to be taken by the physician-in-charge, in consultation with one or more physicians who have been directly involved in the case. It is unsound and undesirable to force the family to make the decision.

* * *

It is recommended as a part of these procedures that judgment of the existence of these criteria is solely a medical issue. It is suggested that the physician in charge of the patient consult with one or more other physicians directly involved in the case before the patient is declared dead on the basis of these criteria. In this way, the responsibility is shared over a wider range of medical opinion, thus providing an important degree of protection against later questions which might be raised about the particular case. It is further suggested that the decision to declare the person dead, and then to turn off the respirator, be made by physicians not involved in any later effort to transplant organs or tissues from the deceased individual. This is advisable in order to avoid any appearance of self-interest by the physicians involved.

It should be emphasized that we recommend the patient be declared dead before any effort is made to take him off a respirator, if he is then on a respirator. This declaration should not be delayed until he has been taken off the respirator and all artificially stimulated signs have ceased. The reason for this recommendation is that in our judgment it will provide a greater degree of legal protection to those involved. Otherwise, the physicians would be turning off the respirator on a person who is, under the present strict, technical application of law, still alive.

* * *

NOTES

NOTE 1.

GEORGE P. FLETCHER
LEGAL ASPECTS OF THE DECISION
NOT TO PROLONG LIFE*

* * *

If one were to have a legal standard endorsing the physician's decision not to prolong life, should the standard be limited to the case of a doomed comatose patient with a flat EEG reading? Consider how this case blends so gradually into many related cases. First, there is the case of the doomed comatose patient who still shows some signs of brain activity. Does this patient *deserve* prolongation of life? Neither he nor his brother with a flat EEG reading can enjoy the beauties of life on earth. Why should we keep them alive? Secondly, compare the case of the doomed but conscious patient who can perceive

* 203 *Journal of the American Medical Association* 65, 68 (1968). Reprinted by permission.

the world about him but who suffers from excruciating pain. Is the fact of consciousness and the fact of an EEG reading sufficient to say that this man must be kept alive? In analyzing the physician's legal obligation to prolong a patient's life, we should keep in mind the infinitely graduated spectrum from the clear cases to the cases that are far from clear. . . .

* * *

It will not do for the medical profession to demand that we lawyers devise a legal definition of death. There might be many uses of a legal definition of death; one might wish to know the time of death to apply rules on the disposition of the decedent's estate. But this is not what medical practitioners have in mind. It seems that they should like to have a clear standard for deciding when and when not to render aid to their dying patients. Sweden's Dr. Crafoord has proposed that a patient be declared legally dead when his EEG reading is flat. The standard is clear and easy to apply, but it is morally insensitive. Should one totally disregard all the other factors: the likelihood of recovery, the family's financial position, the patient's expressed wishes, other demands on hospital facilities and the attending physician's time? Even if we could formulate a just resolution of these conflicting factors today, would it be a resolution that would remain fair in the face of medical innovation? It surely would not. What one regards as excessive and extraordinary today might well become commonplace in a few years. A legal standard of death, which would define the limits of the doctor's duty to his patient, would be an overly rigid solution to a problem that changes dimensions with each medical innovation.

NOTE 2.

CARL E. WASMUTH AND BRUCE H. STEWART
MEDICAL AND LEGAL ASPECTS OF HUMAN
ORGAN TRANSPLANTATION*

* * *

Recently, physicians from the Karolinska Institute received international attention when they removed a kidney from a 40-year-old dying woman and transplanted it into the recipient. The donor had suffered a cerebral hemorrhage and was brought into the neurosurgical clinic in

a comatose condition. Her condition had been pronounced hopeless. While she could not, herself, be asked to consent to the removal of the kidney, the operation was performed with her husband's approval. She died in a respirator two days after operation. Professor Crafoord defended the action and the principle. He said that he and his staff had previously agreed that in cases in which irreparable damage to the central nervous system had occurred, and in which the prognosis with 100 per cent certainty be deemed hopeless, the possibility could be considered of removing a kidney for transplantation before what is currently interpreted as "death" had occurred. It was his opinion that if the physician were to wait until death, in the conventional sense, the possibility of a successful transplantation would have decreased tremendously. The position taken by the Swedish physicians is based upon a liberal interpretation of the definition of death. In their particular case, neither respiration nor circulation had ceased and the patient was not, according to the information at hand, dependent upon either of these mechanical means for support. The brain may have been irreversibly damaged, although neither respiration nor circulation had failed.

* * *

NOTE 3.

J. B. BRIERLEY, J. H. ADAMS, D. I. GRAHAM,
AND J. A. SIMPSON
NEOCORTICAL DEATH AFTER CARDIAC ARREST—
A CLINICAL, NEUROPHYSIOLOGICAL, AND
NEUROPATHOLOGICAL REPORT OF TWO CASES*

* * *

It is now generally accepted that a patient who has suffered severe brain damage—e.g., as a result of head injury, cerebrovascular accident, or cardiac arrest—whose electroencephalogram (E.E.G.) is isoelectric (strictly defined), who is totally areflexic and whose respiratory and therefore cardiac function depends upon mechanical ventilation is already dead. It is less well appreciated that, in the specific situation of cardiac arrest, spontaneous respiration, coordinated movements, and also reflex activities at brainstem and spinal-cord levels may return in occasional cases despite the persistence of an isoelectric E.E.G. In this situation the critical clinical ques-

* 14 *Cleveland-Marshall Law Review* 442, 467 (1965). Reprinted by permission.

* 2 *The Lancet* 560, 564-65 (1971). Reprinted by permission.

tion is whether consciousness and intellectual activity will or will not be restored.

Patients with cardiac arrest and irreversible brain damage rarely survive for more than a few days, but in the two cases reported here unconsciousness with an isoelectric E.E.G. persisted for five months after cardiac arrest [at which time the patients died following pulmonary complications]. In case 1, eye-opening, yawning with associated movements, spontaneous respiration, and certain reflex activities at brainstem and spinal-cord levels were present; while in case 2 the resumed central nervous activity was restricted to spontaneous respiration and certain brainstem and spinal-cord reflexes. In both cases, neurophysiological investigations led to the conclusion that the neocortex was dead while certain brainstem and spinal centres remained intact. Subsequent detailed neuropathological analysis confirmed this prediction in each case.

* * *

These two cases permit, probably for the first time, a precise definition of "cortex death" as a sequel of cardiac arrest. "Cortex death," or preferably "neocortical death," implies a persistently isoelectric E.E.G. and the absence of sensory evoked responses in the neocortex, together with the resumption of spontaneous respiration and of certain brainstem reflexes.

In contrast, "brain death" or "total brain death" implies a persistently isoelectric E.E.G. and the absence of any reflex activity and of spontaneous respiration, so that cardiac function depends upon the continuation of mechanical ventilation. . . .

* * *

In case 2 spontaneous respiration and brainstem reflex activity were resumed a few minutes after the cardiac arrest. In case 1, brainstem and spinal reflex activity were demonstrable on the 2nd day, although mechanical ventilation had to be maintained for 17 days. Thereafter the clinical state of the two patients was identical. On the 6th day, neurophysiological investigations in case 1 established death of the neocortex and the preservation of certain reflex activities up to the level of the geniculate bodies. It cannot be overemphasised that the subsequent neuropathological examination in case 1 confirmed in detail the predictions based upon the neurophysiological assessment "in vivo."

In the specific context of cardiac arrest, we

consider that the existence of irreversible neocortical destruction can be established within a few days of the arrest provided that drugs with a central depressive effect are not being given. If any element of doubt should then remain, neocortical death could be confirmed by the appropriate neuropathological examination of a biopsy specimen (a 1-1.5 cm. cube) taken from the posterior half of a cerebral hemisphere.

Once neocortical death has been unequivocally established and the possibility of any recovery of consciousness and intellectual activity thereby excluded, the question must be asked, although this patient breathes spontaneously, is he or she alive? The decision whether or not to continue intensive care in the present era of organ transplantation is contingent upon the answer to this question. However, where a definition of death is concerned "This is a general problem, *prima facie* not at all particularly associated with transplantation." Perhaps the most important consideration is the suffering imposed upon the relatives by a person with whom they can no longer communicate but who breathes without the aid of a machine.

According to the Ad Hoc Committee of the Harvard Medical School, a person who resumes spontaneous respiration after cardiac arrest, yet exhibits an isoelectric E.E.G., is to be regarded as "alive," while another surviving the same accident, also with an isoelectric E.E.G. but whose cardiac function depends upon mechanical ventilation, may be regarded as "dead." Clearly this distinction between "alive" and "dead" attaches cardinal importance to the function of respiration and none to those higher functions of the nervous system that demarcate man from the lower primates and all other vertebrates and invertebrates.

Thus, according to the [Harvard Medical School] both the present patients would be regarded as "alive," although the neurophysiological assessment, made during life, that the neocortex was dead in each, was confirmed by the neuropathological examinations.

These two cases, together with the two of Lewis which survived for 22 days and 2¼ years, may be regarded as products of the present era of intensive care and they may not long remain unique. Their documentation in clinical and neuropathological terms represents a challenge to any definition of life that is unconcerned with the functional and structural integrity of the neocortex.

[iii]

*Cape Town Symposium**Experience with Human Heart Transplantation**

* * *

PROFESSOR BARNARD: . . . I think many a man in the terminal stages of heart failure (and you have often had patients with severe pain and they have said, "please let me die") who is really sick and has a poor blood supply to the brain from poor cardiac output, would say: "Oh please leave me alone, I want to die." But I don't think that the patient can decide whether he wants to die or not. I think that as doctors our duty is to give the patient all the therapy and all the treatment that is available to us. To say that the patient must have a will to live—I don't quite understand that. I think that he is very severely ill, that he just does not have the will to live.

DR. GRONDIN: Dr. Barnard, I think we could correct this. You are right, the patient may not at this terminal stage have the will to live; but I think if we replace this statement by that of a stable personality, it is a broader term and it eliminates some of the hysterical individuals we sometimes meet.

PROFESSOR BARNARD: Well, that is, of course, not the patient being examined at that stage by a psychiatrist, to decide whether he now has a stable personality; you must go into his background and find out from that whether he has a stable personality. But I would ask you, Dr. Grondin, would you turn down a patient and say: "No, you must die, because you don't have a stable personality"?

DR. GRONDIN: I think one should elaborate further, Dr. Barnard. There are some patients who, because of their psychiatric status, are not worth saving and we have all had this experience in cardiac surgery. Sometimes we ask ourselves the question: "Was it worth all that effort?" and even though it is a very difficult. . . .

PROFESSOR BARNARD: I would hate to make that decision myself.

DR. GRONDIN: Between who is fit and who is unfit, yes, but as a general statement, there are really some individuals who will never be able to take the post-operative care and the post-operative seclusion that a heart transplant involves.

DR. KANTROWITZ: I am not sure, Dr. Grondin, that I would agree. I don't take the attitude that

I make decisions about whether a patient can receive the best treatment available on the basis of his emotional stability or whether he hated his mother. I don't think that has anything to do with the fact that this patient is suffering from an organic lesion that is correctible, and that I can do something about it. I think that making decisions about treatment on the basis of the patient's emotional stability is very dangerous and I don't think doctors should become involved in it.

PROFESSOR BARNARD: I want to ask the psychiatrists: when they have a patient who is mentally deteriorated to the stage where he defaecates in bed and eats his faeces and is certainly not a worthwhile citizen, if that man develops pneumonia, will they stop treating that man and allow him to die?

DR. GRONDIN: Are you asking a psychiatrist or are you asking me?

DR. CACHERA: In Paris now, for renal transplants patients who are selected for a graft are examined before operation by a psychiatrist. The conclusion of the psychiatrist plays a role in the final selection of the potential recipient.

PROFESSOR BARNARD: Well, do you think that's correct?

DR. GRONDIN: I do think that it is correct, Dr. Barnard. Let me give you an example that you certainly will agree with. In the heart valve surgery cases there are a lot of patients that you know will never be able to follow an anticoagulant regime adequately, and this has become a problem with heart valve replacements. I know of several patients who, because of their inability to follow such simple rules as taking pills every day, and watching their prothrombin levels, have died of embolism; and there is certainly a lower limit of intelligence and co-operation on the part of the patient that you must require, if you are going to embark upon such an operation.

PROFESSOR BARNARD: But I know of patients who have had infections due to their inability to take antibiotics, who have died—so do you stop their treatment?

DR. GRONDIN: No, but I think you must admit that between giving antibiotics, and undergoing a heart transplant, there is a big difference.

PROFESSOR BARNARD: So, actually you are just making things easier for yourself.

DR. GRONDIN: No, I think we are thinking of the patient—the patient who will have a heart transplant will need a close follow-up and needs to be intelligent enough to understand his situation and how to cope with it. Doctors who treat diabetic

* H. A. Shapiro, ed. New York: Appleton-Century-Crofts 266-273 (1968). © 1969, Butterworth & Co. (South Africa) Ltd. Reprinted by permission.

patients require from them a minimum of intelligence and understanding. I am not talking about emotionally disturbed patients. I am talking about the mentally deteriorated patient.

DR. KANTROWITZ: I think we are on very dangerous ground. We all, I am sure, make these decisions about whether one should operate on a patient—for replacement of a mitral valve or for incision of a carbuncle—on the basis of examining and assessing the total patient—this is called being a doctor, and we do the best that we can. I don't believe that the psychiatrists, for whom I have great respect, are in the best position to assess the total problem, particularly when it is organic—when the major problem, the condition that is bringing about the patient's death, is an organic problem which is amenable to the surgical approach. I think the surgeons should make the decision whether or not to operate.

DR. GRONDIN: But we are not talking about who makes the decision, we are talking about a minimum requirement in the selection of a recipient. It was mentioned earlier when we discussed this topic that we would like a patient with a reasonably stable personality; not only that, but also with an understanding of what is going on, and it has been rewarding for survivors of heart transplants to see how well they behave, in spite of the somewhat miserable social and emotional conditions which they endure in the recovery period.

DR. ROSS: Mr. Chairman, I think Dr. Schrire has something to say, and I think we would like to hear some audience participation.

PROFESSOR SCHRIRE: This discussion has clarified very clearly the difference between surgeons and physicians. You have a whole group of surgeons who have been talking about the patient's selection and so on. The surgeon sees the patient, by and large, when he is presented as a problem as to whether he should operate or not. He doesn't look at the patient over a period of years and years during which the average doctor or cardiologist gets to know this patient. By the time a heart transplant patient is transferred for surgery, generally the physicians or cardiologists have seen him over a period of many, many years, usually 10–15 years. No surgeon has lived with his patient before the operation. Although Professor Barnard has certainly said many times he wouldn't turn down patients—it is very obvious why. We turn down patients every day of the week, but he would be horrified. I agree absolutely with Dr. Grondin. We turn down patients all the time who cannot take anticoagulants. We

never present them to our surgeons. Many of our problem cases never come to the surgeons. The physician lives with his patients for years and years, before and after the operation, and that's why I was very concerned initially.

I don't agree with Dr. Kantrowitz. I think that I would not refer patients for a major procedure, such as a heart transplant, which is completely unknown territory, if the patient is, for example, a depressive who hasn't the least bit of interest in life, whom you can only keep alive by giving him drugs; and you only know these patients if you live with them for a long time. I don't think it is fair for the surgeon to make the decision, without the advice of physicians (it need not be cardiologists) who know their patients.

DR. PIERCE: One of the most gratifying experiences in the renal transplant patients, is to see the transformation in the personalities and the outlook of patients, once their organic problem has been corrected. Many of these patients have had many years of decreasing capacity. If one would look at them and say what their potential might be, it would be easy to grossly underestimate their possibilities. I remember very clearly a man who was withdrawn, who could barely get out of bed, whose limbs were so thin that, if you can imagine it, some of the other patients who were in not too different a situation, poked fun at him. Well, after this man's transplant, he became an outgoing individual, he regained his interest in reading, in studying and in doing things, and you wouldn't recognize him as the same person.

It is true that there are patients with difficult personalities and low intelligence levels which can greatly magnify the problems of management, but I would like to submit that, in the present state of knowledge, it is very difficult to predict in which patients this will prove to be an insurmountable obstacle.

PROFESSOR BARNARD: I think that is very important, because even when Professor Schrire sees his patient for the first time, the man already suffers from heart disease and his personality and outlook on life must be changed as a result of that.

Jim, let me ask you a question. You have been working with the psychiatry department to select patients for many, many years now—how many have you turned down because their brains are not suitable?

DR. PIERCE: Well, some of our best results in terms of rehabilitation have been in patients whose intelligence levels were not too high. I

should point out that, in children and patients who do not have normal intelligence, one has to take a special precaution to ensure that they take their immunosuppressive drugs every day. This means that another individual who is responsible has to give them the medicine and see that they take it.

PROFESSOR BARNARD: But that also applies to the treatment of diabetes with insulin.

DR. PIERCE: That's correct. It is a point in management and not to say that we can't operate on children because they are not responsible in taking their medicines—the mother just has to give it to them, that's all.

PROFESSOR BARNARD: Yes, but Professor Schrire says that the patient can't take his anticoagulants, so you must turn him down for surgery. He would also say, then, I won't give insulin to a man who has got diabetes because I am not sure he will take his insulin.

PROFESSOR SCHRIRE: I didn't say so. I must impress upon Professor Barnard, and others here, that conditions that occur in the United States of America do not necessarily apply to every other country in the world. There is just not the available help for them and one has to take this into account.

* * *

DR. KANTROWITZ: . . . I am not sure that Professor Schrire is right. Professor Schrire has taken a point of view which is not unusual. Many internists who deal frequently with their patients over prolonged periods of time, make decisions affecting their patients' welfare, their living or dying. Now Dr. Barnard has pointed out that if a cardiac patient is referred to his room the decision is made unemotionally; after all, if you don't see the patient every week, you are not so likely to be emotionally involved with him. You may not want to take the chance of exposing this patient to an operation which admittedly carries a risk. I maintain, as Dr. Barnard does, that such decisions are much better made by a group of doctors who have had a great deal of experience in making them, and are not emotionally involved with the patient.

I believe, sir, that you do your patients a disservice by not sending your patients to a group of men who will make an unemotional decision.

DR. ZERBINI: I believe that the selection of the patient must be done by a team, a large team of cardiologists, surgeons, psychiatrists and so on.

DR. KANTROWITZ: Yes, but no psychiatrist. No rabbi, no priest and no psychiatrist.

DR. ZERBINI: We have one, but the decision for the indication of surgery must be done at a meeting of all these people together, not only the surgeon and not only the cardiologist, but the group.

DR. GRONDIN: Dr. Zerbin, I think you have touched the right point. The decision to operate on such a patient does not only belong to the surgeon, nor does it only belong to the cardiologist. I think it has to be a decision taken by a team of doctors.

DR. KANTROWITZ: And I don't think it belongs to a man who is emotionally involved and is not qualified. The decision whether this patient will benefit by a heart operation should be made by people who are qualified in heart surgery.

DR. GRONDIN: Oh, no question about that.

DR. MOWBRAY: I just wanted to say, if Dr. Kantrowitz is talking about an unemotional group of people selecting patients and he considers that, at the moment, he is one of an unemotional group of cardiac surgeons, I cannot agree.

PROFESSOR BARNARD: We have Dr. van der Spuy, who is the head of the Cardio-Thoracic Unit at one of our universities in Pretoria, who would like to say something.

DR. GRONDIN: Dr. van der Spuy, I think I would like you to conclude this discussion.

DR. VAN DER SPUY: I sincerely hope that I will, if you all agree with me.

The thing that has been occupying my mind here is the selection of the recipient—the whole problem in this congress actually turned to rejection. We have been talking about the psychiatric aspect as far as the recipient is concerned, except that we haven't been talking about rejection. Now the thing that I want to know is this, and this concerns the recipient vitally, should we tell the recipient that this is a palliative operation? We have been hearing about so many patients waiting and so many patients that we are going to operate on, as if we are going to cure them. We are only going to prolong their lives, in a small percentage (as the position stands now) for a few weeks or a few months. What about informing the patient? If we are absolutely honest with the patient, then all my objections fall flat; but, as far as I am concerned, the essence of the whole thing is this, that we must take the patient and his relatives into our trust and say, this is the problem—now do you agree to have an operation?

PROFESSOR BARNARD: I think you must treat the patient the same way in which you would treat a

patient who has a carcinoma of the lung—which is also really a palliative operation in most cases.

DR. VAN DER SPUY: I think, reading from press reports and patients approaching one, that patients think this operation is curative. They ask me: "Is this chap going to live; is he going to reach the age of 80 years?" We know beforehand that this patient is doomed, according to our present knowledge. I believe that we are misinforming our future patients. We are not gaining the confidence of our future patients, because we are probably, for our own benefit, for the personal benefit, for the egoist each one of us is, we are withholding the essence of the whole matter—this patient will probably be dead in a few months' time. Thank you.

DR. GRONDIN: There is no doubt in the patients' minds, because they read the newspapers and they know that the longest survival so far is 6 months. When we propose a heart transplant to an intelligent patient, he knows very well that there have not been any long-term survivals but, even though we look upon a heart transplant at this moment as a palliative procedure, it might prove to be curative and provide a long-term cure.

When one talks about rejection, one might say that one is implanting a foreign heart, and the body has to accept it. I think, from the psychiatric point of view also, that there should not be any rejection to the operation. . . .

* * *

NOTE

PIETRO CASTELNUOVO-TEDESCO

CARDIAC SURGEONS LOOK AT TRANSPLANTATION
—INTERVIEWS WITH DRs. CLEVELAND, COOLEY,
DEBAKEY, HALLMAN AND ROCHELLE*

* * *

There are also problems of conscience in relation to the donor, however much an attempt may be made to rationalize them. Dr. Cooley recalls, "Well, I was worried because I was taking the heart out of the donor while it was still beating and putting it over here, and that meant the cadaver over there was completely wiped out. No question of life or death! I satisfied myself completely that death was in the process at the time we removed the heart and I didn't worry

about those things. I didn't worry whether the donor was dead or alive. . . . My concern was primarily with the recipient and everyone. . . .—the public, most physicians—were more concerned with protecting the rights of the donor. Well, to me the donor was dead. He didn't have any real rights . . . [except those] exercised by his relatives and next of kin, but the one who really had some rights was the recipient. Therefore, we wanted to see that he got the best chance to live and there are ways one could jeopardize his chances by, say, . . . trying to satisfy everyone that this donor was completely wiped out and waiting until the heart was almost at the point of cessation entirely. Then you say, okay, now we'll take it out and put it over here. So you are giving the recipient a badly abused organ, which is not fair to that recipient." Dr. Hallman described similar feelings even more starkly, ". . . it gives you the impression that you have . . . influence over life and death . . . When . . . [we] take the heart out of a donor, we've gone through the medico-legal procedures that . . . [say that] the patient is legally dead when the brain is dead but yet you are the one who makes the final blow and takes out the heart and this is a peculiar feeling the first time you do it . . . I guess just like an executioner who has to pull the switch on the electric chair because it's his job. It bothers him the first time, but the more times he does it, the less it bothers him. . . . This was upsetting to me personally the first time I did it, but the more I did it the easier it became . . . But the first time you do it you have the feeling as if you are killing the patient. The only justification that one can have for doing [it] is that the patient is for all practical purposes . . . dead and that everybody has agreed to this. . . ."

* * *

[iv]

Paul H. Blachly

*Can Organ Transplantation Provide an
Altruistic-Expiatory Alternative to Suicide?**

* * *

When President Eisenhower was sustaining repeated heart attacks, at least 20 persons offered their own hearts for transplant. At other transplant centers this same sort of offer has been made for persons unknown to the donor. Public solicitations for kidney donors have been successful in San Francisco. Dr. Harrison Sadler at

* Pietro Castelnovo-Tedesco, ed.: *Psychiatric Aspects of Organ Transplantation. 3 Seminars in Psychiatry* 5, 13 (1971). Reprinted by permission of Grune & Stratton, Inc.

* 1 *Life-Threatening Behavior* 6, 8-9 (1971). Reprinted by permission.

the Langley Porter Institute has been impressed by the salutary effect of such organ donation on the life pattern of unrelated donors. He describes a woman leading a meaningless anhedonic existence who after organ donation experienced a satisfying sense of well-being and ability to feel satisfaction in interpersonal relationships. There are other reports that kidney donors generally experienced a sustained feeling of satisfaction and of being "noble."

Could it be that sacrifice has a psychotherapeutic potential that we have overlooked? Sacrifice seems quite uncommon in our culture, unless one wishes to consider our periodic wars. We know that some suicidal persons view their actions as sacrifice.

* * *

Suicide seems to diminish during periods when major sacrifices are demanded, as in times of war. It is in such circumstances that the intensity of egoism and anomic is diminished as the individual participates in a common social goal.

Now we can come back to our unreachable egoistic-anomic suicidal person. Is it possible, then, that such highly individualistic suicidal persons could follow the route that sacrifice has followed in history and could be induced to give a partial sacrifice for a total human sacrifice? If such a partial sacrifice could satisfy an altruistic purpose, then not only would benefit accrue to the suicidal person but also to the physically ill person who would be restored to health through such sacrifice. What psychotherapist has ever suggested to a depressed person that he donate a pint of blood?

It is often said that we can not give love until we have received it. I suspect there is another population, one which rarely seeks psychotherapy, which can not accept love until it has given. I suspect that Dr. Sadler's patient who could not deal with persons in a satisfying way until she had given one of her lifesaving kidneys found that she could think of herself as a lovable person only after she had given part of herself.

It would seem to make sense, then, for a suicide prevention service to use as one resource a mobile organ bank. A mobile organ bank might be a group of persons who are willing to donate various organs so that others might live. Those who might want to donate their heart (suicide) could likely be encouraged in most cases to give a partial sacrifice such as a kidney

or regular blood donation. The time required for the thorough immunological studies the surgeons need could be used for thorough psychiatric evaluation and treatment. At the University of California San Francisco Medical Center a waiting period of two to three months is imposed between the time of offering donation and actual surgery, which permits time for careful assessment of motivation.

It is, of course, true that certain donors seek to donate because of the dramatic attention-seeking rewards; but how do these people differ from those who commit suicide for the same reason? Does it not reflect an emotional need that might be best resolved through the psychiatric attention possible in an organ bank?

Dr. Sadler feels that the act of giving in itself is not sufficient for permanent improvement if the donor has insufficient "ego strength" or cannot make a transference to the institution or transplant team. History reveals that sacrifice is a periodically repeated behavior; except for blood donation this is impossible with organ donation. Apparently the process of organizing groups of persons who have donated organs is already underway, which may provide the kind of postdonation support that is sometimes necessary. The organ bank conducted on a group basis should provide benefits superior to those of the isolated donor giving to an isolated recipient in that it reinforces the group solidarity, decreasing the egoism and anomic.

It may turn out that efforts to prevent suicide may best be achieved through means that do not emphasize the word "suicide." Opportunities to save the lives of others through sacrifice of part of oneself offered to a population of potentially altruistic but anomic, egoistic persons might prove more successful than offers of psychological "help" or "therapy." Unlike help or therapy such a sacrifice could enhance the person's sense of dignity and self-determination, while permitting him to rejoin the human race on his own terms.

It is hard to deal with the inevitable case who, despite all therapeutic effort, would continue to insist upon suicide. Until our mores change to permit such a person to end his own life in a dignified way that would permit utilization of his organs, we will continue to insist that he not do it, thus permitting continuation of the present wasteful idiosyncratic methods. One would think that the stigma that the friends and relatives attach to a suicide would be much lessened if they knew several persons would live as

a result. Perhaps it is premature to ask whether it is immoral for a person not to give an organ if another person can thereby live.

* * *

NOTE

BELDING H. SCRIBNER
ETHICAL PROBLEMS OF USING ARTIFICIAL
ORGANS TO SUSTAIN HUMAN LIFE*

* * *

[I]f I knew that I had a fatal disease I would seriously consider volunteering to donate one of my kidneys while I was still well. As far as death is concerned, I would like to be able to put into my will a paragraph urging that when my physician felt that the end was near, I be put to sleep and any useful organs taken prior to death. . . . I think the ethical and legal guidelines should be devised to permit me and others to volunteer in these ways.

* * *

d. **Deciding about the Delegation of Authority to Control, Review, and Reformulate the Process?**

[i]

*National Conference of Commissioners on
Uniform State Laws
Uniform Anatomical Gift Act†*

An act authorizing the gift of all or part of a human body after death for specified purposes.

SECTION 1. (Definitions)

(a) "Bank or storage facility" means a facility licensed, accredited or approved under the laws of any state for storage of human bodies or parts thereof.

* 10 *Transactions of American Society for Artificial Internal Organs* 209, 211 (1964). Reprinted by permission.

† Final Draft as approved on July 30, 1968. The National Conference of Commissioners on Uniform State Laws is composed of law professors, lawyers, and judges, representing every state, whose function is to help make state laws more uniform and up-to-date. This Act was the product of three years of intensive study by a special committee of the conference. Earlier drafts of the Act were reviewed by medical and scientific groups, including the Committee on Tissue Transplantation of the Division of Medical Sciences of the National Research Council.

(b) "Decedent" means a deceased individual and includes a stillborn infant or fetus.

(c) "Donor" means an individual who makes a gift of all or part of his body.

(d) "Hospital" means a hospital licensed, accredited or approved under the laws of any state and includes a hospital operated by the United States government, a state or a subdivision thereof, although not required to be licensed under state laws.

(e) "Part" includes organs, tissues, eyes, bones, arteries, blood, other fluids and other portions of a human body, and "part" includes "parts."

(f) "Person" means an individual, corporation, government or governmental subdivision or agency, business trust, estate, trust, partnership or association or any other legal entity.

(g) "Physician" or "surgeon" means a physician or surgeon licensed or authorized to practice under the laws of any state.

(h) "State" includes any state, district, commonwealth, territory, insular possession, and any other area subject to the legislative authority of the United States of America.

SECTION 2. (Persons Who May Execute an Anatomical Gift)

(a) Any individual of sound mind and 18 years of age or more may give all or any part of his body for any purposes specified in section 3, the gift to take effect upon death.

(b) Any of the following persons, in order of priority stated, when persons in prior classes are not available at the time of death, and in the absence of actual notice of contrary indications by the decedent, or actual notice of opposition by a member of the same or a prior class, may give all or any part of the decedent's body for any purposes specified in section 3.

- (1) the spouse,
- (2) an adult son or daughter,
- (3) either parent,
- (4) an adult brother or sister,

(5) a guardian of the person of the decedent at the time of his death,

(6) any other person authorized or under obligation to dispose of the body.

(c) If the donee has actual notice of contrary indications by the decedent, or that a gift by a member of a class is opposed by a member of the same or a prior class, the donee shall not accept the gift. The persons authorized by subsection (b) may make the gift after death or immediately before death.

(d) A gift of all or part of a body authorizes any examination necessary to assure medical acceptability of the gift for the purposes intended.

(e) The rights of the donee created by the gift are paramount to the rights of others except as provided by section 7(d).

SECTION 3. (*Persons Who May Become Donees, and Purposes for Which Anatomical Gifts May Be Made*)

The following persons may become donees of gifts of bodies or parts thereof for the purposes stated:

- (1) any hospital, surgeon, or physician, for medical or dental education, research, advancement of medical or dental science, therapy or transplantation; or
- (2) any accredited medical or dental school, college or university for education, research, advancement of medical or dental science or therapy; or
- (3) any bank or storage facility for medical or dental education, research, advancement of medical or dental science, therapy or transplantation; or
- (4) any specified individual for therapy or transplantation needed by him.

SECTION 4. (*Manner of Executing Anatomical Gifts*)

(a) A gift of all or part of the body under section 2(a) may be made by will. The gift becomes effective upon the death of the testator without waiting for probate. If the will is not probated, or if it is declared invalid for testamentary purposes, the gift, to the extent that it has been acted upon in good faith, is nevertheless valid and effective.

(b) A gift of all or part of the body under section 2(a) may also be made by document other than a will. The gift becomes effective upon the death of the donor. The document, which may be a card designed to be carried on the person, must be signed by the donor, in the presence of 2 witnesses who must sign the document in his presence. If the donor cannot sign, the document may be signed for him at his direction and in his presence, and in the presence of 2 witnesses who must sign the document in his presence. Delivery of the document of gift during the donor's lifetime is not necessary to make the gift valid.

(c) The gift may be made to a specified donee or without specifying a donee. If the lat-

ter, the gift may be accepted by the attending physician as donee upon or following death. If the gift is made to a specified donee who is not available at the time and place of death, the attending physician upon or following death, in the absence of any expressed indication that the donor desired otherwise, may accept the gift as donee. The physician who becomes a donee under this subsection shall not participate in the procedures for removing or transplanting a part.

(d) Notwithstanding section 7(b), the donor may designate in his will, card or other document of gift the surgeon or physician to carry out the appropriate procedures. In the absence of a designation, or if the designee is not available, the donee or other person authorized to accept the gift may employ or authorize any surgeon or physician for the purpose.

(e) Any gift by a person designated in section 2(b) shall be made by a document signed by him, or made by his telegraphic, recorded telephonic or other recorded message.

SECTION 5. (*Delivery of Document of Gift*)

If the gift is made by the donor to a specified donee, the will, card, or other document, or an executed copy thereof, may be delivered to the donee to expedite the appropriate procedures immediately after death, but delivery is not necessary to the validity of the gift. The will, card or other document, or an executed copy thereof, may be deposited in any hospital, bank or storage facility or registry office that accepts them for safekeeping or for facilitation of procedures after death. On request of any interested party upon or after the donor's death, the person in possession shall produce the document for examination.

SECTION 6. (*Amendment or Revocation of the Gift*)

(a) If the will, card or other document or executed copy thereof has been delivered to a specified donee, the donor may amend or revoke the gift by:

- (1) the execution and delivery to the donee of a signed statement, or
- (2) an oral statement made in the presence of 2 persons and communicated to the donee, or
- (3) a statement during a terminal illness or injury addressed to an attending physician and communicated to the donee, or
- (4) a signed card or document found on his person or in his effects.

(b) Any document of gift which has not been delivered to the donee may be revoked by the donor in the manner set out in subsection (a) or by destruction, cancellation, or mutilation of the document and all executed copies thereof.

(c) Any gift made by a will may also be amended or revoked in the manner provided for amendment or revocation of wills, or as provided in subsection (a).

SECTION 7. (*Rights and Duties at Death*)

(a) The donee may accept or reject the gift. If the donee accepts a gift of the entire body, he may, subject to the terms of the gift, authorize embalming and the use of the body in funeral services. If the gift is of a part of the body, the donee, upon the death of the donor and prior to embalming, shall cause the part to be removed without unnecessary mutilation. After removal of the part, custody of the remainder of the body vests in the surviving spouse, next of kin or other persons under obligation to dispose of the body.

(b) The time of death shall be determined by a physician who attends the donor at his death or, if none, the physician who certifies the death. This physician shall not participate in the procedures for removing or transplanting a part.

(c) A person who acts in good faith in accord with the terms of this Act, or under the anatomical gift laws of another state (or a foreign country) is not liable for damages in any civil action or subject to prosecution in any criminal proceeding for his act.

(d) The provisions of this Act are subject to the laws of this state prescribing powers and duties with respect to autopsies.

SECTION 8. (*Uniformity of Interpretation*)

This Act shall be so construed as to effectuate its general purpose to make uniform the law of those states which enact it.

* * *

[ii]

State of Kansas

*An Act Relating to and Defining Death**

* * *

A person will be considered medically and legally dead if, in the opinion of a physician, based on ordinary standards of medical practice, there is the absence of spontaneous respiratory

and cardiac function and, because of the disease or condition which caused, directly or indirectly, these functions to cease, or because of the passage of time since these functions ceased, attempts at resuscitation are considered hopeless; and, in this event, death will have occurred at the time these functions ceased; or

A person will be considered medically and legally dead if, in the opinion of a physician, based on ordinary standards of medical practice, there is the absence of spontaneous brain function; and if based on ordinary standards of medical practice, during reasonable attempts to either maintain or restore spontaneous circulatory or respiratory function in the absence of aforesaid brain function, it appears that further attempts at resuscitation or supportive maintenance will not succeed, death will have occurred at the time when these conditions first coincide. Death is to be pronounced before artificial means of supporting respiratory and circulatory function are terminated and before any vital organ is removed for purposes of transplantation.

These alternative definitions of death are to be utilized for all purposes in this state, including the trials of civil and criminal cases, any laws to the contrary notwithstanding.

* * *

NOTE

IAN MCCOLL KENNEDY
THE KANSAS STATUTE ON DEATH—
AN APPRAISAL *

* * *

[T]he lip service paid by the courts to outdated concepts of death . . . can create havoc in the law, in the light of medical developments. But the changes that must come should be brought about through case law, through recognition by the courts, in cases before them, of the prevailing medical opinion as the law. Legislation may make for certainty, but at what cost to future flexibility? For, in an area as fast moving as this, the flexibility to respond to further medical developments must be the keystone of the law, and this is not an attribute usually associated with legislation. [W]hat reason can there be for legislating? The answer often put forward is that the doctor will never know where he stands in the absence of firm guidelines and will always

* House Bill No. 1961, approved March 17, 1970; Sessions Laws of Kansas, Ch. 378 (1970).

* 285 *New England Journal of Medicine* 946-947 (1971). Reprinted by permission.

be in fear of litigation arising from an act of his that, although medically entirely valid, by the existing standards is still of only doubtful legality. But, of course, this is no real answer. Let us have guidelines by all means. They are essential. But let them be set down by the medical profession, not by the legislature, so that the body best equipped to evaluate and examine them can always have them under review, rather than depend on the time-consuming and often whimsical processes of the legislature. Now, this recommendation presupposes the existence of a strong professional body able to control and sanction anyone who practices that profession. The British model of the British Medical Association comes to mind: a self-regulating body to which matters of practice can safely be left since it has wide powers of sanction and is not afraid to use them. The American medical profession is not at all as well regulated. My view is that it should remedy this lack with all speed. In the absence of responsible self-regulation and the setting and enforcing of proper standards, the task will be assumed by some other body, most probably the legislature. If one accepts, as I do, that the matters properly within the competence of a profession should be dealt with by that profession, whose views would then be accepted, if it could be shown that they were informed and objectively arrived at, the intervention of the legislature is regrettable.

... Furthermore, whatever changes may from time to time become necessary can be made by the simple act of the courts' giving recognition to the then prevailing views of the profession. When I speak of "consensus view" and "prevailing views of the profession," it may appear that to appeal to such a consensus ignores the fact that I stress throughout that this is a fast-changing scientific area. There is an answer to this doubt. At any given time a wide range of opinions may be held by doctors. Only some, however, will gain the approval of the vast majority of doctors, after being discussed and debated in the usual ways. These opinions, and there need not necessarily be only one view, would represent the consensus of informed opinion. As has been argued it may well be that the profession should look for ways of giving some kind of "official approval" to certain views, so that doctors who then continue to follow unacceptable ideas will be in breach of the required standards of conduct and thus liable to sanction.

* * *

2.

In Administering Research

a.

Who Should Participate, within What Structure, in State Regulation?

[i]

*Advisory Group on Transplantation Problems
Advice on the Question of Amending the
Human Tissue Act 1961**

* * *

Kidney transplantation has reached the development stage and is an established therapeutic measure. Grafting of other organs is still in the research phase. It may well be that in the course of time surgeons will be able to use this technique on a wider scale as a means for saving life by grafting other organs, but the best working assumption seems to be that the rate of development will not be uniform.

* * *

[T]wo fundamental objectives are to be achieved. First, each individual's right to decide whether he would wish his organs to be used after death must be respected. Second, transplant teams should have a readier and greater supply of organs. The courses open fall into two categories: options of action, and options of reinforcement to follow through changes.

(a) OPTIONS OF ACTION

(i) *No change.* If the law can properly be interpreted in the interests of transplantation (that is, if the "person lawfully in possession" can be taken to mean the hospital or its officers for the critical time, if the "reasonable enquiry as may be practicable" can be held to be a flexible commonsense statement that doctors should try to obtain the consent of relatives but that practicability must pay regard to the extremely limited time available, and if "surviving relatives" can be taken to mean those in the immediate degrees of kinship), then it could be said to be tolerable from the point of view of surgeons

* Sir Hector MacLennan, M.D., Chairman. National Health Service (Cmd. 4106). London: Her Majesty's Stationery Office 3, 6-8 (1969). Reprinted by permission. [The advisory group, appointed by the Health Ministers, consisted of five physicians, a nurse, a theologian, a lawyer, a social scientist, a journalist, and a businessman.]

engaged in transplantation to leave the law as it is. The merit of taking no action would appear to be flexibility; its disadvantages, the lack of clarity in which the general public and the professions would continue to find themselves and the risk of legal action against doctors who had acted in good faith. . . .

(ii) *Limited amendment.* By this is meant removing the ambiguities in the Human Tissue Act. It would imply clarifying that the "person lawfully in possession" was the hospital authority during the time between death and the time when next of kin or executors claim the body; defining the persons with a right to be consulted who should be the next of kin; and defining the minimum procedure of enquiry.

(iii) *Double contract.* By this is meant a single public and central register for both consents and objections recorded during life. This would have the advantage, from the point of view of the public, of recording their wishes either way, and of indicating the movement of public opinion to the further end of enabling the authorities to judge when any further action might be acceptable. Its great disadvantage is the uncertain position of those who neither expressed an objection to their organs being used after death, nor indicated that they would be willing to donate parts of their body. It could, however, be associated with limited amendment ((ii) above).

(iv) *Contracting out.* Provided that an effective mechanism for recording objection exists, this means that surgeons should be able to remove organs unless there were definite indications that the deceased had objected. The Group is advised that this would require a change in the law, but understands that certain other countries (Denmark, Sweden, Israel, Italy and France) have legislation in this sense. Implementation would depend on public acceptance and on there being a register of information as in double contract to which transplant teams could have speedy access.

(b) REINFORCEMENT

(i) *Publicity.* The public needs information as to the procedures under existing law on the use of human tissue and on the certification of death. If it were decided that the basis of the law must remain as "contracting in" the progress of transplantation would depend upon enrolling donors. Government sponsorship would be needed, and also delicacy of touch. The form of presentation should lay emphasis on the fact that the donation of an organ can save life. How-

ever, while making it clear that this is a decision for the individual, the Health Ministers could properly make it clear that, in their view, this would be a laudable act.

(ii) *Identification of potential donors or objectors.* This would have to be durable, immediately recognisable, and unique. Ideally, the identification would be carried on the person at all times. In the longer run, the public may come to accept the desirability of carrying medical record cards with details of some other factors, e.g., allergy, of importance in a medical emergency. The uses of such a card are being considered by the Standing Medical Advisory Committee. Voluntary addition of a record of willingness or unwillingness to use of organs after death would help to put this question in perspective. A decision depends on other factors and may not be favorable yet.

(iii) *Enrolment of cohorts.* The Group is advised that a person of years mature enough to form a proper judgment and of sound mind can give consent to the use of organs after death just as consent can be given to operations at age 16. This opens the way to approaches to groups of young people at school, college or university. If contracting in were to be the basis, this means might produce better results than unselective encouragement aimed at the general public.

(iv) *The right to object.* The individual or his parent or guardians should have a right to object which must be made effective. If a register of objections is kept, the public must be aware of it and have access to it. There would be a need for publicity and postage-paid cards readily available at public offices so that the individual might contract out by the stroke of a pen, upon giving his personal details. In addition, it would be necessary to provide for automatic exemption of persons who could not give a valid consent such as persons under 16 and mentally disordered.

* * *

NOTES

NOTE 1.

RENAL TRANSPLANTATION BILL*

* * *

2. It shall be lawful to remove from the body of a human person, duly certified as dead, any kidney or kidneys required for the direct

* See 762 *Parliamentary Debates, H.C.* (5th ser.) 810 (1968).

purpose of saving the life of another sick human being, unless there is reason to believe that the deceased during his lifetime had instructed otherwise.

3. Section 2 of this Act does not apply to any person who is:—

- (a) mentally insane, or
- (b) mentally handicapped, or
- (c) below the age of 18, or
- (d) 65 years old or more than that age, or
- (e) deprived of his liberty by the conviction and judgment of a court, or
- (f) a permanent resident of a hostel, home, or institution for the aged, the disabled, or the handicapped.

4. For the purposes of section 2 of this Act, a death certificate must be signed by not less than two medical practitioners, one of whom shall have been registered for at least five years, but neither of them shall be the surgeon conducting the renal transplantation.

5. For the purpose of section 2 of this Act, the qualified medical practitioner responsible for the welfare and safety of the donor or potential donor must be a person other than the qualified medical practitioner responsible for the welfare and safety of the recipient or potential recipient.

6. No person shall be under any duty, whether by contract or by any statutory or other legal requirement, to participate in any treatment authorised by this Act, to which that person has a conscientious objection.

7.—(1) The Minister of Health shall within three months of the passing of this Act establish a Central Renal Registry wherein any objector to the transplant of his kidney may duly register his objection in a form to be decided by the Minister.

(2) Information as to any objection duly registered in the Registry shall be available on demand to any hospital in the United Kingdom of Great Britain and Northern Ireland, and shall be treated as sufficient evidence of an instruction for the purposes of section 2 of this Act.

* * *

NOTE 2.

ALFRED M. SADLER, JR., BLAIR L. SADLER,
E. BLYTHE STASON, AND DELFORD L. STICKEL
TRANSPLANTATION—A CASE FOR CONSENT*

* * *

[T]he Uniform Anatomical Gift Act prepared by the Commissioners on Uniform State

Laws represents a responsible and realistic model for reform that not only is badly needed but will be widely accepted. We further believe that, *when obtaining organs or tissue for transplantation, the fundamental principle of informed consent should be maintained, and that, if the present consent framework is adequately streamlined and modernized (as is done in the Uniform Anatomical Gift Act), the principal legal constraints will be eliminated without compromising other important rights and sensitivities.*

* * *

. . . Dukeminier and Sanders . . . suggest that the principles of consent and voluntary donation should be discarded in favor of allowing tissue removal by a physician without his having to give notice to anyone. They propose that a surgeon should be allowed to remove cadaver organs "routinely . . . unless there were some objection entered before removal. The burden of action would be on the person who did not want the organs removed to enter his objection." Under this system, the donor could object during life to the taking of his organs after death. The next of kin could also object to the use of a deceased's organs before removal, provided that the deceased did not specifically authorize donation.

The question, as they see it, is where the burden of action should rest: with the surgeon to obtain consent, or with the next of kin to object. They believe that only by shifting the burden to the next of kin will an adequate quantity of organs be obtained.

This argument is dubious for several reasons. The first is that, in the system proposed, the burden actually remains with the responsible surgeon to assure himself that no objection has been raised either by the deceased himself before death or by the next of kin after death. To absolve himself of this burden adequately would require an inquiry tantamount to obtaining consent itself.

Moreover, it is certain that there are some people who would object to tissue use on religious grounds (as recognized by Dukeminier and Sanders) or because of other beliefs. Such people, if not immediately available at the time of death of a relative, might object strongly and vigorously after the fact. They could forcefully argue that, because they did not know of the demise of their next of kin, they could not exercise their authority to enter an objection to tissue removal. Any system based on this premise would need to include a method of registering

* 280 *New England Journal of Medicine* 862, 866 (1969). Reprinted by permission.

objection in a manner to make this information readily available to the interested surgeon. Otherwise, grave constitutional questions, such as the abridgement of religious freedom or the denial of due process, could invalidate the system. . . .

Dukeminier and Sanders assert that the "bereaved survivors usually do not want to know what has happened to the body of the deceased in the hospital" and to ask a relative of someone who is about to die "for the kidneys may seem a ghoulis request." We submit that current medical practice strongly shows that this kind of request is usually not offensive when properly presented and the need sensitively raised. . . . Not to be told of such a removal or to be informed only after the fact would be "ghoulis" indeed.

As further support for their argument of telling nothing to the next of kin, they cite an example of a detailed description of autopsy procedures or embalming technics as being the usual practice in obtaining permission for autopsy. These authors confuse the obtaining of adequate "informed consent" for such procedures with a detailed technical explanation of them. One asks for an autopsy but does not describe the fine points of the procedure in intimate detail. Similarly, one asks for permission to remove an organ for transplantation without enumerating every nuance of surgical technic. Properly informed consent is admittedly difficult to define, but a discussion of it must be based on currently accepted medical practice.

* * *

[ii]

*Compulsory Removal of Cadaver Organs**

The proliferation of heart transplants within the last eighteen months has raised the hopes of those suffering from organic diseases. At the same time, the publicity accompanying these operations has focused public attention on the need for a supply of healthy organs. . . . A possible solution may be a statute which authorizes the compulsory removal of cadaver organs. . . .

* * *

The fifth amendment to the United States Constitution and similar provisions in most state constitutions, require the payment of "just compensation" whenever the government takes property for a public use. The questions to be considered here are, first, whether the involuntary

removal of cadaver organs constitutes a taking of property for public use; and, second, what amount will satisfy the just compensation requirement.

One of the most vexing problems in eminent domain cases involves the concept of "taking." Whether a particular governmental act requires compensation will often turn on the label which the court will place on such an act. If the act constitutes a taking, compensation will have to be paid; if it amounts to a regulation, no compensation is required.

[A] physical invasion of private property has always constituted a taking. The entire interest affected by the condemnation need not be taken; even when the physical invasion is so minor as to be "practically trifling," a valid claim for compensation will be found. The involuntary removal by the state of cadaver organs, therefore, would appear to involve an exercise of the government's eminent domain powers rather than a regulatory measure. . . .

* * *

[C]onsidering the state's interest in preserving lives, it is difficult to conceive of a court invalidating an organ removal statute because no "public use" is present. The basic purpose of the public use requirement—to prevent governmental excesses by disallowing condemnation where the object is a purely private gain—would not be disserved by a statute under which all of society stands to gain. [A]lthough no more than one person could receive a particular organ, every member of the public would have a right to receive cadaver material if he were in need of it.

. . . The last, but perhaps the thorniest issue . . . concerns "just compensation." [T]he next of kin appears to have a compensable claim whenever the deceased's organ is removed; the question is, how is this claim to be assessed?

Traditionally, when the property taken has an ascertainable market value, this value has been employed to determine the amount of compensation. When no market value exists, the courts have allowed the "intrinsic" value of the property to be shown. This value may be determined by considering such criteria as age of property, condition, location, original cost and adaptability. A variation of this rule is the "value to the owner test," which takes into account the owner's personal use for the property.

Unfortunately the market, intrinsic, and personal value tests are all basically tests of economic value and are practically impossible to

* 69 *Columbia Law Review* 693, 695-696, 699-703, 705 (1969). Reprinted by permission.

apply to commodities such as cadaver organs which have never been bought and sold. . . .

* * *

. . . The involuntary removal of the organs, will, at least in the beginning, inflict a disproportionate burden on some individuals. Although the burden is in the form of an injury to the emotions of the next of kin, the law has traditionally carved out a special niche for this kind of emotional distress. Thus, although mental anguish is not an item of damages in most breach of contract actions, it has been compensable when the breach occurred in a contract for burial.

Similarly, the involuntary removal of a cadaver organ should entitle the next of kin to compensation. Since the exact amount would be difficult to ascertain, the statute itself should provide for it. It would be relatively simple, for example, to set a schedule of fees—perhaps varying in amount with the nearness of the relationship between the survivor and the deceased.

Freedom of Religion

The first amendment forbids the enactment of laws which "prohibit" the free exercise of religion. At least one article has suggested that a compulsory removal statute may pose "grave constitutional problems respecting freedom of religion." And it is likely that some religious sects will be able to show that their doctrines command them to bury the dead intact.

Statutes which run afoul of the free exercise clause may burden religious practices either directly or indirectly. . . . Direct infringement occurs when a law forbids the individual to engage in practices which are required by his religious beliefs. One of the best known cases involving such a statute was *Reynolds v. United States*. At issue was the conviction of a Mormon under a statute which prohibited polygamy in federal territories. Although Mormons were required at that time to practice polygamy under "penalty [of] damnation" the Court upheld the conviction. After consideration of the adverse social consequences of polygamy, the Court held that no exception need be made for those motivated by religious belief.

* * *

An indirect infringement on free exercise, on the other hand, occurs when a statute makes it more difficult or expensive to be faithful to a set of beliefs, although no religious practices are proscribed. The test which the Supreme Court

applies when determining the validity of such a statute was set out in *Braunfeld v. Brown*. In *Braunfeld*, an Orthodox Jewish merchant contended that a Sunday closing law forced him to choose between forsaking his faith by keeping his business open on Saturday or going out of business. The Supreme Court found that a burden was clearly placed on free exercise, but it held, nevertheless, that the statute was constitutional. The Court established the following rule:

[I]f the State regulates conduct by enacting a general law within its power, the purpose and effect of which is to advance the State's secular goals, the statute is valid despite its indirect burden on religious observance unless the State may accomplish its purpose by means which do not impose such a burden.

* * *

Assuming that legitimate religious objections were raised to the application of a compulsory organ removal statute, it is clear that the kind of burden created by such a law would be a direct one. If an individual believed that his faith required that he be buried intact, the statute would not merely make it difficult or expensive to follow this religious command; it would make it impossible. In determining the statute's validity the courts would look to the state interest in bringing about the desired result of the statute. Presumably, this would involve a finding that a state could reasonably see a need for a large supply of organs and that procurement of cadaver material is a proper area of state concern. There can be no doubt that both findings could eventually be made. However, the problem with a statute of this type is that although it directly burdens religious practices, it does not reflect any state policy in favor of eliminating these practices. Therefore, exceptions need not thwart state policy. In this way the statute resembles those which indirectly burden free exercise and, perhaps, will be made subject to the same test of validity. If that is the case, the states adopting such a law would have to show that they could not obtain an adequate number of organs without treading on religious practices.

* * *

The ultimate resolution of this issue will not be easy; the competing interests are unusually strong and emotion-laden. A legislature should not, however, hide behind the Constitution and fail to face the essentially ethical question presented. Neither the first nor fifth amendment is

a bar to the compulsory taking of organs. Whether enough public support could be mustered to pass such a law is an open question. . . . The burden rests on the medical profession to acquaint the public with the acuteness of the problem. The point must be made that a death resulting from the unavailability of an organ is neither inevitable nor must it be viewed simply as a statistical occurrence. It must be seen for what it is in fact: a senseless tragedy which could be avoided by overcoming needlessly restrictive taboos. . . .

NOTE

CODE OF VIRGINIA AUTHORITY OF CHIEF MEDICAL EXAMINER OR DEPUTIES TO PROVIDE ORGANS FOR TRANSPLANT (1970)

§ 19.1-46.1 In any case where a patient is in immediate need for an internal organ as a transplant, the Chief Medical Examiner or his deputies where a decedent comes under their jurisdiction, who may provide a suitable organ for transplant and there is insufficient time to contact the next of kin of the decedent in order to maintain the viability of the organ to be transplanted, and no known objection by the next of kin is foreseen by the Chief Medical Examiner or his deputies . . . may in their discretion where providing the organ for transplant will not interfere with subsequent course of the investigation or autopsy provide such organ on the request of the transplanting surgeon.

b.

Who Should Participate, within What Structure, in Professional Regulation?

[1]

Liz Roman Gallese
Medical-Ethics Panels Are Set Up
*to Resolve Dilemmas on Research**

* * *

In some cases . . . researchers trying to achieve medical breakthroughs are coming into sharp conflict with ethics committees worried about patients' welfare. After several years of conflict, Dr. Adrian Kantrowitz, a noted heart surgeon, left Maimonides Medical Center in Brooklyn late last year for Sinai Hospital in De-

troit. With him went a group of 20 surgeons, nurses and researchers and \$2,500,000 of federal funds for heart research.

"I was ready to perform a heart transplant a year or so before Dr. Christiaan Barnard (the South African physician)," Dr. Kantrowitz says. But the Maimonides ethics committee refused to grant approval because "it had never been done before," Dr. Kantrowitz contends. When the committee finally approved the proposal about a year later, he says, Dr. Barnard had already done the world's first heart transplant, on Dec. 3, 1967. Dr. Kantrowitz did his first heart transplant three days after Dr. Barnard's operation.

Dr. Jacques Sherman, acting director of Maimonides, denies Dr. Kantrowitz's description of events and says his transplant proposal was approved a year or so before he performed the operation.

Another and more recent clash at Maimonides involved Dr. Kantrowitz's attempts to use a mechanical pump to aid in bringing heart attack patients out of shock. The mechanical pump was to supplement the heart's own pumping action.

"There's usually a 95 per cent mortality rate for these patients, but I was able to bring 60 per cent of them out of shock," although not all of them survived, Dr. Kantrowitz says. After initial experiments, the Maimonides ethics committee rejected further work "because I couldn't save all my patients," Dr. Kantrowitz says.

Again Dr. Sherman of Maimonides differs. He says the ethics committee rejected the research only at first because the proposal failed to contain an adequate definition of heart patients in shock. He adds that once the proposal was rewritten, it was approved.

* * *

NOTES

NOTE 1.

LYMAN A. BREWER, III
CARDIAC TRANSPLANTATION—AN APPRAISAL*

* * *

The great difficulty in obtaining donors for cardiac transplantation makes the future of cardiac transplant appear to be very limited. When one considers the fact that about a million people die of heart disease each year in this country, the potential need for cardiac trans-

* *The Wall Street Journal* 1, col. 6; 17, col. 3 (April 14, 1971). Reprinted by permission of *The Wall Street Journal*.

* 205 *Journal of the American Medical Association* 691-692 (1968). Reprinted by permission.

plants appears to be great. Yet many of them would not be suitable subjects for this surgery. And too, if cardiac transplantation develops beyond the present experimental stage and becomes one of proved worth, then enormous moral problems would arise: Who would get the seldom available transplant? This is a problem that should be solved by clinicians and not lay groups. In emergency and disaster situations, the doctors traditionally decide who should be operated on first, who should receive the blood transfusion, or special attention, and so forth. Thus, there has always been a reliance upon the basic wisdom and integrity of the physician. Lay boards, the clergy, government commissions, and hospital administrators will be less well qualified to make these awesome decisions.

* * *

In the last analysis, it is preferable that the medical profession control circumstances under which cardiac transplants are performed. Rigid laws passed by the legislature, rules laid down by legal and clerical boards or other lay groups, might becloud rather than clear the atmosphere. The medical profession should seek and be cognizant of the opinions of these other segments of society so that no phase of the problem will be overlooked. However, the sine qua non of the practice of medicine is integrity of the physician and the surgeon in treating the patient. Without it, the filling-in of forms and reports to comply with rigid rules and to justify the operative procedure is meaningless. . . .

* * *

NOTE 2.

FRED ANDERSON
WHO WILL DECIDE WHO IS TO LIVE?*

* * *

Physicians maintain that uniquely medical questions are involved here, that they should be answered by those whom training and professional insight have equipped to provide the correct answers. In the exercise of their duty they feel that they are hampered by the intrusions of lay people (chiefly journalists and lawyers) who misunderstand both the high standards of medical practice involved and the unique qualities of judgment that physicians possess. . . . But in

choosing between two housewives with defunct kidneys, who are in the same general state of health, is a physician more competent than a layman to select one for dialysis? Even the medical staff at one Seattle hospital does not think so; there, a lay panel decides.

As needless as the encroachment may seem, if we are to establish decision-making procedures that point to the best use of the advances of medical science, physicians must face more and more challenges to their absolute right to decide. What to physicians may appear to be the most specialized advances, thus definitely medical in nature, may present society with the broadest kind of fundamental problems. This is not to say that after policy decisions are argued out in committees, on public forums and if necessary before legislatures, that a committee should decide whether to turn off respirators. Nothing could be worse than to bureaucratize and diffuse decisions even more than they already are in this early team-age society. But there are ways to educate individual decision-makers, or to threaten them, or to encourage them to consult a variety of persons before shouldering individual responsibility.

The opinion of the Harvard committee on brain death is not clearly right or wrong; the question is still open, and before it can be answered adequately the best thoughts of many, including theologians, philosophers, economists and jurists, along with physicians, must be heard. . . .

* * *

NOTE 3.

DELFORD L. STICKEL
MEDICOLEGAL AND ETHICAL ASPECTS
OF ORGAN TRANSPLANTATION*

* * *

. . . The usual approach to . . . difficult decisions is that of consultation to obtain more than one medical opinion, and in some circumstances it is legally required that multiple concurring opinions be documented. Further medical and scientific advances conceivably will eventually reduce the determination of time of death to a simple set of criteria that will be applicable to all pronouncements of death. If such criteria are generally established and used in everyday medical practice as the standard basis for pronouncing

* *The New Republic* 9, 10 (April 19, 1969). Reprinted by permission of *The New Republic*. © 1969, Harrison-Blaine of New Jersey, Inc.

* 169 *Annals of the New York Academy of Sciences* 362, 365-366 (1970). © The New York Academy of Sciences, 1970. Reprinted by permission.

death and are widely accepted legally and by the general public, then the exercise of judgment will be less crucial than it presently is. Until such criteria are developed, however, there appears to be no alternative to securing and documenting multiple concurring medical opinions to support the judgment rendered in situations deemed at present to be too crucial to be left to one person. In practice, it is difficult to document multiple opinions in situations that arise on short notice, as is the case with many vital organ donations; but such difficulties probably are surmountable.

As a backup of consultation prior to the fact, review after the fact is common practice in hospitals. Examples, of course, are clinicopathological conferences, review of surgical cases by tissue committees, deaths and complications conferences, and case reviews in service or departmental conferences. Such retrospective case reviews undoubtedly exercise a favorable influence on the quality of medical judgment and patient care. It may be appropriate now to add a hospital committee for the review of the terminal care and the determination of time of death of patients who actually became or who were considered as possible vital organ donors. Ideally, such a committee should include representation of the transplant team, the physician who attended the donor as a patient, and physicians with responsibility for neither donor nor recipient.

* * *

NOTE 4.

LEO ALEXANDER
ETHICAL AND LEGAL BASE LINES FOR
PROFESSIONS AND COMMUNITY*

* * *

[T]he great safeguard in the thousands of years since Hippocrates has been the mutual approval and dependence of the physicians on the medical scientists. . . . Now, apparently, we have lost this safeguard.

At one time I thought it was due to the intervention of a third party—the state or organizations such as drug companies—and the intrusion of their interests. Are we now asking for other third-party intrusion? We evidently want to balance one third-party intrusion, the governmental and the commercial interest, with another

third-party intrusion, somebody who can look over our shoulders and give us their advice.

[T]he one person who I believe bears the ethical crux in this situation, and who should never be asked, is the patient's relative. Such a request would place an intolerable burden of guilt upon him. Dr. Visscher has pointed out very clearly the problem of relatives' urging the doctor to "pull the plug." I believe this is dangerous, and I would stand above that. I believe that such a decision must be made by the doctor, alone with his God and his conscience.

As a psychiatrist, I can say that if relatives ask him to pull the plug, he must never do it on that basis. That would place a burden of lifetime guilt upon them. No person will be able to bear that. The doctor must have the courage to bear that guilt if he ever chooses to do as suggested, in view of the tenets of our sacred profession.

At one time the doctor was supposed to have direct authority from the Lord, just like the priest, and, I think, very rightfully, because there are certain decisions a doctor must have the courage to make by himself.

In my own personal practice, I've taken care of many people. I never actually "pulled the plug;" it was never necessary, because death always comes soon enough. There are some impatient relatives, naturally, but I wouldn't play along with them at all. . . . But certainly the last person I would ever let make a decision is a relative; that would be dangerous.

In other words, if I were ever tempted to pull out the intravenous apparatus, it would be to save the patient's veins; I would never let the relatives believe otherwise; that would be a great mistake. . . .

NOTE 5.

FRANCIS D. MOORE
GIVE AND TAKE*

* * *

[T]here is always the ethical and humane problem involved in the exploration of any new field of medical or surgical treatment. Mortality has been very high in certain kinds of homotransplantations. It is not enough to tell the patient that "there is no other hope." If he is in full possession of his faculties, he should be given a clear picture of the hazards involved, and allowed to

* 169 *Annals of the New York Academy of Sciences* 334-335 (1970). © The New York Academy of Sciences, 1970. Reprinted by permission.

* Garden City, N.Y.: Doubleday and Co., Inc. 166 (1964). Reprinted by permission of W. B. Saunders Co.

join in the decision. Yet under no circumstances should the final decision be left in the hands of the patient; he has not the education, background, nor dispassionate view necessary to make a decision in his own best self-interest. The doctor must take the time and trouble to help educate the patient far enough along the road, so that when the patient joins in the decision, he does so with some idea of the alternatives. It is up to the doctor to advise, and to seek the patient's consent.

* * *

NOTE 6.

LEON R. KASS
A CAVEAT ON TRANSPLANTS*

* * *

Although there have always been deaths that occurred because the physician was occupied with another patient, the health of an individual has rarely depended necessarily on the demise of another. This has acutely troubled physicians involved in kidney transplants. One surgeon, whose work involves a search for potential donors of kidneys for his clients, said of himself: "I am the vulture hiding at the foot of the bed."

However, most doctors will more or less easily accommodate this tension. They are prepared by their familiarity with death, by their sound judgment about when dying is irreversible and by their clear sense of the value of transplantation.

The dying patient and his family have different problems. Is everything reasonable being done to save the patient, to return him to a more than vegetating condition? Confidence of the patient in his doctor and in his chances for recovery are important for the patient's will to recover and sometimes for the recovery itself. Even when—or perhaps especially when—recovery is impossible, it would be reprehensible to add to the pain and grief the suspicion that the dying patient was being sacrificed for his value as spare parts.

Joshua Lederberg has clearly stated the problem: "We must preserve the confidence of every patient that his physician's dedication to his welfare is uncontaminated by the patient's utility as a biological resource for some other, possibly worthier patient."

* *The Washington Post* B-1, cols. 2-3 (January 14, 1968). © 1968, *The Washington Post*. Reprinted by permission.

But we must go further than Lederberg. We must consider the consequences of transplantation of vital organs for society at large. Lederberg expresses a concern for the preservation of confidence; he is discussing the image of the doctor. I would add that we must insure that the confidence remains deserved, that we must also preserve the truthfulness of that image. We must see to it that no doctor indeed sacrifices his patient's welfare for the sake of his utility as a source of spare parts.

That such practices might be likely under tyrannical regimes is of course obvious, but our society is not immune. Consider the possibility that a high-ranking Government official suffers a massive heart attack and requires a new heart to survive. Might not even the best of physicians be tempted to ease up on the treatment of a critically ill patient deemed less worthy?

Is it too far-fetched to imagine that people might be asked to step forward and volunteer their organs under these circumstances? If no volunteers were available, would mercy-killing or murder be excusable in order to provide a new heart for the statesman? If we are willing to send men involuntarily to their death in battle for the welfare of their country, is it not conceivable that we may someday expand that notion of the general welfare to include the health of our leaders?

* * *

[ii]

*Executive Committee of the International
Society of Cardiology
Statement on Announcement of Cardiovascular
Experiments**

Since the time of Hippocrates, the medical profession has preserved the ethics governing the extent of the information conveyed to the public at large and the way in which it is conveyed. With the availability today of modern media for mass communication there is a greater need to ensure that such information is spread in a responsible manner.

We deplore the fact that in recent times medical and surgical experiments have become matters of public entertainment and even sensationalism. Such a trend can only bring discredit to the profession as a whole and indirectly misrepresent to the public, who are not in a position to judge the implication of such developments,

* *News from the International Society of Cardiology* 8-9 (July 1968). Reprinted by permission.

the dangers and limitations inseparable from such procedures in their initial phase.

While it is not possible to control the behaviour of those who seek instant publicity, the Council of the International Society of Cardiology feels that a lead must be given by responsible members of the profession. One method of ensuring more ethical behaviour and avoiding extremes of anxiety or misplaced hope is to suggest strongly that no new procedures, either medical or surgical, are released to the lay press before being published in the reputable medical journals after full scientific evaluation.

* * *

NOTE

RENÉE C. FOX

A SOCIOLOGICAL PERSPECTIVE ON ORGAN
TRANSPLANTATION AND HEMODIALYSIS*

* * *

The degree and kind of attention that the mass media have accorded to organ transplantation has served a number of functions. It has publicized the need for live and cadaver donors, introduced the lay public to the new conception of "brain death," and helped families and local communities to raise funds for prospective organ recipients. In the opinion of at least one investigator, by dramatizing unsolved medical problems, most notably rejection reactions and tissue typing, the press has helped to interest more researchers to work in these areas. However, the extensive, often theatrical coverage of transplantation has also created certain problems for the medical profession and for the recipients and donors involved. It has invaded the confidentiality and privacy to which the physician and patient, individually and collectively, are ethically entitled. It has encouraged physicians, or put them under pressure, to report their clinical trials to the lay public before submitting them to the trained judgment and criticism of colleagues through channels such as professional publications. In the eyes of some physicians, it has facilitated self-advertising, competition, and commercialized behavior on the part of certain members of the profession in ways that many feel violate the universalism, disinterestedness, and collectivity-orientation of the medical and scientific community. Furthermore, numerous

medical spokesmen have expressed the opinion that the publicity transplantations have received may have "misled" the general public in two key regards. On the one hand, it may have given them a "too optimistic" impression of the present state and promises of transplantation; on the other, by excessively emphasizing the role of the physician as a "taker of organs," it may have undermined public trust in his function of healer and guardian of life. ("Can anyone ever again be sure that physicians will do all that can be done to save him rather than regard him as a potential spare-parts supermarket?")

C.

Should Research Design and Scientific Merits Be Evaluated?

[i]

Board on Medicine of the National Academy
of Sciences
Statement on Cardiac Transplantation*

Progress in medicine depends largely on the cautious extension to man of a body of carefully integrated knowledge derived from programs of basic and developmental research in the laboratory. Extension to man is itself an investigative process that must meet the same meticulous scientific standards that obtain in the laboratory, and the extension can appropriately be started only when the total body of knowledge has reached a certain point. It is clear that this point has been reached in the case of cardiac transplantation.

* * *

[It is the considered view of the Board on Medicine of the National Academy of Sciences

* Walsh McDermott, M.D., Chairman. 18 *News Report of National Academy of Sciences* 1-3 (March 1968). Reprinted by permission. [The National Academy of Sciences is an organization of distinguished scientists and engineers devoted to the furtherance of science and its use for human welfare. Although it is not a government agency, it is called upon by its Congressional charter of 1863 to serve as an official adviser to the federal government in matters of science and technology. The Board on Medicine was formed by the Academy in November 1967 to study the social functions of medicine. It is composed of two biologists, a biophysicist, a psychologist, two economists, a lawyer, a nurse, and fourteen physicians, among them the president of the American Medical Association, the director of the National Institutes of Health, and a number of medical school deans.]

* 169 *Annals of the New York Academy of Sciences* 406, 421-422 (1970). © The New York Academy of Sciences, 1970. Reprinted by permission.

that, for the present, cardiac transplantation should only be carried out in those institutions in which all of the following criteria can be met:

1. The surgical team should have had extensive laboratory experience in cardiac transplantation, and should have demonstrated not only technical competence but a thorough understanding of the biological processes that threaten functional survival of the transplant, i.e., rejection and its control. Investigators skilled in immunology, including tissue typing and the management of immunosuppressive procedures, should be readily available as collaborators in the transplantation effort.

2. As in any other scientific investigation, the overall plan of study should be carefully recorded in advance and arrangements made to continue the systematic observations throughout the whole lifetime of the recipient. The conduct of such studies should be within an organized framework of information exchange and analyses. This would permit prompt access by other investigators to the full positive and negative results. Thus the continued care of each recipient would be assured the continuing benefit of the most up-to-date information. Such an organized communication network would also permit the findings to be integrated with the work of others and assist in the planning of further investigative efforts. In this way, it would be possible to ensure that progress will be deliberate and that the experience from each individual case will make its full contribution to the planning of the next.

3. As the procedure is a scientific investigation and not as yet an accepted form of therapy, the primary justification for this activity in respect to both the donor and recipient is that from the study will come new knowledge of benefit to others in our society. The ethical issues involved in the selection of donor and recipient are a part of the whole complex question of the ethics of human experimentation. This extremely sensitive and complicated subject is now under intensive study by a number of well-qualified groups in this country and abroad. Pending the further development of ethical guidelines, it behooves each institution in which a cardiac transplantation is to be conducted to assure itself that it has protected the interests of all parties involved to the fullest possible extent.

Rigid safeguards should be developed with respect to the selection of prospective donors and the selection of prospective recipients. An independent group of expert, mature physicians—

none of whom is directly engaged in the transplantation effort—should examine the prospective donor. They should agree and record their unanimous opinion as to the donor's acceptability on the basis of the evidence of crucial and irreversible bodily damage and imminent death. Similarly the prospective recipient should be examined by an independent group of competent physicians and clinical scientists including a cardiologist and an expert in immunology. In this instance the consulting group should also record their opinion as to the acceptability of the recipient for transplantation on the basis of all the evidence including the presence of far advanced, irreversible cardiac damage and the likelihood of benefit from the procedure.

Enumeration of the above criteria is based on the conviction that in order to obtain the scientific information necessary for the next phase in this form of organ transplantation, only a relatively small number of careful investigations involving cardiac transplantation need be done at this time. Therefore, the Board strongly urges that institutions, even though well equipped from the standpoint of surgical expertise and facilities but without specific capabilities to conduct the whole range of scientific observations involved in the total study, resist the temptation to approve the performance of the surgical procedure until there has been an opportunity for the total situation to be clarified by intensive and closely integrated study.

NOTE

LYMAN A. BREWER, III
CARDIAC TRANSPLANTATION—AN APPRAISAL*

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The scientific data accumulated concerning the cardiac transplant should be released first through regular medical channels, medical journals and meetings, and not handed out to the lay press for prior presentation.

Because cardiac transplantation is technically no more difficult than some current cardiac operations, many cardiac surgeons may be tempted to perform this procedure, since it is well within their technical grasp. This being true, it is hoped that the operation will never be performed as a status symbol to the surgical team or hospital embarking on this surgery. Nothing

* 205 *Journal of the American Medical Association* 691, 692 (1968). Reprinted by permission.

would cause more discredit to the procedure in particular and to surgery in general than the precipitous plunging of many surgical teams in the United States and throughout the world into this type of surgery with its high mortality and uncertain future. Certainly, however, at this stage of development of this operation, it is inadvisable to have a regulating board to determine the surgical and research capabilities of the surgical team and institution. Rather should the innate ethical and surgical good sense and temperate professional restraint in each cardiac group prevail.

* * *

[ii]

Allen S. Fox

*Heart Transplants—Treatment or Experiment**

Time magazine [29 Dec.] quotes Christiaan Barnard, with regard to the Washkansky heart transplant, as follows: "I wouldn't like to call this operation an experiment—it was treatment of a sick patient. Although Washkansky died, I don't think we have any evidence that transplantation is not good treatment for certain heart diseases." There are serious reasons to question the validity of the first of these assertions; the second is not much more than a general expression of faith.

Two different kinds of problems must be solved before transplantation surgery may be regarded as treatment rather than experiment. The first is that of surgical technique. . . . Actual performance of the Washkansky operation was not needed to know that Barnard and his associates, or other similar groups, had reached the point in experience, skill, daring, and sophistication to carry it out with technical success.

The second problem, that of overcoming the genetic barrier to transplantation, is the more critical one. . . .

There are ways . . . of minimizing the histocompatibility barrier. Matching of red blood cell types is elementary. Matching with respect to transplantation antigens is more pertinent to this discussion. This is most conveniently accomplished by the detection of individual leukocyte antigens with suitable isoimmune antisera (leukocyte typing) or by the use of matching tests such as mixed leukocyte cultures (MLC typing). The results of both of these kinds of

tests are at least partially predictive of transplantation success. . . .

Although a full scientific report of the Washkansky case is not yet available, sufficient information has been provided by the press to make an evaluation with respect to this second problem. The importance of the sex difference between donor and recipient cannot be evaluated. Apparently red blood cell typing was performed in advance of the operation. Apparently, also, limited leukocyte typing was performed, but not until after the operation had been initiated. One may infer from press reports that MLC or other matching tests were not performed. Obviously no prior attempt was made to match donor and recipient with respect to transplantation antigens. There is every indication from available information that they were actually incompatible, as most unrelated donor-recipient combinations would be if chosen at random.

Under these circumstances massive immunosuppression and radiation were judged to be required and were applied. It is not surprising, therefore, that the patient died of pneumonia. One must conclude that the histocompatibility problem was not dealt with in the Washkansky case, even within available limits. The operation should not be justified as treatment, and if it was an experiment it must be judged as premature and poorly designed. . . .

* * *

d.

Should Consent Be Supervised?

[i]

*He Had a New Heart for a Week and Didn't Know It**

The 23-year-old, happy-go-lucky cowboy had journeyed hundreds of weary miles east from Brazil's harsh Mato Grosso plateau. Dressed in rags one morning last April, pain hammering at his heart, João Ferreira da Cunha joined hundreds of poor who arrive daily between 4 A.M. and 6 A.M. at São Paulo's Hospital das Clínicas for free treatment.

A highly qualified surgical team, including one doctor who had worked at Dr. Christiaan Barnard's side for a week in South Africa, picked the cowboy out of the throng for South America's first heart transplant, performed May 26th.

* 159 *Science* 374 (1968). Copyright 1968 by the American Association for the Advancement of Science. Reprinted by permission.

* *Medical World News* 9-10 (July 12, 1968). Copyright 1968, McGraw-Hill, Inc. Reprinted by permission.

But, medical observers close to the scene now contend, the illiterate da Cunha agreed to the operation without beginning to comprehend its nature or seriousness. A week afterwards, sitting up in his bed and strumming his guitar, he heard a news broadcast detailing the recovery of a celebrity with his name. The young patient turned to his nurse and asked, "Who is the radio talking about?" The nurse replied, "Why, it is you!" Da Cunha was amazed.

* * *

Fully informed consent was impossible in da Cunha's case, say his doctors. Asked whether the team could give him a new heart, he said, "Yes, anything to stop the pain," apparently without understanding at all what the operation meant.

Afterwards, still unaware of his precarious condition, da Cunha joyously rose from his bed on June 17th and walked about his hospital room. His heart went into fibrillation almost immediately. After repeated crises, he died on June 22nd. Autopsy disclosed that his body had not rejected the heart. Rather, a clot had formed in an iliac vein, had been carried to the right ventricle, and lodged in the bifurcation of the pulmonary trunk, causing heart failure.

* * *

[T]he Brazilian surgeons point out at the same time that no ethical questions are raised by da Cunha's lack of informed consent. If a man is incapable of understanding an operation he vitally needs, they say, there is no choice but to proceed. And there has been no outcry in the Brazilian medical community. In an underdeveloped nation, illiteracy and ignorance are common. Besides, add the surgeons, da Cunha was psychologically better off not knowing and worrying about his risks.

* * *

[ii]

Barney G. Glaser and Anselm L. Strauss
*Awareness of Dying**

* * *

Our conception . . . of a patient's response to direct disclosure is based largely on our inter-

views with patients, doctors, and nurses in the cancer wards of a Veterans' Administration Hospital. In this hospital the normal procedure is to tell every patient the nature of his illness; as a result, many patients are told of a fatal illness.

By and large the patients in these wards are in their middle or late years, of lower-class status, and in destitute circumstances. Since their case is free, they are captive patients—they have little or no control over their treatment, and if they do not cooperate their care may be stopped. If a man goes "AWOL" the hospital is not obliged to readmit him, or if it does readmit him, it can punish him by denying privileges. Because the patients lack financial resources, they typically have no alternative to their current "free" care, and lower-class status accustoms them to accepting or to being intimidated into following orders from people of higher status. Since these captive lower-class patients cannot effectively threaten the hospital or the doctors, the rule at this hospital is to disclose terminality regardless of the patient's expected reaction. . . .

* * *

Disclosure of fatal illness to patients in this hospital has two major characteristics. First, the patient is told that he is certain to die, but not when he will die. . . .

Second, the doctors typically do not give details of the illness, and the type of patient under consideration usually does not ask for them. Primarily, this is a problem of communication: a doctor finds it hard to explain the illness to a working-class patient, while lack of familiarity with the technical terms, as well as a more general deference to the doctor, inhibits the patient's impulse to question him. In addition, not giving details is a tactic doctors use to avoid or cut down on talk with the patient and to leave him quickly. . . .

* * *

Some patients accept their fatal illness but decide to *fight* it. Unlike denial behavior, this fight indicates an initial acceptance of one's fate together with a positive desire to somehow change it. . . .

* * *

The search for a way to fight the fatal illness can . . . lead a patient into a clinical experiment. If he does not win his own battle, he at

* Chicago: Aldine Publishing Co. 122-123, 130-132, 185-193 (1965). Copyright © 1965 by Barney G. Glaser and Anselm L. Strauss. Reprinted by permission of Aldine • Atherton, Inc.

least may help future patients with theirs. The chance to contribute to medical science does not, however, sustain the motivation of *all* research patients. Some, realizing things are hopeless for themselves and finding the experimental regime too rigorous to bear, try to extricate themselves from the experiment. If the doctors decide to carry on anyway, these patients sometimes interfere with the experiment by pulling tubes out, by not taking medicine, or by taking an extra drink of water. Some attempt auto-euthanasia.

* * *

Although it contradicts the usual priorities in patient care, a patient dying in a medically "interesting" way, or suffering from an "interesting" condition, may receive special attention as an object of study and as a teaching "case." This increased attention does not necessarily make the unaware patient suspicious. He may feel that his chances of recovery are improved by the attention of so many doctors. The unaware family, too, may become very hopeful when they find numerous experts concerned with the patient's condition.

Hope for the patient wanes, however, and even turns to high suspicion if his case is so "interesting" that the doctors decide to keep him alive "for the rest of the semester" and start applying various kinds of equipment to prolong life. Medical equipment can be one of the surest indicators to patients and families that death is certain, but is being delayed. Once aware of dying, the patient may then have to ask for his own death, to put a stop to undue prolonging. A nurse told of a patient who was "kept alive for over three weeks on a pacemaker for teaching purposes." This was so hard on both the patient and her family that the patient, knowing she would die, told the doctor to stop the pacemaker. She was dead within thirty-six hours.

* * *

The goal of recovery, with its high priority for the doctor's attention, can be reinstated, at least provisionally, by enrolling the dying patient in a clinical research project. In general, the basic legitimate condition for this proposal is the doctor's absolute certainty that, given present knowledge, there is "nothing more to do" for the patient in any available hospital. (For patients with sufficient personal financial resources, "available" hospitals may include those in Brit-

ain, France, and Germany.) At this time, the family and patient must be presented with the facts of "nothing more to do," even if they were hitherto unaware. Then they are given the alternative: to risk the research with its promise of recovery, however slight. The negative side effects of the treatment or drug are not always presented. If the patient is adult and sentient, he must consent in writing; otherwise a family member must consent. Sometimes, however, "captive" patients are put on a study drug unawares. Parents who "donate" their child often do so without letting the child know that he is dying, so that the closed awareness context is maintained, at least in the beginning.

Recruitment into research is timed according to the current type of death expectation and the availability of a testable treatment. Among patients in the "nothing more to do" phase there are more potential research cases than research experiments. A cancer patient, for instance, certain to die, may have been lingering for months when a new chemical drug to be tested is sent from the National Institutes of Health to the hospital; the patient is then asked to be a research case, with, if necessary, an attendant change in his awareness. Unaware patients and families may be converted to awareness for naught, if they do not agree to the experiment. The longer a patient lives in the "nothing more to do" phase, the more likely it is that an effort to recruit him for research purposes will occur which may alter his own and his family's awareness.

On the other hand, sometimes an experiment requires waiting until a particular dying patient has reached the "nothing more to do" phase. Having watched the patient closely, until they are virtually certain of his impending death, doctors negotiate with patient or family immediately to try a new drug or a transplant, for example. . . .

* * *

For patients who are *not* to be recruited for research, however, especially when experiments with a high probability of saving the patient are going on at the hospital, doctors have a stake in maintaining a closed awareness context for both patient and family. For, if the family became aware that the patient was certain to die, they might demand that the patient be given the experimental drug or that the new machine be tried. Since for most experiments, resources are lim-

ited, there are not enough chances to go around. This situation becomes even more difficult for the doctors when the news media make known that a new machine or drug with great promise is being tested. In a university medical center, of course, both the facilities for research and the pressure to give a patient a chance to participate are much greater than they are elsewhere.

A patient can also volunteer for basic rather than clinical research. In basic research the objective is to find possible cures, not to test potential ones, so there is no implicit change back to the goal of recovery. Yet for a lingering patient the hope is always present that "his" project will succeed in finding a cure, and he will be the first subject to recover. Thus, some people volunteer to continue their dying at the National Institutes of Health, for example, where basic research is done along with clinical research.

In clinical research, the chief drawback for all concerned is that it takes time, and this means that for some patients life will be unduly prolonged. Once committed to the research, the patient and his family are expected to see it through to the end. Certainly most research doctors are highly committed; generally, their attitude was, "If it is a study, we go all out." One doctor did say, "If a patient is in the study and *near death*, we provide ordinary treatment. Don't use extra measures just because they are in the study. If he is in agony, I wouldn't keep a man alive just because of a study."

Nurses, on the other hand, tend to go along with research in the beginning, but their collective mood in response to undue prolonging is "Why not let him die?" When the doctors continue to prolong the patient's life, the nurses often feel frustrated by their helplessness in being unable to let him die. Occasionally they refuse to acknowledge the legitimacy of the research effort—the well-being of future patients—suspecting that the research patient is really being exploited for personal career purposes, and making statements like: "They keep them alive until the research report is written." Yet, the nurses remain helpless since, as one put it, "Usually you hate to say anything like, 'Why not let him die?'"

Resolution of this problem of unduly extending research patients' lives often depends on the awareness context. If the patient is unaware, as in the case of a child committed by his parents, or a comatose adult, then family members must decide. This is not an easy decision to make, because often they can see the possible benefit to future patients and so feel morally obligated to

allow an indefinite prolonging. As one nurse said, "The mother felt obligated, if it teaches them something."

Aware patients react to prospective prolonging according to their death expectation—whether they think of themselves as lingering (time of death unknown) or believe that without excessive staff effort they would die quickly. A patient who thinks he will linger anyway may expect the research to make a possibly uncomfortable fate less so; hence he will probably stay with the study. But if he feels that the research is increasing his discomfort, he may ask to be released from it so that he can live out his last weeks in comfort. A patient, who is aware that without research medication or equipment he will die quickly, must weigh this against the pain of having his life prolonged, and decide accordingly. Again, this is a difficult decision to make, and a patient's intention to remain in the study is always subject to reversal.

Because the equipment necessary to prolong life may be so elaborate, many research patients readily become aware that death would come within a few hours or days if they were not in the project. Thus, when prolonging becomes very painful, the patient is apt to lose any moral commitment to the research he might have had, abandon any prospect of recovery, and want simply to be left alone to die. A basic principle in clinical research is that a subject should be allowed to withdraw when he feels that continuation is mentally and physically impossible. But this principle is most appropriately applied to clinical research patients who are either not certain to die, or who are expected to linger on fairly comfortably for weeks or months. They have a moral right to save themselves discomfort; imminent death is not the issue.

A patient expected to die quickly if released from the experiment, on the other hand, may find it difficult to get out of the research if he is not in undue pain. The doctors' point of view may be that his comfort, to be attained through his imminent death, is less important than the success of the experiment if it can be achieved in a few more days or a week. A patient in this situation can withdraw most easily by having his family request it, but family members are not always willing to do this. Much as they might like to help the patient, they may be influenced by the potential benefits to medicine in prolonging his life, or they may still harbor the hope that recovery is a real possibility. If the patient negotiates for dismissal, doctors, who tend to be

highly committed to the research, usually try to persuade him to go on with the research, using the idea that it is better than immediate death.

A patient who succumbs to a doctor's argument, however, may have second thoughts after the doctor leaves and try to take measures into his own hands, in spite of his personal obligation to the doctor and the potential benefits to mankind. One research patient, having recovered from the side effects of chemotherapy, was sent back for more. He asked the nurse to remove his restraints, and she agreed, saying they would be ordered back on in the morning. The patient nodded that he understood. After the nurse left the room, he wrote on a slate that he didn't want to go back for more treatment and pulled his catheter out. When the nurse returned, she found him in a pool of blood. She did, however, keep him from killing himself.

Nurses who adhere to the "let him go" belief, based on the comfort goal, try to help the research patient. They may ask the doctor indirectly why he does not let the patient die, by asking why he is prescribing a treatment—for example, tracheotomy or more blood—that will prolong life. The doctor's reply is likely to be on the order of "because he needs it!" So the nurse either must ask directly, "Why not let him die?" or must carry out her tasks of helping to prolong the patient's life, with no satisfactory answer. Other nurses—only a few—simply walk out, indicating they will not give the treatment or prepare the patient. In reply one doctor said to a departing nurse: "I think we ought to give him the blood right now!" One nurse felt morally obligated to help a patient in his struggle if he said he wanted out. She said, "When he tells me that I want to die, it is at this point that I would go right up to the doctors and say, 'Let him die.'"

As we have noted, the research proposal itself may disclose to the patient that he will die, and the change of awareness sometimes induces depression. In part, however, the proposal reinstitutes the recovery goal, and this carries a "lift" for patients whose awareness has just been transformed, as well as for those who are already aware. Indeed, an apparent reprieve often does occur in the first days or weeks of the experiment: tumors go down, transplants work, the progress of the cancer is halted, and so on. But often the new treatment eventually fails, the patient's awareness is transformed back to the "nothing more to do" phase, and his depression is all the worse because he has lost a renewed hope. . . .

3.

In Reviewing Decisions and Consequences

a.

Through Governmental Action?

*Trial to Test MD's Role in Death of Heart Donor**

The physician's role in the death of a heart transplant donor is being challenged in a Milwaukee court.

Lloyd G. Johnson, 23, has been charged with manslaughter in the death of Robert E. Buelow, 30 . . . following a fight in which Buelow struck his head on the pavement, receiving severe brain damage. Buelow was kept alive by artificial means and later his heart was transplanted into the body of Mrs. Elizabeth Anick, 49 . . . by physicians at St. Luke's Hospital, Milwaukee.

* * *

Johnson's attorney indicated he would maintain Johnson struck Buelow in self-defense after Buelow swung at him.

The defense also is expected to raise the question of who is actually to blame for the death of the mortally injured heart donor—the man who caused the initial injury or the physicians who removed his heart?

Thomas Dougherty in the district attorney's office commented that the case poses some complex medical and legal questions, but he stressed that the physicians performing the operations and the hospital definitely "are not on trial."

He explained Helen Young, MD, county medical examiner, was notified by the heart surgeons of the impending operation. Dr. Young was called in before the transplant was conducted, and she talked with District Attorney David Cannon, he said. Dr. Young also participated as an observer during the actual transplant surgery.

. . . Dougherty said the official finding was that Buelow died of severe skull fracture and cerebral hemorrhage. He said the prosecutor's office does not anticipate any finding in court that the cause of death was anything other than the trauma by the blow and fall of the victim to the ground.

If the cause of death cannot be tied to the trauma, Dougherty said, there is little doubt that there is adequate foundation for the state's

* *AMA News* 2 (November 11, 1968). Reprinted by permission.

charge of injury by conduct regardless of life, for which the penalties are the same as manslaughter.

* * *

NOTE

MAN KEPT ALIVE AS KIDNEY DONOR*

At an inquest here tonight on a man who received severe head injuries in a brawl last month, a jury was told that he was kept alive for 24 hours on a respiratory machine so that one of his kidneys could be taken for transplanting in another man who was dying from kidney trouble.

The jury decided that the removal of the man's kidney had nothing to do with his death, which they accepted had been caused by brain injuries, and returned a verdict of manslaughter against Henry Hall. [He] was committed to Durham Assizes by the Coroner . . . to answer a charge of causing the death of John David Potter . . .

Hall . . . was alleged to have admitted in a statement that he had butted Potter twice in the face. Potter had fallen backwards on to his head.

Dr. R. H. Appleby, of Newcastle General Hospital, said that about 14 hours after admission Potter stopped breathing. He was put on the machine for 24 hours.

Dr. Appleby said in his opinion when Potter ceased breathing on June 16 he had virtually died, though from the legal point of view it would be correct to say he died when the heart ceased beating and the circulation ceased to flow on June 17.

Mr. John Swinney, consultant neurological surgeon at the hospital, said he was told that Potter was technically dead and sought permission from Mrs. Potter for consent for removal of the kidney for transplanting. This was given. The Coroner said that he was asked for consent which he gave, but he had supposed that the kidney would be taken after the man's death.

* * *

After the kidney had been removed, the respirator was turned off and there was no spontaneous breathing or circulation. Had there been no intention of taking the kidney there would have been no point in putting Potter on the machine.

* * *

After the inquest, Mr. Swinney said the kidney was given to a man aged 30, who died three weeks after the operation from cerebral haemorrhage. Mr. Swinney said he felt the case had advanced medical research and that the operation could be regarded as a success.

b.

Through Public Scrutiny?

[i]

John D. Arnold, Thomas F. Zimmerman,
and Daniel C. Martin

*Public Attitudes and the Diagnosis of Death**

* * *

By and large, there was little public concern about the subtleties involved in the diagnosis of death until the cardiac transplant became a reality. During most of the 20th century, the public has shown a nearly complete acceptance of the prevailing professional practice in regard to the diagnosis of death. This has not always been the case. If one examines the literature of the 19th century, it becomes apparent that the *diagnosis* of death has concerned a fairly large number of writers. A prominent example of this is Poe's essay on premature burial. In addition, it is possible to cite several hundred pamphlets and tracts written between 1700 and 1900 on the fallibility of the diagnosis of death. These collectively provide testimony to the existence of a public apprehension about premature burial.

The reason for this concern had to do with specific cases which came to the attention of the public. . . . T. M. Montgomery reports on the moving of the Fort Randall Cemetery in 1896:

We found among these remains, two that bore every evidence of having been buried alive. The first case was that of a soldier that [*sic*] had been struck by lightning. Upon opening the lid of the coffin, we found that the legs and arms had been drawn up as far as the confines of the coffin would permit. The other was a case of death resulting from alcoholism. The body was slightly turned, the legs were drawn up a trifle and the hands were clutching the clothing. In the coffin was found a large whisky flask. Nearly 2 per cent of those exhumed here were no doubt victims of suspended animation.

Alexander Wilder, MD, in a pamphlet entitled "Burying Alive, a Frequent Peril," mentions several cases:

* 206 *Journal of the American Medical Association* 1949, 1950-1954 (1968). Reprinted by permission.

* *The London Times* 9, col. 3 (July 26, 1963). Reprinted by permission.

One, a six-year-old boy who was exhumed after 25 years and found to have the arms bent over the skull, one leg drawn up and the other bent over it. Another case is of a man, 35, who was buried 48 hours after the diagnosis of death from scarlet fever. He was exhumed two months later. The coffin was found to have the glass front shattered, the bottom kicked out and the sides sprung. The body lay face downwards, the arms were bent and in the clenched fists were handfuls of hair.

The following notes appear in an 1877 issue of the *British Medical Journal*.

A correspondent at Naples states that the Appeals Court has had before it a case not likely to inspire confidence in the minds who look forward with horror to the possibility of being buried alive. It appeared from the evidence that some time ago, a woman was interred with all the usual formalities, it being believed that she was dead, while she was only in a trance. Some days afterwards, when the grave in which she had been placed was opened for the reception of another body, it was found that the clothes which covered the unfortunate woman were torn to pieces, and that she had even broken her limbs in attempting to extricate herself from the living tomb. The Court, after hearing the case, sentenced the doctor who had signed the certificate of decease, and the major who had authorized the interment each to three month's imprisonment for involuntary manslaughter.

Actually very little is known of the accuracy of the several methods of diagnosing death either in the 19th century or the 20th century. Except for the electrocardiogram and the electroencephalogram, it appears that medicine has acquired no new tools for determining the functional state of organs critically important in the diagnosis of death. Although the EEG and the ECG are new and sophisticated supplements to the old techniques, they are not often used today in the diagnosis of death. Except in the very recent past, medical education has appeared to be relatively indifferent to this problem. . . .

* * *

[O]f a group of hospital interns and residents, who were graduates of approximately 15 medical schools, not one could remember having been instructed in medical school concerning the requirements for the diagnosis of death. One young intern on his first real test asked the nurse for instructions.

* * *

Unlike the situation in the 19th century, the 20th century practice of embalming all persons

pronounced dead has served to remove any mistakes from public view. In the 19th century, it was the public view that aroused concern. In fact, this concern may have been one of the factors leading to the introduction of embalming. In America, embalming is almost universal, although not legally required. In Europe, embalming is not so widespread, but postmortem medical examinations are. . . .

* * *

It is believed useful to make systematic attempts to assess public concern and to involve the public in a dialogue about the vital issues raised by new concepts dealing with the diagnosis of death. To this end, two preliminary studies of public attitudes and perceptions were made to give perspective to historical data. . . .

* * *

1. The public is giving thought to the issues of how death is determined. In the samples of opinion surveyed, 69 per cent responded that they had thought frequently or occasionally about the topic prior to the time of interview. There is evidence the information emanating from the mass media regarding heart transplants had stimulated much of this thought.

2. The public thinks of death in terms of cessation of cardio-pulmonary functions. Two thirds of individuals surveyed thought that death occurred when the heart stopped or breathing has ceased or both. Only 9 per cent thought of death in terms of irreversible loss of cerebral function. . . .

3. The public has an inaccurate concept of the mechanics associated with diagnosing death. This inference is supported by two types of findings. First, there is some confusion about who is responsible for saying a person is dead. While all people that were involved in the assessment thought that physicians or the coroner or both were responsible, there was considerable variation. Some individuals felt that only the decision of one physician was required, others said two or more physicians must agree. Still others responded that both a physician and the coroner must make the determination. A few individuals indicated that the coroner alone is responsible. . . .

* * *

Except for the medical examiner system, the coroner need only be 21 years of age and an American citizen.

Ninety-two percent of people questioned thought that a death certificate is required for embalming. In actual practice . . . this is not the case. As new life-support techniques increase the need for precision in the pronouncement of death, the dissonance between practice and perception will become an increasingly important factor.

4. The public will desire consensus about the practices of death pronouncement. This is supported by historical evidence, as well as by the individuals surveyed. A subsample of people were given an explanation of the importance of changing the method of determining death in the specific case of the single-organ transplant. Potential margins of error and problems were discussed. That "the rules of the game be made very clear to everybody" sums up well the response. Furthermore, there was evidence that the diagnosis of death in light of new technology should be regarded as more than a medical problem. Because of the far-reaching social implications, the individuals surveyed see the issue in a social framework.

* * *

[ii]

*Statement of Senator Walter F. Mondale,
Minnesota—March 7, 1968**

. . . I think these hearings will constitute a classic document of statements and of discussion in this field which will be unique in our nation's literature, and from which could flow not only the creation of this commission, but also advancement of medical science; an improvement of health care; and a far more responsible and rational handling of the moral and social dimensions which undoubtedly exist as a part of those developments.

* * *

[T]hese advances and others yet to come [raise] grave and fundamental ethical and legal questions for our society—who shall live and who shall die; how long shall life be preserved and how shall it be altered; who shall make decisions; how shall society be prepared.

* * *

* Materials in this section are reprinted from *National Committee on Health Science and Society—Hearings on S.J. Res. 145 before the Subcommittee on Government Research of the Senate Committee on Government Operations, 90th Congress, 2d Session (1968)*.

[T]his society is in a constant race to keep up with advancing technologies, understand them, and see that they are put to constructive use. We have been too late, too secret, and too superficial in too many cases.

* * *

. . . I have seen first hand the techniques that are used to develop this new technology; the sorts of things that must be done; the indispensable freedom that the researcher and the health practitioner must have. But I do not see any conflict of interest between a rational study of this issue, the taking of important, rational steps, and the preservation of this fundamental function. Indeed, I see them as complementary. The notion that somehow ignorance of what medical technology is producing protects the scientist better than public understanding is one which I am unable to accept.

I think the medical professional has a right to ask us to give him the resources and the elbow room he needs to fulfill his function. But I think that same professional must understand that society has a stake in what he is doing, and that society must know not only what he is doing, but the implications of his efforts.

* * *

Shortly after I came to the Senate, a bill was introduced which, in my opinion, would have sharply restricted animal research. At the University of Minnesota I think it is fair to say that we have gone very far in this field, and there has been a remarkable dividend, to human health and to animal health, from the experimentation that has occurred there. That is one of the reasons for our advance in transplantation technology.

Doctors from the university came to me and said, "Senator, this is a very, very serious thing. The public does not understand this problem. They think it is a case of mutilating dogs. They do not understand it. And if we are not careful, we are going to destroy one of the basic sources of medical knowledge, and new medical knowledge."

I listened to them and I said, "You are right." And I introduced legislation to protect against the inhumane treatment of dogs, and to provide funds to assist in the proper care, treatment, and feeding of animals, including dogs, but at the same time to leave the medical profession free to do the experimentation that it needs—humane research.

But I think there is something instructive there. I think what it tells us is that those who really believe in advancing medical knowledge have far more to gain from public understanding than public ignorance. That was an emergency situation. We could have taken steps in this field. Fortunately, I think we came up with a measure that was workable.

But I would hope the medical profession would approach these hearings not as a risk or a danger, but as an opportunity to put their work in proper perspective; to promote public knowledge of what they are doing; and to foster what I am sure will be broadened and more sophisticated public support.

* * *

NOTES

NOTE 1.

TESTIMONY OF DR. ADRIAN KANTROWITZ,
DIRECTOR OF SURGICAL SERVICES, MAIMONIDES
MEDICAL CENTER, BROOKLYN, NEW YORK—
MARCH 7, 1968

* * *

In recent months, the pioneering achievements of Dr. Christiaan Barnard and others in the field of human heart transplantation have attracted understandable—if sometimes lamentably confused—attention. Public interest in the phenomenon of transplantation of organs from one human being to another has tended to obscure the at least equally bright promise of what we call heart-assist devices. I think we should bear in mind that such devices are likely to be even more important than transplantation in the future treatment of human heart disease.

Be that as it may, both paths of experimentation have already led to substantial achievement. Both must be followed with maximum energy, creativity, and skill by persons now in the work and by others who, it is hoped, will be drawn to it.

* * *

[N]o constructive purpose is served by representing the first human heart transplantation procedures as a sudden breakthrough, as if the idea had sprung full-blown from someone's brain and was perhaps a product of ill consideration as well as inspiration. The operations were breakthroughs only if a clinical trial—a forward step—can be adorned with so grandiose a label.

* * *

This brings me to a second focus of confusion—the question of whether experimental heart surgery contains ethical, moral, social, legal, economic, and political problems of a quality or magnitude never before encountered. As you know, this question has been raised on innumerable occasions not only in the general press but in journals of science and medicine. I am grateful that the subcommittee has invited comments.

The ethics of heart transplantation or of the implantation of a heart-assisting device are, first of all, the ethics of medicine, the ethics of reverence for human life. Where implantation of a heart-assisting device is contemplated the ethical problem is summarized in a few words: can the patient survive by any other known means? If the answer is affirmative, the physician recognizes that the patient is not a candidate for experimental use of a heart-assisting device. But if the patient is beyond the help of established procedures, it is entirely ethical to try to save his life with an experimental heart-assisting device which has demonstrated its effectiveness in animals.

The same process of ethical thought determines a patient's candidacy for heart transplantation. The process is not different from that which takes place in the mind of the physician prior to deciding whether a patient is an appropriate candidate for some new drug. Will anything else probably help the patient? Will the new drug expose the patient to unnecessary risk? Obviously, no surgeon would consider removing a human being's heart and replacing it with another except as a last-ditch effort to save life, all other possibilities having been exhausted.

* * *

Clinical trials are a far cry from the final accomplishment of a fully tested and substantiated procedure. As trials they are undertaken in the knowledge that failure is inherent in risk—and risk is synonymous with trial. And trials need the most searching scrutiny and review by the medical investigator's peers. The tradition of conducting these trials in a careful, orderly fashion, and of awaiting scientific evaluation before proceeding further is of vital importance to the public, and is hardly served by premature, over-emphatic publicity.

On the other hand, the public has the right to information about projects for which it pays the bills. Furthermore, biomedical research could hardly have achieved the levels of governmental and private support to which it has become ac-

customed if the press had not been attentive to interesting developments in years gone by.

But does the public need to know at 2:45 A.M. what may have happened in a surgical amphitheater at 2:43? And need the scientific investigator pause at the most stressful point in his effort to save life, need he then become a television personality, a sage, an answerer of sensational questions? Does this serve the public well? I think not.

* * *

SENATOR HARRIS: You view the transplantation of the human heart as experimentation at this stage, or is it a therapeutic procedure, or does it depend upon the particular case?

DR. KANTROWITZ: I do not think there is any question, Senator, about this. Not only in my opinion, but in the opinion of all of us who have done this procedure in humans, this is a highly experimental procedure. It is far from worked out to the point where it should be offered to the public. . . . It should be done—no question about this—it must be done—this is no longer a choice—it will be done, whether it is going to be done here or in South Africa or in Paris or Moscow—it is going to be done. It is a procedure that is going to be explored, and quite properly should be explored.

* * *

We are stepping into areas in the development of medicine where a certain amount of courage and boldness is necessary for success. I do not think this is really different than in any other business. I am sure this is true in your own affairs, where courage and boldness are needed. I am not sure committees have established a reputation for courage and boldness. They apparently survive much better being careful, not taking any chances.

But this is not the way progress is made. At least in my estimation. Progress is made by people who have some understanding of the problem, and enough courage to have the willingness to fail, because failure is part of success; it is part of the scientific process. My main concern is that a committee should not set up guidelines without the help of that segment of the medical profession which has some experience in developing these kinds of things. . . .

* * *

NOTE 2.

TESTIMONY OF DR. CHRISTIAAN BARNARD,
DIRECTOR OF SURGICAL RESEARCH,
MEDICAL SCHOOL, UNIVERSITY OF CAPE TOWN,
CAPE TOWN, SOUTH AFRICA—MARCH 8, 1968

* * *

[I]f you mean by this commission that you should have a qualified group of doctors belonging to that institution where the transplant is being done, then I could say I have nothing further to say, because this is done all over the world where transplantations are done. They have a group of doctors qualified and understanding the problems of organ transplantation which decide whether a patient should be selected for a transplant of such an organ, and decide on the various legal and medical aspects of this operation—and moral.

* * *

But if you are trying to set up a commission which is different from the one that I have indicated, I must say that I think you are seeing ghosts where there are no ghosts. If I am in competition with my colleagues of this country, which I am not, and were I completely selfish, then I would welcome such a commission, because it would put the doctors who embark on this type of treatment so far behind me, and hamper the group of doctors so much that I will go so far ahead that they will never catch up with me.

* * *

SENATOR RIBICOFF: [T]his has become a public issue because the public is paying the cost—society as a whole is paying the general costs. . . .

Now, who makes the decision? Should one doctor or a team of doctors be the sole ones to make the decisions as to who lives or dies?

DR. BARNARD: [L]et me give you something to compare that with.

Who pays for the cost of war? The public. Who decides where the general should attack and how he should attack? . . .

* * *

. . . The general is qualified to make that decision. And, therefore, he is qualified to spend the public's money the best way he thinks it is fit to spend it.

You cannot have control over these things. You must leave it in the people's hands who are capable of doing it.

SENATOR RIBICOFF: So not only the operation, but the person who would be the donee, in your opinion, should be left entirely to the medical team?

DR. BARNARD: Yes, sir.

* * *

Senator, by wanting to set up a commission, you must have one of two reasons. Either you are seeing new problems, or you are not satisfied with the way the doctors have handled problems in the past. That is the only reason you can ask for a commission.

SENATOR MONDALE: Don't you think some of the questions that have been asked today could profit by a further exploration by a responsible commission?

DR. BARNARD: But have you in our report of our cases—have you found any questions that could be explored by a commission, and could be clarified by a commission?

SENATOR MONDALE: Well, we have gone into the question of, when can a heart be made available, what should be the rights of the donor to select the donee. If there are only a limited number of transplants possible and a much larger number of people who will live or die, who receives the benefit of having his life being saved, with surgery that costs, by your estimates \$30,000 each, and maybe \$45,000 in the United States? How are those economic problems solved? Is there enough money being poured into this research to accelerate it, so that we can save more lives? What about the degree to which we are making these skills available more widely? What about the necessary facilities and the rest? Don't you believe these problems are the appropriate issues for the public to be concerned about?

DR. BARNARD: Well, I think that you are now mentioning problems which I think a commission would handle very well, as deciding to give money for research, and problems like that. But I think we must distinguish between what this commission is going to do. Is this commission going to decide on medical problems, and how the various transplant teams should handle a medical problem? If you ask me whether I think a commission should be necessary for that, I would disagree. But if you think that one should have a commission to decide whether money

should be poured into research because we now have these new techniques, and this may need more money, and aspects like that, I would agree that there you need a commission; but not to help the doctor to make his decision.

* * *

. . . Commissions have been set up to decide on various medical advances in the past. These commissions . . . have hampered the progress of medicine in nearly every case where such commissions intervene; because they were not qualified to deal with the various aspects.

SENATOR MONDALE: I would like you to comment on one other issue—and once again, I mean it in the finest sense.

There is a quotation from one of the great clergy of our country that relates to the surgery that you performed in South Africa. I would like to quote from Rabbi Raskus who said this:

Is it all right to have the heart of a Negro inside you, beating for you, giving you life, but not all right to have him live next door? Is it perfectly permissible to use the kidneys of Negroes for one's welfare, but then to deny them the rights of employment and the opportunity to better their minds through education and protect their right to the pursuit of happiness?

* * *

DR. BARNARD: You see, sir, the statement that you have just read has been made by a man who does not understand medicine. And that is why he raises this issue. Because to a medical doctor, there are no boundaries, and we do not know any boundaries. And therefore we do not think along the lines that he has thought. For me to have taken out the heart of a colored man and put it into a European body was not an issue at all, because there was no difference for me between the two. And this is the danger you run into, when you have people making statements and deciding on things to be done they are not qualified to do.

* * *

NOTE 3.

TESTIMONY OF DR. OWEN H. WANGENSTEEN,
PROFESSOR EMERITUS OF THE UNIVERSITY OF
MINNESOTA MEDICAL SCHOOL, MINNEAPOLIS,
MINNESOTA—MARCH 8, 1968

* * *

Senator, I was a little worried by your letter in which you indicated . . . you had written to

200 people interested in the field; that you were going to study the problem and to suggest to the President and to the Congress directives which would do something for the field.

Now, if you mean support of research, that is good. I share Dr. Barnard's concern and worry over getting people into this field on the fringes, who do not really know much about the heart of the problem—the conscionable, dedicated, experienced people who are working day by day with the problem—these are the people who can speak knowledgeably and who can and must be trusted.

* * *

... If you are thinking of theologians, lawyers, philosophers, and others to give some direction here for the ongoing and for the development in this field, I cannot see how they could help. I would leave these decisions to the responsible people doing the work.

* * *

I think it is about like peeling an apple. The fellow who holds the apple can peel it best. I cannot conceive of 20 people holding an apple, and a man trying to get in there to peel it.

SENATOR MONDALE: ... I think there is also an assumption underlying some of the testimony that medicine has an option by which the public can be prevented from participating in these problems.

Is that in fact the case? Or is it to be assumed that the public will be involved, and rather an issue whether they will be involved in a sophisticated, responsible way, or whether we will be acting out of ignorance or prejudice, because of the absence of a responsible approach. ...

* * *

NOTE 4.

TESTIMONY OF CHIEF JUDGE DAVID L. BAZELON,
U.S. COURT OF APPEALS FOR THE DISTRICT OF
COLUMBIA CIRCUIT, MARCH 28, 1968

* * *

[S]ome mechanism will be needed for recording all these decisions. The impulse for this idea came from a session I attended at a large university general hospital on a Monday morning at 9 o'clock, when . . . they were to decide which of seven patients who were in need of dialysis would get the three places. And the decision was made that morning to select them. I was allowed to sit in on this meeting. The heads of the staff of the hospital were there. After they had gotten through with their discussion, which took about an hour and a half, they turned to me and said "What values do you bring from your end of the society that you think would bear upon these questions?" I was a little shaken by what I had just been through. I said "I have no wisdom except . . . the decision you made today should not be made behind those closed doors. Those doors ought to be open."

They said you mean we should have people in here who are not doctors or professionals?

I said—"No, make the decision now, you have to make it now. But let everybody know about it, let everybody know what went into it. Was it because he could pay money, or was it because he was young, or was it because he had a family, or was it because he was going to make a contribution to society—whatever was involved in deriving the decision."

Over time the public is going to react to this—but they are not going to know with that door closed.

* * *

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