Compensating for Research Injuries
The Ethical and Legal Implications of Programs to Redress Injured Subjects
Volume 2. Appendices

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Volume Two: Appendices

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research
Compensating for Research Injuries

The Ethical and Legal Implications of Programs to Redress Injuries Caused by Biomedical and Behavioral Research

Volume Two: Appendices

June 1982

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research
President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

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Social and Philosophical Perspectives
A Social Perspective on Compensation for Injured Research Subjects

Judith P. Swazey, Ph.D.*
Leonard Glantz, J.D.†

Introduction

Since the mid-1950's, the issue of compensating subjects for injuries related to their participation in research has been addressed from legal, economic, public policy, and, to a lesser extent, moral perspectives.† The purpose of this paper is to place the topic of compensation for injured subjects in a historical and socio-cultural context.² That context includes a perspective on the arena of research with human subjects, in which the compensation issue is embedded, as well as broader currents of societal concerns, attitudes, and values that influence, and are influenced by, research involving human subjects. Such a framework, we feel, is essential to understanding the issues around compensation, as well as to understanding why the subject has been afloat but unresoloved for a quarter of a century and why it is now under the purview of a Presidential Commission.

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February 1981

**The paper is based, in significant measure, on themes that emerged during a November 25, 1980 consultants' meeting of the President's Commission, convened to discuss socio-cultural aspects of compensating injured subjects. The meeting was attended by Mr. Alexander M. Capron, Mr. Alan Weisbard, and Ms. Barbara Mishkin of the Commission staff; Commissioner Renee C. Fox; and as consultants Professors Roy LeBove, Barbara Rosenkrantz, Stephen Toulmin, and the Authors.

†Mishkin, B. Background paper on compensation for research-related injuries, President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Nov. 1980.
Historically and socially, this paper places the compensation issue within the framework of the efforts to protect human subjects that were generated most specifically by the Nuremberg War Crimes Trials. Related topics that we have identified as providing a perspective on compensation issues include the nature of human subjects research, the social roles or attributes of research subjects, the gift-exchange dimensions of being a research subject, and the question of why, in 1980-81, there again is a surge of interest in and debate about compensating injured subjects.

Given the paucity of relevant historical and social science research and literature bearing on these subjects, this paper should be read as a provisional essay that, in large part, suggests topics needing more study and elaboration. We are not directly addressing the question of whether injured research subjects should be compensated, or, if so, what the form and substance of a compensation program or programs might be. However, we do share two views that emerge in the paper. First, available evidence indicates that compensation has not been a "significant problem" in terms of numbers of injured subjects or costs. Secondly, however, we feel that it is a significant issue socially and morally, irrespective of its actual magnitude, because of what it says about our values and attitudes toward the role of human subjects. And, with Childress, we would agree that compensation ought to be provided at least for research-related injuries under the moral principle of compensatory justice.*

The Protection of Human Subjects

Efforts to protect human subjects reflect an ambivalence in individual and social views regarding research. On one hand there exists an understanding that research is a social good and provides us with beneficial knowledge and techniques. On the other hand there are concerns and suspicions about the motives of researchers, the consequences of research and the use of human beings as experimental objects.4

* We are not, here, drawing distinctions between "normal" volunteers and patients or between therapeutic and nontherapeutic research; we are using "research" in the sense advocated by the National Commission For the Protection of Human Subjects, as distinct from nonvalidated practices or innovative therapies.5


4 Nelkin, D., and Swazey, J. Science and social control: controversies over research on violence, in H. Skolc, ed. SCIENTIFIC EXPERTISE AND
The very name of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research assumes a need to “protect” such subjects, while the title and content of M. H. Pappworth’s book, Human Guinea Pigs, demonstrates how a segment of the population views research on human subjects.

Concerns about the ways that human subjects could be used (and abused) in the name of research were solidified by the revelations of the Nuremberg War Crimes Trials. The resultant Nuremberg Code was the first formal ethical statement of the need to set standards for protecting the rights and welfare of human subjects. Societal concerns about human experimentation, however, have a long tradition. As early as 1767 an English judge condemned the use of a new device for setting broken bones. The judge found that use of the device was a “rash action” and said “he who acts rashly acts ignorantly.” As a more recent example, an American judge stated in 1926 that “a failure to employ the methods followed or approved by his school of practice evidence either ignorance or experimentation on his part. The law tolerates neither.”

Of course, both medicine and research have changed since these blanket condemnations were issued. However, they provide a perspective on one view of research, and indicate the widely shared belief that research subjects need protection.

Assuming that one believes that human subjects either need or deserve protection, such protection can arise before, during or after the involvement of human subjects. The goal of the Nuremberg Code is to offer protection to subjects both before and during research. It lists criteria for research which should not be conducted (e.g., where there is an a priori belief it will cause death or disabling injury) and discusses how it should be conducted (e.g., to avoid all unnecessary physical and mental suffering). The Code also gives the subject the power of self protection by stating that the “voluntary consent of the human subject is absolutely essential.” Not only does this mean all subjects must be free to refuse to participate at the outset, but also that they may withdraw their consent during the research if they so choose. Consent therefore works to protect the subject before and during research.

An additional before-the-fact protection involves the review of proposed research by someone other than the investigator. In


Owens v. McCleary, 313 Mo. 213, 281 S.W. 682, 685 (1926).
1971 the National Institutes of Health promulgated *The Institutional Guide to DHEW Policy on Protection of Human Subjects*, which required institutional review of research prior to its being conducted. This was codified into an institutional review board system in 1975. These institutional review boards are supposed to assure that the benefits of the research outweigh the risks, and that subjects give an adequately free and informed consent. The focus, then, is to prevent harm and to protect individual autonomy.

None of these mechanisms respond to the question "What happens if these safeguards fail and the subject is injured regardless of our efforts?" We believe that this is one of the reasons why the question of compensation has arisen and is important. It is a logical extension of the mission to protect human subjects from harm. Once an injury has occurred it cannot be undone, but its impact on the individual can be reduced by compensating him for his loss.

We would also point out that this concept is far from new. When Walter Reed studied yellow fever in Cuba each volunteer was paid $100.00 'to participate' but received an additional $100.00 if he contracted the disease.

Our willingness or unwillingness to compensate research subjects is indicative of our attitudes toward them. During the Nuremberg War Crime Tribunals the defense lawyers demonstrated that in one experiment involving infecting conscientious objectors and prisoners with malaria, the conscientious objectors were insured and the prisoners were not. Part of the colloquy follows.

Q. Witness, on the basis of your great experience, don't you have any idea why there was this distinction? You are an expert in all these fields.

A. Well, I presume it was out of sympathy for the C.O.'s. The soldiers in the Army were insured by the government, and, I thought—I should believe that might have been thought to be a good idea to insure the C.O.'s for the same reasons that they were taking experiments that had a small amount of hazard in them.

Q. Was there sympathy not felt in the case of prisoners who had volunteered for experiments on behalf of the general public?

A. I had nothing to do with that or determining the conditions. Thus I cannot answer "yes" or "no."

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The Present Climate of Concerns about Compensation

As the foregoing quotation indicates, discussion of whether or by what means injured research subjects ought to be compensated is not a new topic. Its legal and policy dimensions have been aired, largely by academics, for some 25 years, and by the Federal government for a decade. But it has generally been a low key dialogue, conducted within small circles, and seemingly has never been a "hot" enough issue to be resolved at a Federal policy level.

Federal Initiatives

The fact that NIH developed three compensation proposals during the 1970s, and that the compensation question has been part of the mandate of three Federal-level commissions concerned with biomedical ethics, is both part of the answer and part of the question of "why the interest and discussion?" In terms of identifying an organized "constituency" that has generated and sustained discussion of compensation for injured subjects, it is the Federal government through its various task forces and reports. Why this has been the case, however, is not clear from published documents. beyond the fact of the government's role as a major sponsor and conductor of research involving human subjects.

The very fact that this discussion has been carried on for so long, even without resolution, is indicative of the strength of the perceived need to protect human subjects through a compensation mechanism.

Relief from Liability

It should also be noted that the issue of compensation is not merely of interest to those who wish to protect subjects. By having a no-fault compensation system similar, perhaps, to workers' compensation, it would be possible to relieve sponsoring organizations from liability.*

As is widely known, the drug manufacturers would not produce swine flu vaccine until the Federal government agreed to indemnify them against loss from suits filed by injured recipients of the virtually untested vaccine.1 The desire to limit the legal liability of sponsors also stems from the realization that injury from new drugs and devices may not become apparent for years or even generations.

* Surprisingly, there seems to be no interest on the part of investigators to support a no-fault compensation system even though it might give them some measure of protection from lawsuits. One can speculate that this is due to the fact that there are virtually no lawsuits against investigators arising out of research activities.

The Role of Bioethics

As the activities of the National Commission, the Ethics Advisory Board, and President's Commission suggest, the development and influence of the "bioethics movement" during the 1970s seems to be another factor that has stimulated concern with compensating injured research subjects. Although the bioethics literature that deals directly with this topic is slight, human experimentation has been a major focus of analysis by those engaged in the application of ethics to medical arenas. Like the topic of research with human subjects, the bioethics movement needs more historical and sociological study for us to fully appreciate its nature and import. In this context, the creation and role of the National Commission, the Ethics Advisory Board, and the President's Commission are phenomena that merit analysis, for it is by no means self-evident why "bioethics" has thus entered the arena of Federal health/medical policy deliberations during the 1970's and 1980's.

Regulations and Laws

Closely interrelated with the attention that bioethics has paid to human experimentation has been the development of regulations and laws governing research with human subjects. The development of institutional review boards, in particular, as a system designed in principle to protect the rights and welfare of subjects, has made sponsors, investigators, and institutional officials far more aware of the legal and ethical issues involved in human subjects research, including injury-related compensation. Attention to compensation issues was fostered, most prominently, by the hotly debated "Interim Final Regulation" issued by HEW in November 1978, requiring a consent form to include a statement about whether or not a subject will be compensated for injury in terms of the provision of medical care. This requirement has been incorporated into the new DHHS regulations on research involving human subjects.

Broader Societal Concerns

Concerns about compensating injured subjects, then, are one facet of social, ethical, and legal concerns about the conduct of research with human subjects that have been marked in

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16 46 FED. REG. 8365, sec. 46.116 {a} (6), Jan. 26, 1981.
American society since Nuremburg. But these concerns, in turn, have been generated and responded to in relationship to broader societal concerns, which human subjects research both reflects and has helped to foster.

At many levels, from many quarters, and on many fronts, for example, there is an enhanced concern about "victims"—real, imagined, or potential—of all kinds: of human experimentation, medical and psychiatric care, environmental hazards, the educational system, socioeconomic deprivation, crime and so on. There also is a related awareness of and concern about groups with inequality in bargaining power—research subjects, patients, the residents of a Love Canal, "9 to 5" employees, etc. These various concerns evoke thought about, and in some cases actions predicated on, our views about individual and collective rights and responsibilities.

Those who are members of groups who have suffered in the past due to their unequal and unfair treatment have, since the 1960's, come to insist that their rights be recognized, and that they be afforded fair treatment. The Civil Rights movement has forced us to examine our values and treatment of certain unfairly treated groups. We have very recently in our social history come to recognize the rights of women, prisoners, mental patients, tenants, military personnel, children, teachers, homosexuals and a variety of other groups. These movements have clearly had an impact on thinking about the "rights of research subjects," and cause us to examine our treatment of and responsibilities toward members of this class of persons.

Viewed in this broad societal context, the issue of compensating injured research subjects is but one of many issues that should compel us to articulate our standards of personal, institutional, and governmental responsibilities. What, for example, are or should be our moral principles about justice as fairness, and how in turn do we concretely act (or fail to act) on cases involving compensatory justice?

Another, related social current has been an intertwined populist questioning, doubt, and suspicion about "big" and "powerful" institutions such as government, medicine, and science, and about the authority and power that we have vested in experts of all kinds. In the area of research with human subjects, this current is seen in apprehensions about the ways researchers and research agencies, including the Federal government, can mislead, exploit, or injure subjects in the name of patient welfare, scientific progress, or public good. Widely publicized reports of projects such as the Tuskegee syphilis study and the Jewish Chronic Disease Hospital cancer experiments, and revelations about the CIA's LSD experiments and biological warfare testing accidents at Dugway proving ground, have been lightening rods for attracting attention to problems in the governance of research.
and the protection of human subjects. Indeed, the Tuskegee study and the CIA’s LSD experiments required an examination of how we should compensate injured subjects.

Recognition of the possibility that research subjects, however inadvertently, might suffer injury, and the sense that such injuries ought to be compensated for, also are linked to what seems to be a pervasive societal malaise or preoccupation with problems of uncertainty and anxiety about danger and risk. The sense that in many aspects of our lives we have become “a nation of guinea pigs” is reflected in a lexicon of phrases that capture our concerns and counter-concerns about uncertainty and risk (necessary risk, acceptable risk, risk-acceptance, danger-of-danger, risk-of-risk, uncertainty-of-uncertainty), and a new occupational category of institutional “risk managers.” As Cournand observed in 1977, “The American public is being swept by a medical epidemic characterized by doubt of certitude, recognition of error, and discovery of hazard.”

Spreading Risks and Costs
One facet of our widespread concerns about risk and uncertainty that is particularly germane to the compensation issue involves the ascertainment of the true costs and risks of research and who should bear those costs and risks. One of the costs and risks is the impact of injury on research subjects. We can choose to have the injured subject bear this cost or spread the cost via a compensation program. In this way those who benefit from the research would help bear its costs and risks. Viewed this way, the goal of such a scheme is to reduce a potential harm to subjects and increase the responsibility of its benefactors. Thus, although a program to compensate those suffering from black lung raises the price of coal, and general workers’ compensation insurance may raise the cost of goods, these higher costs more accurately reflect the “true” cost, and serve to protect those who provide us with goods and services.

To look at this issue from another point of view it could be asked, "What social and cultural values would be furthered by refusing to compensate injured research subjects?" It might be argued that such a program would be unduly expensive. It would seem this argument would be based on an assumption that there is a great deal of injury caused by research. All available evidence would seem to indicate otherwise, but if it were true this would be a stronger argument to compensate those individuals.

It might also be argued that such a system might be too difficult (and expensive) to create and administer. That is, it would require a major expenditure of personnel and funds to administer a program that would benefit a few who are insignificantly harmed. There is no doubt that the creation of such a program creates sophisticated problems. How is "harm" or "injury" to be defined, who is to decide if it occurred in individual cases, on what basis should the amount of compensation be calculated, and numerous other problems must be solved. It may even be determined that such a system would be so costly in comparison to the good it would do that it should not be developed. Should these practical difficulties result in a compensation program not being developed, it might be the "right" choice—but a choice which sacrifices the furtherance of other social-cultural goals.

The idea of the shifting of the burden from the subject to another entity in the essence of fault is also not new. There are a number of older cases that stood for the proposition that "if a physician sees fit to experiment with some other mode, he should do so at his peril." These cases, strictly speaking, deal with innovative therapy, not true research. But they are quite clear that the risk of loss should be with the researcher, not the subject. Such a rule served to deter reckless research, as well as shift the burden to the person who might most benefit from the research—the researcher learns even from unsuccessful procedures that do not benefit subjects.

What seems to us, as to others, to be a present inequity in the lack of a consensus about a policy for compensating injured subjects may be illustrated if we think about research in terms of its two major participants—investigator and subject. If a program was proposed that would place the entire burden of non-negligent research-induced injury on the investigator there is every likelihood that it would be rejected promptly as being unjust and counterproductive. It also would be rejected because investigators, unlike subjects, form a constituency, have power, are capable of self-protection, and are able to assess and assert their self-interests. We certainly do not propose such a system, but use it to point out the unfairness of the present situation. Subjects bear this burden, whether larger or small, because of

their social role and the quirk of personal injury law, not because of social policy or theories of justice.

Research and the Human Community

A final example of why there seems to be a social climate that evokes attention to the issue of compensating injured research subjects is a more positive one than those discussed thus far. It involves the ways in which biomedical research and therapeutic innovations such as dialysis and transplantation constitute a paradigm of several cultural, moral, and religious problems with which modern Western society is grappling. In its ideal form, the relationship between investigator and subject is seen as very different from that evoked by the Tuskeges of human experimentation. Ideally, the investigator-subject relationship is seen as the prototype of the new solidarity toward which modern man is groping. A vision is invoked of a society conducive to the establishment of relationships in which individuals of diverse backgrounds and conditions "collaborate, in equality and trust to realize 'distinctively human ... noble,' melioristic goals." It is in this sociocultural and moral context, as discussed in a later section, that we see the importance of the gift-exchange dimension of being a research subject.

Research and Human Subjects

Part of the difficulties that have surrounded legal and policy efforts to deal with the issue of compensating persons for research-related injuries, it seems to us, resides in our lack of understanding about the development, social roles and attributes of clinical research and its participants. The centrality of research in medicine, particularly in American society in recent decades, makes it easy to forget that the role of the professional clinical investigator and the institutionalization of clinical research are historically recent, 20th century developments.

The topics related to research and human subjects that we would flag as particularly relevant to placing the compensation issue in a historical and sociocultural context include the following.

• How has "research" been defined, particularly that involving human subjects, in terms of the interrelationships between its content, methods, and objectives?

The continuing discussion about whether or how we should distinguish between therapeutic and nontherapeutic research, for

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26 Ibid. p. 381.
example, bears on the compensation issue if one wishes to make the "type of research" in which a subject has participated a relevant criterion for a compensable injury. Here, the question is usually framed in terms of whether we ought (morally, or as a matter of social policy) to compensate only those who participate in research not intended to potentially benefit a medical problem that afflicts them. Such a direct benefit, presumptively, removes the "altruistic" or gift-giving component of being a research subject for the good of society, and therefore makes an injury non-compensable in terms of principles of compensatory justice.

A related variable, to some, turns on distinctions between "normal volunteers" and "patient subjects," with only the former category viewed as potentially eligible for compensation. (A parallel argument that we have heard is that it is morally acceptable to pay "normal volunteers" for their participation in research, but not those classified as "patients").

Here, we would only note briefly that distinctions between therapeutic and nontherapeutic and normal volunteer and patient can become complex, both medically and socially. In terms of compensation, policy decisions will have to wrestle with the question of whether the intent of the investigator or of the subject are relevant variables. Or alternatively, for example, in the case of patients should the question not be intentionality but whether there is an added component of risk by virtue of a research dimension to a patient's care and treatment?

Decisions about compensation also bring into play broader sociomedical questions about what it is that constitutes "research," and in turn being a "research subject." Most would agree that not everything deviating from standard practice constitutes research. But where then are the boundaries to be drawn? Is a physician using an approved drug for an unapproved purpose engaging in research, and the recipient of that drug thus a research subject? Or, as proposed by the National Commission for the Protection of Human Subjects, does such drug use, innovations in surgical procedures, etc. fall into a category of "non-validated practices" rather than "research"? In a compensation program designed to cover only subjects in Federally sponsored research, these questions can be avoided by operationally defining as "research" that which is funded or reviewed as research. This solution, however, begs the broader social as well as medical question of how research is to be defined, and by what criteria.

- How has clinical research changed during the 20th century in terms of its social structure and organization?

This question, which is about the sociology of modern medical research, involves examining changes in the settings and modes

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of organization and operation of the research in which investigators and their subjects are involved. While not rigidly separable into discrete phases, clinical research has evolved, particularly since World War II, into an "industry." There has been a progressive shift from the type of small, collegial, personally intensive units such as those depicted in the 1950's by Means and Fox to larger, more impersonal, and bureaucratic enterprises in industrial and governmental as well as university-based settings. The growth of a clinical research industry is linked with certain changes in the social roles and attributes of research subjects, and both in turn are important dimensions of understanding the direction of concerns about the conduct and objectives of human subjects research.

- **How are research subjects and their role perceived?**

This question, we believe, is central to decisions about compensating subjects for research-related injuries. Moral claims and political and legal arguments for or against compensating injured subjects rest in part on our perceptions of what it is to be a research subject—what the act entails and what social role it involves.

Like research itself, our views of the research subject are ambivalent and shifting. For example, one can think of three quite differing societal images of the research subject since the 1950's. In the 1950's, a predominant view was that of the research subject as hero or as selfless societal benefactor. Patients who also served as subjects, such as those portrayed in Fox's *Experiment Perilous*, the physician-investigators who carried on medicine's long tradition of autoexperimentation, and the normal (healthy) persons who volunteered to contract malaria, inhale new nerve gases, be injected by curare, etc. were recognized, valued, and often celebrated for giving of themselves to advance medical knowledge and technique. The Walter Reed Society, composed of some 500 persons who had volunteered for high-risk experiments, embodied a view of research subjects as identifiable, often heroic societal benefactors.

[One of the] functions of the Walter Reed Society is that of granting recognition to human guinea pigs. Membership is by invitation, and each member receives a certificate commending him for the self-sacrifice through which he has made a gift toward greater knowledge for the maintenance...

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23 Davidson, B. *So he took the cobra venom and shot it into his arm*, COLLIERS, NOV. 1, 1952, pp. 52-55.
of health, the relief of suffering, and the prolongation of life to all peoples of the earth.

During the 1960's there was a dramatic shift in our image of the research subject, from hero to victim. Public revelations about the research projects associated with the names thalidomide, Tuskegee, Willowbrook, and the Jewish Chronic Disease Hospital, linked with recent memories of the human experimentation conducted in Hitler's Germany, focused attention on the possible abuses of the rights and welfare of subjects in the name of research. The importance of research, and the necessity and value of the research subject, continued to be affirmed. But now, drawing too from other events in society such as the Civil Rights movement and the war in Vietnam, there was an added emphasis on the need to protect such subjects—to prevent them from becoming victims.

The growth of the clinical research "industry" during the 1960's and 1970's helped to shape another image of the research subject, one that seems to predominate today. As research increased in volume, especially with the growth of Phase 1 drug studies and large controlled clinical trials, it became organizationally more bureaucratized and the role of the research subject became more routinized and less visible. Research subjects have become less readily identifiable, either as heroes or victims. While not "employees" in literal terms, we tend to see—or not see—them much as we do the nameless, faceless workers in a large bureaucracy. And, to the extent that subjects are perceived, dimly, as "faceless employees," they have less and less of a constituency who identifies with them and thinks about the role they are playing in society. With respect to the compensation issue, our sense is that normal arguments and political actions are likely to be far more intense in the case of identifiable lives—whether of heroes or victims—than in the case of faceless employees. On the other hand, to the extent we do think of research subjects as like employees, the more apt we should be to think about compensating them for "work-related" injuries.

How the research subject is perceived—by those involved in research and by other segments of society—has links with but is not identical to the question of why persons participate in research. The factors that motivate both investigators and subjects to engage in research, and that both create and offset the strains attending these roles, are important to understanding the psychosocial dynamics of research with human subjects. But, as we view the issues most relevant to compensation, they do not include the complex problem of discerning motives and intentionality.

Research and Gift-Exchange

A dimension of the research subject's role that we see as central to the compensation issue, and one that to our knowledge has not been considered previously, is that of gift-exchange. Legally, one is under no obligation to repay a gift. But the sociological norms of gift-giving are quite different from legal norms. As discussed by Mauss in his classic anthropological work The Gift, the act of gift-exchange is structured by a triple set of "symmetrical and reciprocal norms": the obligation to give, to receive, and to repay.\(^3^3\)

By this [Mauss] meant that under certain socioculturally defined circumstances, an individual or a group is supposed to offer a gift to a particular person. In turn, the person (or persons) to whom the gift is proffered is expected to accept it. The recipient is then under social and moral pressure to balance out the exchange by giving the donor something of equivalent worth. Failure to live up to any of these intertwined expectations produces disequilibrium and social strain that affects the donor, the recipient, and those closely associated with them.\(^3^4\)

The gift or donative element in the act of being a research subject was recognized in the certificate of membership in the Walter Reed Society quoted earlier. It is this facet of being a research subject that underlies the metaphors of heroic action and sacrifice, of incurring risk for the good of others, which have been used particularly with reference to research participants such as those belonging to the Walter Reed Society. But all individuals, we would argue, are giving of themselves in special ways, both literally and figuratively, when they agree to serve as research subjects. Although their role is institutional, it is not a usual one, in part because of the special, if commonly undramatic, ways in which and reasons for which they are asked to give of themselves, physically or psychically, for the good of others. Framed in terms of gift-exchange norms, research with human subjects is a societally valued enterprise. Research is central to the goal of advancing medical knowledge, for the benefit of both individuals and society as a whole, and it is recognized that man is "the animal of necessity" at certain phases of medical research. Under this sociocultural view of research, we are all under a certain pressure or obligation to serve as research subjects; or, in the language of ethics, to bear certain, usually minimal, burdens for the common good based on principles of justice. In turn, we expect society to accept the gift of one's being a research subject, and to then deal with its obligation to repay that gift.

Footnotes:
- Fox, R., and Swazey, J. THE COURAGE TO FAIL, op. cit., p. 6.
How society can or should honor its social and moral obligation to repay the gift being proffered by the research subject is, in itself, an interesting and complex question. But one definable aspect of such repayment seems to us to occur in the case of research-related injuries. The norms of gift-exchange argue sociologically, as does the principle of compensatory justice morally, that we have an obligation to compensate subjects for injuries they incur through the gift they give to society by being a research subject.

"The theme of the gift, of freedom and obligation in the gift, of generosity and self-interest in giving reappear in our society like the resurrection of a dominant motif long forgotten," wrote Mauss. Policy decisions about whether we ought to compensate injured subjects, as Mauss' words remind us, need to incorporate within their matrix the motif of gift-exchange and its reciprocal norms.

Who Are Research Subjects Like? The Pandora's Box Argument

In the often tangled arguments that have been voiced about compensating injured subjects, two recurrent concerns have been (1) that compensation programs would "bring clinical research to its knees" and (2) that compensation programs would open a "Pandora's box" of issues about and demands for similar no-fault compensation policies for persons inadvertently injured as a result of their participation in many other social roles.

The first tocsin is one that we consider to be outside the scope of this paper. It seems to turn on and fears that demands for compensation would be so numerous and the administrative and compensation costs of a program or programs so enormous that we (society) could no longer afford to do research with human subjects. Here we would only note that such concerns (a) rest on thus far unfounded assumptions that could be tested by pilot compensation programs, of which a few are already in existence, and (b) that they bypass the prior and more fundamental social policy question of whether we ought to compensate injured subjects.

The second concern—are we opening a Pandora's box?—is one that we have partially addressed in this paper by examining the social role and attributes of research subjects. Our admittedly provisional analysis suggests that research subjects share some characteristics in common with other classes of persons. For example, like blood, tissue, and organ donors they participate in a gift-exchange act that, sociologically, involves powerful norms of obligations to receive and repay as well as to give a gift of oneself. In certain instances, like volunteer firemen and soldiers, they elect to undertake risks that we recognize as especially heroic or

self-sacrificial in nature. In other cases research subjects are seen as belonging to a class of victims, whose rights and welfare are exploited by more powerful others.

At the same time, however, we cannot identify research subjects as being exactly like any other class of persons who occupy a definable social role. This, in part, is because research subjects do not constitute a readily identifiable group like, for instance, volunteer firemen. One consequence of this is that, with the exception of refusing to participate in research, subjects have little ability to protect themselves. They have no common goal, union, club or lobbying group. Subjects, for the most part, are involved in research for a relatively short period of time and cannot form a self protective organization. They will never collectively be in a position to demand protection and therefore form no constituency. Therefore this form of protection, like those discussed above, must come about not by demands from subjects but from those concerned with their protection.

These considerations are among those that we see as setting research subjects apart from other classes of persons who engage in potentially hazardous activities. To the extent that research subjects are virtually unique in terms of their attributes and social role, social policy decisions about compensating them for injuries thus can be seen as a unique case, one that does not open up a Pandora's box of many classes of compensation for non-negligent injury.

On the other hand, finally, we do see the case of compensation for injured research subjects, in important and appropriate ways, as stimulating us to think about a transcendent range of moral and social policy issues. These issues, as we have suggested, have to do with defining and acting on our views of individual and collective responsibilities as well as rights, with our sense of justice, and with whether we should relate to each other not only as our brother's keepers but our "stranger's keepers" as well.

Compensating Research-Related Injuries: Ethical Considerations

Holly M. Smith, Ph.D.*

This paper constitutes an exploration of the ethical justifications (or arguments against such justification) for providing compensation to experimental subjects for research-related injuries. Many of the pertinent issues have been dealt with extensively in reports commissioned for the HEW Secretary’s Task Force on the Compensation of Injured Research Subjects, and in the paper entitled “Compensating Injured Research Subjects: I. The Moral Argument,” which grew out of James Childress’s presentation before the Task Force.1 Hence I shall not attempt to provide a complete analysis of the problem starting from scratch, but rather confine myself to clearing up possible sources of confusion or error in these previous reports, and to examining aspects of the problem or arguments bearing thereon that have been overlooked in the earlier materials. Consequently this paper will not present a wholly continuous line of argumentation. In the first three sections I will lay down some of the conceptual foundations that are necessary for a clear view of the problem. The fourth section will be devoted to an examination of the arguments that have been, or might plausibly be, offered in favor of compensating injured research subjects. The fifth section will address secondary practical questions, e.g., the question of whether the possibility of abuses can legitimately be taken into account in designing or adopting a compensatory program. To fix ideas I shall primarily concentrate in Section 4 on what I regard as the

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core case: a subject who freely volunteers, without renumeration or other advance consideration, to participate in a research project that is not designed to benefit the subject either medically or otherwise (commonly known as "non-therapeutic" research).

The Varieties of Moral Status

Ethical theory commonly recognizes different types of moral status that an act might have. Thus compensating injured subjects might be wrong, morally neutral, morally permissible, supererogatory, or obligatory to greater or lesser degree.

A case can be made out that compensating injured subjects is at least presumptively wrong. Compensation involves the transfer of funds from one group (the taxpayers who foot the bill) to another group (the injured subjects). Now, a democratic government can be viewed as an agent of the people that merely carries out the people's will. On this view such transfers constitute a free act of the people. However, there are many possible alternative uses for the resources that would be used in compensation—the funds could be used to achieve a higher level of medical or welfare support for the poor, better education, a stronger defense capacity, swifter and surer justice in the courts, less inhumane conditions in the prisons, fewer deaths from starvation among the impoverished overseas, and so forth. It seems plausible that the people have obligations to achieve at least some of these alternative goals, obligations that could be fulfilled (to some degree) by the funds that would be used for compensating injured subjects, but will go unfilled if compensation is chosen instead. Hence the use of funds is presumptively wrong; wrong all things considered unless there are opposing moral considerations in favor of compensation, considerations at least as powerful as those supporting the use of funds for some of these alternative purposes.

Moreover, it is not clear that a democratic government always acts as the mere agent of the people. Sometimes it appears rather as an independent actor that coercively extracts resources from the people to be used for various ends. Such coercive taking of private possessions is wrong unless contrary moral arguments exist to justify it. Hence on this ground as well we can say that there is a moral presumption against the use of public monies for compensating research subjects. If the practice is justified, it must be in virtue of powerful arguments in its favor. Consequently in subsequent sections I shall focus on positive arguments that purport to fill this bill.

From the foregoing we can see that compensation is not a morally neutral act, i.e., one without any moral quality, either positive or negative. If there is nothing positive to be found in favor of compensation, then it is morally wrong. But if positive considerations at least match the negative case, compensation
might assume any of the types of moral status listed above. If the positive and negative considerations exactly balance out, then compensation is merely morally permissible: compensation and failure to compensate have equivalent moral status, neither one being wrong. If positive considerations outweigh the negative case, compensation might be supererogatory: morally superior to failure to compensate, but such that failure to compensate would not be wrong. The classical example of a supererogatory act is that of a soldier who volunteers for a suicidal mission designed to save the lives of his trapped comrades. But some supererogatory acts are merely "favors" of less heroic stature—for example, turning all one's canned goods price-side-up in a supermarket line in order to aid the check-out clerk. Heroic or not, supererogatory acts are acts beyond the call of duty. Alternatively, compensation might be obligatory: morally superior to failure to compensate, and such that failure to compensate would be wrong. Some obligatory acts are only mildly so—failure to perform the act would be wrong, but only a minor dereliction. The obligation not to break into ticket queues is of this order. Other obligatory acts are more stringent—failure to perform the act would be a serious wrong. The obligation not to kill another human being is of this sterner order. There is a good deal of disagreement about where to draw the line between supererogatory acts and mildly obligatory acts. For example, people of a more libertarian stripe consider charitable gifts as obligatory; people of more libertarian inclinations view them as merely supererogatory.

Possible Reasons for Action
The diverse reasons for acting can conveniently be divided into three categories: there are reasons of self-interest; reasons involving beneficial effects on other persons; and reasons that we can call "deontic"—those involving duties arising from considerations, such as justice or fair dealing, that do not simply involve beneficial consequences of the act.

Normally it is supposed that self-interest does not provide a moral reason to perform an act. The fact that becoming a physician would make one happiest over the long run does not establish even a presumption that choosing this career would be morally right. In light of this one might suppose there is no moral presumption in favor of state action that promotes the social good: a collection of individuals who act to promote their own welfare is morally indistinguishable from the single person who becomes a physician merely to promote his or her private happiness. On this view, no moral presumption in favor of governmental insistence that injured subjects be compensated is established by the fact (which we can assume for hypothesis) that compensation would attract more volunteers and so raise the level of medical care available to the citizenry. Such a position seems to be
reflected in Englehardt's comments. But we must not adopt this position too hastily. In cases involving state action to promote "social good," the actor and the beneficiary of the act are often not identical. Increased medical research that would benefit United States citizens would also benefit citizens of other countries, including those that could not fund comparable research themselves. Moreover, many of the beneficiaries would be members of future generations, distinct from the present United States citizens who would be responsible for the promotion of research through compensation, and who would foot the bill. Finally, even within United States boundaries and within the present generation, many of the beneficiaries of such a policy could not be counted among the participants in any decision to pursue it: children, the mentally retarded, and persons (like felons) without a vote would not be responsible for such a decision, and the untaxed poor would not bear the burdens involved in supporting it. Hence the hypothetical fact that compensation would promote "social good" in at least these categories of persons does establish a moral presumption in its favor, despite Englehardt's argument to the contrary.

Actions that produce good effects for other persons are often lumped together under the catch-all title "beneficent acts." However, it is important to recognize that there are different kinds of good effects. For example, one might identify some level of human welfare as minimally acceptable—a sort of "poverty line" below which no one should fall. Some beneficent acts, such as giving money to the Rockefellers, raise the beneficiary above this level, perhaps far above it. Other beneficent acts, such as providing gratis medical care for indigent patients, raise the beneficiary up to the minimum level or at least closer to it. Even if giving ten dollars to a poor person would produce no more happiness than giving a thousand dollars to the Rockefellers, the former act seems morally preferable. When people think of beneficent acts, they often focus only on the sort that raise people above the minimum level, and hence regard beneficent acts in general as merely supererogatory rather than obligatory. Remembering that some beneficent acts improve the position of persons below this minimum level may make it seem more plausible that at least some beneficent acts are obligatory.

Actions for which there are "deontic" reasons form a heterogeneous group. Obligations can arise from a number of deontic sources: one has a duty to keep one's promises and to tell the truth; one has a duty to deal justly—to distribute benefits and

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1 Tristram Englehardt, Jr., A Study of the Federal Government's Ethical Obligations to Provide Compensation for Persons Injured in the Course of Their Participation in Research Supported by Funds Administered by the Secretary HEW, Appendix A, Report of the HEW Secretary's Task Force on the Compensation of Injured Research Subjects (1977), pp. 48-49.
burdens fairly, to punish the guilty, and to rectify past wrongs; one has a duty not to violate the rights of others. Dealing justly with a person does not necessarily involve fulfilling his or her rights; justice may require a criminal to be punished, but we would not say that the criminal has a right to this treatment. A noteworthy feature of obligations arising out of rights is that the right-bearer is in a position to waive the right and so dissolve the obligation.

Engelhardt's and Childress’s discussions reflect the common assumption that an obligation to benefit others is always weaker than an obligation that arises from the necessity to do justice or to fulfill rights. However, this seems false as a general proposition, especially when we consider that some beneficent acts have the effect of raising someone towards (or keeping them from falling below) the level of minimally acceptable human welfare. The fact that considerations of beneficence sometimes outweigh considerations of justice or rights shows that the obligation to be beneficent can be the stronger. The fact that I have promised to meet you for tennis at a certain time establishes a deontically grounded presumption that doing so is obligatory; but the fact that I am the only person available at that same time to begin cardio-pulmonary resuscitation on a heart attack victim establishes a contrary, and stronger, presumption that I ought not meet you for tennis. Deontic obligations can be quite mild, and beneficent obligations can be quite stringent.

Consent

One of the issues to be addressed is the nature of the relationship between the obligation (if any exists) to compensate an injured research subject, and the consent given by that subject to the experiment. To pinpoint the relevant considerations we must distinguish several possible questions.

First we must be clear on the difference between the following two queries:

(A) Ought an injured research subject be compensated who has merely consented to participate in the experiment itself?
(B) Ought an injured research subject be compensated who has consented to participate in the experiment and not be compensated if injury should occur?

The scope, and therefore the effect, of the minimal consent described in Question A is quite unclear. From the fact that a subject signs a form agreeing to participate in an experiment we can infer nothing about his or her state of mind with respect to compensation: perhaps the subject realized that compensation was not promised and so would not be forthcoming, and (mentally) consented to this; perhaps the subject implicitly believed, despite lack of assurance on the matter, that compensation would be forthcoming, and agreed to participate only on this understanding; or perhaps the question simply never occurred to the
subject. In the latter case it is difficult to know what we should say. Fortunately we need not resolve this question, since HEW now requires consent forms to explicitly state that compensation will not be forthcoming when it will not. This means we need not answer question A.

Second, we must note the distinction between Question B on the one hand and Question C on the other:

(C) If an injured subject has consented to participate on the promise of compensation for injury, but would have consented to participate without the promise of compensation, ought the subject to be compensated?

Clearly the answer to Question C is "yes." Once compensation is promised, an obligation to provide it is established, whether or not the subject would have been willing to agree to some other arrangement. But this issue is distinguishable from the following one:

(D) Ought compensation to be offered in advance to subjects who would be willing to participate without the promise of compensation?

Certain of the arguments to be examined in later sections address themselves to this query.

Finally, we must distinguish the following two questions: (E) Ought an injured subject be compensated who has consented to participate without compensation, but who desires compensation after the injury has occurred?

(F) Ought an injured subject be compensated who has consented to participate without compensation, and who does not want compensation after the injury has occurred?

The situation envisioned in Question F is undoubtedly rare, but the answer to this question is obviously "no." We have no obligation to force compensatory payments on someone who does not want them; in fact our obligation is just the reverse. The real problem, then, is raised by Question E.

Arguments in Favor of Compensation
A survey of the relevant philosophical literature reveals seven arguments that have been offered in favor of compensating injured subjects. In the case of some of these arguments, the subject's consent or lack thereof plays little or no role; in the case of other arguments it plays a large role. In this section I will describe each argument briefly, and then examine them in more detail.

1. The argument from beneficence. The costs of compensating injured subjects are outweighed by the good effects to be achieved, both for the injured subject and for society. Hence we ought to compensate.
(2) The argument from the moral tone of society. Compensation functions as a dramatic expression of society’s concern for those who have suffered on its behalf, and hence should be undertaken.

(3) The argument from society’s benefit: When one person acts in a way that benefits the group, the group owes the individual compensation for any resulting harm suffered.

(4) The argument from gratitude. When an individual suffers harm in order to benefit the group, the group owes a debt of gratitude that can be repaid by compensating for the harm suffered.

(5) The argument from harm suffered at society’s behest. When an individual acts at the behest of society to benefit society and suffers harm in consequence, society owes that individual compensation. (Childress)

(6) The argument from H. L. A. Hart’s principle of fairness. According to Hart (and other philosophers), when a group conducts a joint enterprise according to rules and thus restricts their liberty, those who have submitted to these restrictions when required have a right to a similar submission from those who have benefited by their submission. The research subject has submitted to “restrictions” involved in participation in research, and so has suffered; he or she therefore has a right that society, which has benefitted thereby, should now acquiesce in compensating the injury.

(7) The argument from lack of consent to the injury. Even though the subject signs a consent form stipulating that compensation will not be forthcoming, nonetheless he or she only genuinely consents to bare participation, not to the lack of compensation. Hence when injury occurs, it constitutes an unconsented-to violation of personal rights, and must be compensated. (Englehardt)

The Argument from Beneficence. According to the argument from beneficence, there are important good effects to be secured, and bad effects to be avoided, by compensating injured research subjects. If these effects have sufficient magnitude, it is concluded that society has an obligation to compensate; if their magnitude is less, it is concluded that society would perform a supererogatory act by compensating.

The good effects to be achieved may accrue either to the injured subject (or his or her family), or to society. Some of the possible good effects are what we might call material while the

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* Childress, op. cit., pp. 24-25.
* Englehardt, op. cit., pp. 50-55.
others are attitudinal. Thus, for example, the injured subject gains “materially” from provision of medical care and financial compensation for lost wages. There may be “attitudinal” benefits as well, if compensation enables the subject to feel that he or she has been equitably treated rather than exploited by the research establishment. Advocates of the argument from beneficence typically cite, as material gains for society, such effects as the following: elicitation of more volunteers whose participation facilitates more and better research; encouragement through market mechanisms of a higher level of care for research subjects; reduction of loss of productivity from injured subjects; pursuit of risky but highly valuable research that would not be morally permissible without the assurance of compensation; removal of disincentives among researchers stemming from possible liability to civil suit in case of injury to subjects. Attitudinal gains might include the encouragement of good will towards the medical and research establishments, and promotion of solidarity between the sick and the well.

Whether or not these or other effects would actually be produced by a compensation program is an empirical question that I am not in a position to answer. Three related points need to be emphasized here, however.

First, whether or not any given good effect is produced depends to a large degree on the specific nature of the compensation program employed. To take an obvious example, a scheme according to which the facility immediately conducting the research has no direct financial responsibility for compensating injured subjects will have no tendency to encourage such facilities via market mechanisms to employ a higher level of care with respect to their subjects. But the major point here is that we cannot speak of the good effects of “compensation” in the abstract, but only the good effects of some concrete program.

Second, it is not enough to show that a particular scheme would produce certain good effects. It must be shown that the total effects of the scheme—both good and bad—are better than the total effects of not compensating. Certain kinds of programs are likely to give rise to concrete bad effects, and these must be taken into account. For example, because of the difficulty of filtering meritorious claims from non-meritorious ones, and the difficulty of deciding for what classes of injured subjects compensation is morally required, arbitrary distinctions may have to be drawn in determining who receives compensation and who does not. This in turn may unavoidably give rise to the appearance of inequity, and resulting undesirable attitudinal effects among the subjects and population at large. These sorts of effects, as well as positive ones, must be all taken into account.

Third, just as we cannot coherently speak of the effects of compensating simpliciter, we cannot speak of the effects of not compensating simpliciter. For there are many different ways of
not compensating, and in particular many different ways in which the funds that would be used for compensating could otherwise be used—e.g., to finance more research, to finance projects under other federal budgets, or simply left in the taxpayers' pockets. Each of these alternatives would have different effects itself.

One problem the Commission must resolve in this context is that of deciding whether the relative benefits of compensating should be arrived at by comparing a compensation program with the best alternative non-compensation program, or by comparing it with the most likely alternative non-compensation program, which may of course be quite distinct. It may be that the best possible compensation scheme is worse than the best possible non-compensation scheme, but better than the most likely non-compensation scheme. The simplest way out of this dilemma for an advisory body such as the Commission may be to restrict itself to providing a description of the net effect of what it regards as the best compensation scheme, and allow the ultimate decision-making body to compare this with whatever alternatives they regard as live options.

The Argument from the Moral Tone of Society. The argument from the moral tone of society claims that society's choice to adopt a compensatory program, or not to adopt such a program, is expressive in a dramatic and concrete way of certain important moral attitudes. For example, it could be held that adoption of a compensatory program expresses society's concern for those in need of help, gratitude towards those who have sacrificed themselves in order to benefit society, appreciation for the sacrifice involved, solidarity with those who suffer on society's account, and recognition of the altruistic quality of their act. On the other hand, failure to compensate might express less admirable attitudes, for example, willingness to exploit those who for whatever reason are willing to run personal risks that benefit society, callousness to those in need of help, or ingratitude towards those who have aided society. Public expression of the first class of attitudes is highly important, the argument claims, because it establishes the context in which members of society choose their own moral stance towards each other, and in which they evaluate their own significance in the eyes of others. Thus Rawls, for example, argues that "...a desirable feature of a conception of justice is that it should publicly express men's respect for one another. In this way they insure a sense of their own value." 4

I believe this argument, and the phenomenon to which it points, is highly important in the choice of whether compensatory programs should be adopted or not. However, it also seems to me parasitical upon the other arguments, in the sense that it achieves

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Compensating for Research Injuries: Appendix B

no independent standing. It is not important, for example, for society to express gratitude to injured subjects unless gratitude is an appropriate response. Whether or not it is an appropriate response must be independently determined. Nor can society express a sense of justice towards its members by compensating injuries unless justice calls for that compensation. Hence we must first determine whether or not any of the other arguments establish an obligation for society to compensate research injuries; if one or more does so, then the good to be achieved by compensation will be magnified by the fact that, for example, compensation not only does justice but also expresses justice.

The Argument from Social Benefit. The argument from social benefit relies on the simple principle that if a person acts in a way that benefits a group, then the group owes the person compensation for any harm he or she suffered as a result of the beneficial act. Since the injured research subject has acted in a way that benefits society by participating in the experiment, it is inferred that be or she is owed compensation for the injury.

However, this simple principle is clearly false. It is trivial to find cases that fail under the principle, and yet are such that we find no compensation to be morally required. For example, suppose I am an orchestral violinist whose job requires me to practice four hours a day in my home. Unbeknownst to me, the family downstairs from my apartment enjoys listening to my practice sessions. One day I sprain my wrist while practicing, and must miss my orchestra’s next few engagements. According to the simple principle just articulated, the family downstairs owes me compensation for my lost wages—but clearly this is incorrect. I neither knew about nor was concerned to benefit them by my practicing; and they did not listen in with any expectation of having to foot the bill should I become disabled. If anything like this principle is to be accepted, it must be in a much more qualified form. The next three arguments we shall consider may be seen as attempts to formulate a more satisfactory version of this simple idea.

The Argument from Gratitude. According to this argument, there are certain specifiable circumstances in which one person (or group) owes something to another person as a matter of gratitude. Duties of gratitude have three components. For example, suppose a passer-by rescues a woman from a would-be rapist by wrestling with the assailant until he gives up and flees. We would say that the woman owes the passer-by a debt of gratitude, and in that include the following three elements. (1) There are certain feelings of appreciation and gratitude towards the passer-by that would be fitting or appropriate for the woman to experience. (2) She ought to express these attitudes to him (even if she doesn’t feel them at the moment because she is still too stunned by the incident to respond). (3) She owes him compensation for any losses or damage to his own interests that he sustained as a result
of helping her. For example, she ought to offer to replace his
eyeglasses if they are broken, repair his torn jacket, and so forth.
(We often feel that it would be appropriate for him to turn down
such an offer of compensation, at least if the damage has been
slight.)

Debts of gratitude have traditionally been held to be some of
the most fundamental, and most stringent, of all moral require-
ments. Hume, for example, wrote: "Of all the crimes that human
creatures are capable, the most horrid and unnatural is ingrati-
tude, especially when it is committed against parents." Kant
held that ingratitude was one of the vices that are "the essence of
vileness and wickedness." Shakespeare has King Lear exclaim
"Ingratitude, thou marble-hearted fiend, more hideous when
than show'st thee in a child than the sea-monster!" Hobbes had
gratitude required by a Law of Nature, and Richard Price in-
cludes it as one of his six "heads of duty." In recent years,
however, the obligation of gratitude has figured less signifi-
cantly in moral writings. It may be that this stems from too narrow a
focus on the first two elements in the duty, since we now realize
that one can have no obligation, strictly speaking, to experience
certain emotions, and we also realize that expressions of grati-
tude can often be fairly trivial performances, such as writing
thank you notes after social occasions. But these reasons do not
warrant this relative eclipse of the obligation of gratitude, since
the obligation to express gratitude and to compensate one's bene-
factor can be stringent, and the performances required by way of
compensation can be far from trivial. For example, society's obli-
gation to provide medical care for injuries suffered by volunteers
in the military services is clearly an obligation of gratitude. The
obligation to them differs in source from the obligation to injured
draftees, which is a matter of justice. Draftees must be repaid for
what was, so to speak, taken from them against their wills, just as
a person must be repaid when the government seizes his land
under eminent domain. What we owe military volunteers and
draftees is the same, but the sources of the obligations are
distinct.

To determine whether or not society owes a debt of gratitude
towards injured research subjects, we need a precise account of

7 David Hume, A TREATISE OF HUMAN NATURE, bk. III, pt. 1, sec. 1,
quoted in A. John Simmons, MORAL PRINCIPLES AND POLITICAL OB-
8 Immanuel Kant, LECTURES ON ETHICS (New York: Harper and Row,
1963), p. 218, quoted in Simmons, loc. cit.
9 King Lear, I, iv, quoted in Simmons, loc. cit.
10 Thomas Hobbs, LEVITATHAN, chap. 15, quoted in Simmons, loc. cit.
11 Richard Price, A REVIEW OF THE PRINCIPAL QUESTIONS IN MORALS,
chap. VII, quoted in Simmons, loc. cit.
the conditions under which such obligations arise. The best current account of this is provided in an analysis offered by A. John Simmons in Moral Principles and Political Obligations. 12 Two of the conditions mentioned by him are crucial to our question. We may phrase them as follows:

1. The benefactor must be motivated by a desire to help the beneficiary.

According to this requirement, someone who benefits another by accident, or unknowingly, or who is moved by other considerations than concern for the beneficiary, is owed nothing. In particular this is true if the benefactor acts purely out of self-interest. For example, if my neighbor plants a hedge in his yard to afford himself privacy from me, then of course I benefit by gaining privacy from him as well. But since he acted only with his own interest in mind, I do not owe him a debt of gratitude. Or suppose an aspiring politician donates large sums to charitable organizations in order to improve his record and increase his chances of election. The starving Biafrans who are his ultimate beneficiaries owe him nothing. (Of course, they may owe gratitude towards the organization that transmitted the funds; and if they learn of the politician they might feel gratitude, but this attitude is not called for and may even be inappropriate, since in effect he is merely using them to achieve his own ends.)

2. The beneficiary must not only want the benefit but must be willing to have it provided by this benefactor.

This condition provides for the fact that there are some persons to whom we would rather not be beholden, even though that means foregoing the benefit. If you detest your brother-in-law, you may prefer to mow your lawn with a hand mower than accept the loan of his gasoline-powered machine.

Clearly, there are many cases in which an injured research subject can be seen as a benefactor and society as a beneficiary who meet these conditions (and the other intuitively obvious ones Simmons formulates). In these cases society owes a debt of gratitude to the injured subject and must compensate him or her for the losses suffered. Moreover it is appropriate for society to express its gratitude for the beneficial acts; and the clearest and most convincing way it can do this is through the act of compensation itself.

Within the framework established by recognizing society's debt of gratitude towards injured research subjects, several more precise questions can be answered. First, we can gain some foothold on the question of how much compensation is owed an injured subject. It has long been recognized that the content of an obligation of gratitude is often much less clear than the content of some other sorts of obligations, e.g., those incurred as a result of making a promise. In particular, difficult issues are raised.

12 Simmons, op. cit. chap. VII.
when the benefit to the beneficiary is significantly greater than the cost or loss to the benefactor of providing that benefit. But there is general agreement that in such a case the benefactor ought to be compensated at least up to the level of his or her loss. On this model we can conclude that an injured research subject, who is owed a debt of gratitude, ought to be compensated for the medical expenses necessary to restore health, as well as for out-of-pocket financial losses, such as lost wages, and for any pain and suffering experienced. We should remember, of course, that this is a prima facie obligation; if contrary considerations militate against this level of compensation, then it may be correct to reduce it.

Second, we can determine whether or not compensation is owed to a subject's surviving family in a case where the subject suffers a mortal injury. Since the survivors themselves did not act in order to benefit the state, no debt of gratitude is owed to them. Nonetheless, assuming that the deceased cared deeply about them, harm to them counts as harm to the deceased as well; it is one of the evils of death that he or she wished to avoid. Hence the debt of gratitude owed to the subject includes an obligation to compensate his or her survivors for any losses they may suffer through death of the subject.

Third, according to our account of the conditions under which obligations of gratitude are owed, an injured subject is only owed compensation if he or she acted out of concern for society in participating in the research project. Of course it is impossible for society to determine reliably in any individual case whether or not such an altruistic motive was what moved a given subject to participate. Hence a program of compensation can not be rested upon individual determinations. However, it may be possible within reason to define categories of subjects who are highly likely to have acted out of altruistic motives, and categories of subjects who are highly likely not to have acted out of altruistic motives. Two of the latter categories would be the following: (1) subjects who were paid well enough to participate that such payment would induce a reasonable person for reasons of self-interest to undergo both the inconveniences of participation itself, and the risk of otherwise uncompensated injury; and (2) participants in so-called therapeutic research—research from which they can expect benefit for some underlying disadvantageous condition of their own, such as illness. The presumption would be that persons in those two categories participated for reasons of self-interest, not primarily from a desire to benefit society, and hence are owed no compensation by society if they are injured. At least gratitude does not require compensation. Other principles may, however. For example, suppose it is thought that society owes each person, as a matter of justice, some minimum form of medical aid. Suppose further that indigent persons suffering from say, cancer, cannot afford treatment themselves, but are (only) offered free treatment in a highly experi-
mental protocol that may have spectacular results but on balance has less expectation of cure than the current standard form of treatment. If one of the persons who accepts this form of treatment is injured, it would appear that society owes him or her compensation as a matter of justice relating to the original obligation to provide medical aid.

The fourth question to be asked within the framework of an obligation of gratitude is the most difficult. Suppose prospective research subjects, who are motivated by altruism, would agree to participate in the research without receiving compensation for any injuries—that is, they would agree in advance to release society from its obligation to compensate them. If society knows they are willing to do this, may it request them to agree to such a release in advance, and then refuse to compensate them subsequently if they are injured and then want compensation? May society, in effect, ask for a higher level of gift from its prospective beneficiaries—an uncompensated sacrifice? This is a difficult issue. The fact noted before, that a beneficiary owes nothing to a benefactor unless the beneficiary was willing to receive a benefit from that benefactor means that to some degree a prospective beneficiary may pick and choose among its prospective benefactors. For example, suppose my car has a flat tire while I am driving on the expressway. Two passing motorists offer to assist me changing the tire. I remark there is some danger they will get road grease on their clothes, and one says he’s happy to help me even so, while the other says he’d be pleased to help if I will be willing to foot any resulting cleaning bill. May I accept aid only from the former, and not offer to pay for his cleaning bill when his clothes are soiled? It seems as though I may, since I accepted his help, and he offered it, only on this understanding. By analogy, then, it seems as though society could accept help only from prospective research subjects who agree not to ask for compensation if they should be injured.

But this case may be deceptive. It may be that in the flat tire case I can legitimately choose, and then fail to compensate the helpful motorist, because receiving aid in changing my tire is not worth the cost to me of paying his cleaning bill. I would prefer to change the tire myself than receive aid and pay the resulting bill. But what if I would prefer to receive aid and pay the cleaning bill to receiving no aid at all? Then it is not so clear to me that I can legitimately fail to offer to pay his bill. Of course if we had made a straightforward contractual agreement this might be so. But insofar as his offer is a free gift, my compensating him must be a free act as well—not one that he can exact from me, as he could exact performance of a contract or fulfillment of a promise. Since he lacks control in this direction over my act of compensating, it appears he lacks control the other direction as well—that is, he cannot waive his right to compensation, or release me from my obligation to compensate, since he has no right to it. My obligation is not releasable by him. Hence I believe I must still offer
to compensate him for the damage to his clothes, even though he tells me in advance that he is not interested in being compensated. (Of course, if he continued to refuse compensation after the damage has occurred, I cannot force it on him nonetheless. But I must make a genuine offer.)

Thus it appears to me that if society would prefer to have research subjects, and then compensate those who are injured, to having no research subjects at all, then it should offer compensation—even though some of those subjects would have been willing in advance to participate without receiving any compensation. And certainly, even if this conclusion is wrong, compensation remains society's most effective means of expressing its gratitude towards injured subjects, and so is obligatory on this ground alone. Such expression is highly important for maintaining a desirable moral tone within society, and between the research establishment and those who enable it to conduct its work.

The overall conclusion, then, is that in cases where the injured subject has acted out of a desire to benefit society, society owes him or her compensation for the injury as repayment of a debt of gratitude.

The Argument from Harm Suffered at Society’s Behest. In “Compensating Injured Research Subjects,” James Childress advocates a principle according to which society has an obligation of fairness to compensate a person under the following circumstances: (1) the person engages in an activity at the behest of society, (2) the objective function of the activity is to benefit society, and (3) the person is injured because of his or her participation in that activity. A guiding idea for Childress is the point that society voluntarily incurs this obligation through its acceptance or encouragement of the individual's participation. According to this principle, society must compensate injured research victims, since their participation in research is accepted and encouraged by society, the research is aimed ultimately at benefiting society (whatever the private aims of the research subjects might be), and the injured subject has suffered injury because of his or her participation.

It is clear that Childress’s principle is closely related to the principle, just discussed, that one owes a debt of gratitude to an injured benefactor. Notably, Childress’s requirement that the benefactor act at the behest of society seems to play precisely the same role as the requirement (under the principle of gratitude) that the beneficiary be willing to accept the benefit from this benefactor. Thus neither principle implies that society owes compensation to an individual who privately acts to apprehend a criminal and suffers injury in the attempt. Society does not encourage such attempts, and refuses them where possible, pre-

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"Childress, op. cit."
cisely because they often result in injuries that are too high a price to pay for the criminal's apprehension. The principal difference between the two principles is that Childress's principle does not require, whereas the principle of benevolence does, that the benefactor must act out of a desire to benefit the beneficiary. But it is precisely this difference that renders Childress's principle less plausible. For example, suppose society organizes a national lottery, in order to increase public revenues and undercut illegal numbers rackets. I buy a ticket in the lottery, with an eye to making my fortune. Then when my number indeed comes up, I suffer a heart attack from shock. According to Childress's principle, society owes me compensation for my injury, since I participated in the lottery at society's behest, and the objective function of the lottery (although not my private aim) is to benefit society. But according to the principle of gratitude, society does not owe me compensation, precisely because my goal was to enrich myself, not benefit society. I see no intuitive plausibility to the idea that society owes me compensation in such a case. Hence I think we need not accept Childress's principle, but will do better to explain its appeal as a somewhat distorted, and therefore incorrect, version of the principle of gratitude.

The Argument from H. L. A. Hart's Principle of Fairness. According to H. L. A. Hart (and later John Rawls), when a group conducts some cooperative enterprise that requires all to make sacrifices in order to achieve joint benefits, those who have already made these sacrifices have a right that similar sacrifices should be made in turn by any member of the group who has accepted the benefits gained by the enterprise. This principle is intended to articulate why we think the behavior of "free riders" is unfair—people who profit from the sacrifices of others, but refuse to do their share in keeping an enterprise going. A classic case would be someone who keeps his air conditioner set at 68° while everyone else sets theirs at 78° in order to conserve energy during an energy crisis. The person in question derives the benefit (in the form of reduced gasoline prices, etc.) of the others' sacrifice, while himself doing nothing to contribute to the group effort.

As applied to injured research subjects, the idea would apparently be that research is a cooperative enterprise involving society, the investigators, and the research subjects. In a case where a subject has been injured, he has made a sacrifice that enables the enterprise to go forward, but society, if it fails to compensate him, acts as a free rider—it profits from his loss while failing to carry its full share of the burdens necessary to achieve the ultimate goal.

I do not find the application of this principle to the case of injured research subjects very persuasive. For one thing, the principle applies most clearly to circumstances where an ongoing

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enterprise is already in existence, the sacrifices required from each person have been settled upon, some have born their burden already, and now someone else tries to weasel out. But the question facing the Commission is essentially one of what sort of enterprise is to be set up—how research programs in the future should be designed, with compensation or not. Hence the principle has no clear application in this context. Moreover, it appears that some research subjects are willing to participate without compensation for any injuries—i.e., they are willing, so to speak, to allow society to operate as a free rider on their sacrifices. As long as the subjects are not coerced into this agreement (which some may be), it is hard to see how the resulting arrangement can be unjust. For example, suppose the owners of air conditioners got together and agreed that sufficient energy would be conserved if ninety per cent of them set their conditioners 78° while the remaining ten per cent set theirs at 72°. Enough people volunteer for each category. Is there any injustice to the ones who voluntarily set theirs at 78°? It appears not. Similarly, it also appears there is no injustice (deriving from Hart’s principle) to research subjects who voluntarily agree to bear the cost of injuries themselves. Hence Hart’s principle gives us no ground for thinking that compensation is required.

The Argument from Lack of Consent to the Injury. Tristram Englehardt has argued along the following lines.\(^8\) We have an obligation not to injure another person unless he or she consents to the injury. In the case in question, the injured research subject signed a document giving consent to participation in the research and to not receiving any compensation in the event of injury. But despite the appearance created by this fact, the subject has not given valid consent to the actual injury sustained, since he or she did not have the information necessary to really apprehend its character or the probability of its occurrence. Hence consent to the injury (although not to the immediate fact of participation itself) was uninformed and invalid. Since society injured this person without his or her consent, it must compensate for the loss as far as possible.

It is undoubtedly true that many research subjects do not completely grasp the nature of possible injuries they may sustain, or fully realize what the probabilities involved signify. Nonetheless there are many other contexts in which we would feel adequate consent has been given even when the person’s decision-making is handicapped in precisely the same ways. For example, a person who agrees to undergo surgery for the purpose of restoring his or her health may labor under precisely the same cognitive handicaps despite all efforts to make the decision an informed one. However, if mishap occurs, we do not feel that the surgeon or hospital must compensate the person for his or her injury unless it is traceable to some fault of theirs. The person

\(^8\) Englehardt, op. cit.
took a risk, and unfortunately lost, but that does not show that the party who offered that risk must be responsible for the loss. Yet we tend to feel differently about an injured research subject—there is far more plausibility to the claim that he or she is owed compensation. Why should we react differently, even though the consent in the two cases was equally poorly informed? One possible explanation is that the level of information required for valid consent is higher when the act is altruistic than when it is self-interested. But why this should be is wholly mysterious. Another explanation is that the obligation to compensate the research injury case derives from another source altogether, e.g., a debt of gratitude to the injured subject. If this is the explanation, the alleged failure to obtain valid consent plays no role at all in our obligation. Indeed, this seems to me the proper conclusion. Englehardt's argument, then, can be rejected.

**Practical Concerns**

In the fourth section we examined seven arguments that have been put forward in favor of compensating injured research subjects. Of those, only three were found to have merit: the argument from beneficence, the argument from the moral tone of society, and the argument from gratitude. The argument from gratitude was found to clearly imply an obligation to compensate injuries among certain categories of subjects; the argument from the moral tone of society was found to imply this whenever an underlying moral principle (such as gratitude) independently implies compensation is required; and the argument from beneficence was found apt, but its actual implications for compensation await determination of relevant empirical facts concerning willingness of non-compensated subjects to volunteer, etc.

In view of these conclusions, we are now in a position to answer three more practically oriented questions. (A) In determining whether or not to compensate injured subjects, is it morally legitimate to take into account such factors as the likelihood of abuses arising under a compensation program? (B) If it is decided that injuries ought to be compensated, is it morally legitimate to phase in a compensatory program, or initially operate a pilot program in order to develop a database that would facilitate implementation of a wide-scale program? (C) If it is decided to compensate future injuries, is there a retroactive obligation to compensate past injuries? I will answer these questions solely by reference to obligations arising from the principle of gratitude.

Let us first look at question (A). The types of compensatory programs under review by the Commission are open to certain sorts of problems. For example, such a program might be modeled after existing workers' compensation programs, but these programs have particular difficulties in handling claims involving illnesses rather than accidental injuries and in claims involving pre-existing conditions; they have a poor record of weeding
out non-meritorious claims; and their high level of payment encourages the lodging of spurious claims. In effect such a program might amount to a high-level national health insurance scheme for research subjects. Any program will have difficulties along these lines, especially since the principle of gratitude implies that subjects should be compensated for types of subjective injuries and distress that are difficult to prove or disprove. The issue, then, is whether or not a program's vulnerability to this sort of abuse can legitimately be taken into account in deciding whether to implement it rather than some alternative program, or whether to implement any program at all.

We have a tendency to be idealistic about questions of this sort. The temptation is to say, if society has such-and-such an obligation, then it must be fulfilled, even though society must pay dearly in order to do so. But this attitude is too simple. To see this, let us look at an analogous case in which a person has an obligation of gratitude. Suppose a passing motorist helps push my stalled car out of a heavy snow drift, and then, seeing I appear to be wealthy, claims he got car grease on his coat in the process. If his claim is true, then as a matter of gratitude I should offer to pay to have the coat cleaned. But suppose I have substantial reason to think his coat was already soiled when he offered to assist me. And suppose in addition (despite appearances) I have little money to spare, so that if I pay his cleaning bill, I must defer for another month purchase of my son's badly-needed glasses. If there were no conflicting obligation in this case, we might well say that I should pay the motorist's cleaning bill, even though there is only a probability that I have a genuine obligation to do this. But in the actual case I must balance the probability of this obligation to the motorist against the certainty of an obligation to my son, when I cannot fulfill both. And it seems as though the balance may be struck against the motorist—by refusing to pay his bill, or refusing to pay the whole of his bill—if the obligation to him seems less stringent than that to my son, or if the probability of an obligation to him seems low enough.

The case of compensating injured research subjects is similar. Perhaps a certain program would fulfill society's actual obligations to legitimately injured subjects better than any other program could do. But at the same time it would involve spending public funds for payments to individuals who have no legitimate claim to compensation—persons whose alleged injuries are nonexistent, or whose injuries were not caused by their participation in the research program. If society implements this compensatory program, it will fulfill its obligations of gratitude, but at the same time it will be prevented from fulfilling other obligations that could be discharged by funds that under this program will "compensate" spurious claims. On the other hand, there is available an alternative compensatory program (e.g., one that disallows claims for pain and suffering that would involve many fewer payments to spurious claimants, but would also involve failure to
pay some injured subjects to whom society is genuinely under an obligation of gratitude. But because this alternative program would be less expensive, it would allow society to discharge some of its competing obligations in other arenas. In such a situation, the possible spurious obligations of gratitude and the competing obligations must be weighed against each other, and it seems clear that it will sometimes be right to strike the balance in favor of the less permissive, and therefore less expensive, compensatory program. In short, when society is under several competing obligations, it may—and indeed must—take the probability of abuses into account in deciding which compensatory program to implement. In an extreme situation it may turn out that vulnerability to abuse dictates refusal to implement any program at all, since chances are that society can discharge more and weightier obligations by turning its attention to another sphere altogether.

Precisely the same reasoning may support a phased-in program, or the initial use of a pilot program. Because public funds have important possible alternative uses, it is mandatory to use them as efficiently as possible. Where no data exist to establish what the most efficient use in a given area is, it is permissible to first establish the most efficient way to fulfill social obligations in that area before attempting to actually fulfill them by some hit-or-miss procedure. A slower start may mean that some social obligations in that area will never be fulfilled, but it will also mean that competing obligations elsewhere can be fulfilled in the meantime, and that as little money as possible will ultimately be wasted on non-obligatory activities. Hence the answer to question (D) is that it may well be morally legitimate to phase in a compensatory program, or to initially operate a pilot program before attempting to establish a nationwide program.

Question (C) must be handled differently. Suppose it is decided (let us assume: correctly), to compensate future injuries to research subjects. Is society then under an obligation to compensate retroactively as well—i.e., to compensate those injuries that occurred before the compensatory program was adopted? The principle of gratitude straightforwardly implies that the answer to this question is yes: mere passage of time does not destroy a debt of gratitude. However, society's obligation to compensate the subjects who signed consent forms stipulating there would be no compensation in the event of injury may be somewhat diminished. These subjects formed no expectation of such compensation, placed no reliance on it, and may feel no injustice at not receiving it. I argued previously that their signing such a form cannot be interpreted as releasing society from its obligation, as they might release society from a promise. Nevertheless, because of their understanding of the situation, compensation may be less important in their lives than it would be had they not signed such forms, and so it may be true that the resources necessary to compensate them could properly be used to fulfill stringent obligations elsewhere. At least this may be true for subjects who
Ethical Considerations

sustained only minor or moderate injuries; for those who were severely harmed, or those whose injuries have not abated, compensation probably retains enough importance that the obligation survives.

Conclusion

In this paper I have examined the arguments that might be offered in favor of compensating injured research subjects. After some initial clarification of the relevant normative concepts, seven arguments were scrutinized. Of these, only three proved acceptable: the argument from beneficence, the argument from the moral tone of society, and the argument from gratitude. Since the implications of the first of these depend on empirical judgments that I am not in a position to make, and the impact of the second depends on independent establishment of some underlying argument, the conclusion of this paper is that the primary source of an obligation to compensate injured research subjects is an obligation of gratitude on the part of society to compensate those who have acted in order to benefit society and suffered thereby. Not all research subjects fall into this category; for example injured subjects of so-called therapeutic research do not. In the last section I have explored the implications of this obligation in light of the practical difficulties involved in implementing a compensation program. I have argued that such difficulties may legitimately be taken into account, both in choosing which program, if any, to implement, and in deciding whether to implement any compensatory program at all.
Consent and Compensation

Bernard R. Boxill, Ph.D.*

Introduction

Is there an ethical justification for compensating research-related injuries even if the subjects agree to participate in the research knowing such compensation is not available? Further, what sorts of things, in general, should be compensated for? Should only injuries be compensated for? In particular, should subjects be compensated for pain, embarrassment and mental distress caused by research they agree to participate in?

I begin with the first question. Imagine that subjects are wanted for a certain experiment. Candidates are interviewed. They are told, and made to understand and appreciate, what the risks are. When the chances of injury are very small, people tend to think that the injury will not happen. Candidates for the experiment are disabused of that error. They are made to understand that, however small the chances of injury are, it could happen. Moreover, they are warned that there is overwhelming evidence that there will be no money for compensation for injuries caused by the experiment. They critically examine the evidence themselves and come to agree and believe that there will indeed be no money for compensation for research-related injuries. The sponsors of the experiment have the same evidence and sincerely have the same belief. No one is duped or confused. Now suppose that some person, say S, agrees to participate, and that, as luck would have it, though no one acts maliciously or negligently, that the experiment causes S injuries that S was warned the experiment could cause. The question is whether there are good reasons for compensating S. If there are, the

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sponsors of the experiment may have to try to find funds for this purpose even if they sincerely believed, on the best evidence, that such funds would not be available.

What reasons could there be for compensating S? The most compelling is that S has a right to compensation. It may be that persons who participate in research for the general good have a right to be compensated for the injuries they suffer as a result of the research. On the other hand it may be that persons who participate in research believing that compensation is not available tacitly waive that right. But before that question can be tackled it must be established that research subjects have rights to compensation for research-related injuries. Perhaps they do not. Perhaps they have rights to compensation for research-related injuries only if they agree to participate on the condition that they be compensated if they suffer research-related injuries. If so, subjects who agree to participate in research knowing or believing compensation for research-related injuries is unavailable would not have rights to compensation. A person cannot consistently agree to participate in research on the condition that he be compensated for research-related injuries if he believes he cannot be compensated for such injuries. However, even if research-subjects do not have rights to compensation for research-related injuries, it does not follow that there are no reasons for compensating them for such injuries. There may be reasons to do something for somebody other than that he has a right to it.

These preliminary problems indicate that before the problem posed can be solved we must settle the problem of the nature of compensation. This is the task of the section which follows. There I take up the intuitively most compelling case for saying that compensation is due. This is the case where one person harms another in the process of transgressing against his rights. This is not the kind of case that arises where subjects are injured in research they agree to participate in, but is useful to explore as the clearest situation where the injured has rights to compensation. In the next section I consider the case for saying that subjects of research have rights to compensation for research-related injuries. In the final section I return to the question of what the consequences of any agreements they make are.

The Nature of Compensation

Not every case of helping others is a case of compensating them. Whenever there is a genuine case of compensation there is also a party with a duty to help, and there are cases where a party has moral reasons to help though not a duty to do so. Consider, for example, a motorist with a flat tire but within easy reach of garages and telephones. Stopping to help may be a nice thing to do and this may be a reason for stepping to help, but the passer-by to whom the motorist is a stranger have no duty to do so.
But even when we have a duty to help, fulfilling that duty may not be a case of compensation. For example, we have a duty to help the severely injured, but that duty is a duty of charity not a duty of compensation. Further, the duty to compensate requires more of us than the duty to act charitably. To act charitably we need only relieve suffering, but to compensate we must make the injured person, in some sense, "whole again."

We have a duty to help the injured that is quite different from the duty of charity when we ourselves have inflicted the injury on the other and have done so in the act of transgressing against his rights. Further, the duty here is not only to help. It is a duty to enable the victim to make himself whole again. Here at last we have a case where we can properly speak of a duty to compensate. If X has a right that his body not be interfered with and Y deliberately throws acid in X's eyes and blinds him, Y has a stringent duty to compensate X, that is, he has a stringent duty to make X whole again. What further distinguishes this case from that of charity is that X here has a right to exact Y's compliance with his duty, or in short has a right to compensation from Y. In this case, X's right to compensation follows from the fact that Y injured him in the act of transgressing against his rights. To say that X has a right to something is to say that he ought to be secure from others' interference in his possession and enjoyment of it. At a minimum this means that others should be deterred from interfering, and that if they are not, and their interference damages what X has a right to, that X has a right that they repair the damage. Having rights would be a vain and empty thing were this not the case.

But does compensation require that we bring the injured person back to his former position, the position he occupied before he was injured, or does it require that we bring him to the position he would have come to had he never been injured. These positions need not be the same. At the point that a person is harmed his fortunes may have been on the rise. If so, the position he would have come to had he not been harmed is better than his position before he was injured, that is, his "former" position.

If we assume as a premise that a person who has a right to something has a right to whatever he derives from it, then a person who has a right to something ought to be assured not only of possessing and enjoying it, but also of possessing and enjoying whatever he derives from it. If so, a person whose rights are transgressed against has a right not only that his injuries be repaired but also that he receive whatever he would have come to enjoy had his rights not been transgressed against, and compensation would require not only that we bring the injured person back to his former position, but to the position he would have come to had he not been injured.

But, taken as a blanket claim, the premise that a person who has a right to something has a right to whatever he derives from
Compensating for Research Injuries: Appendix C

it is surely false. I may have a right to my dexterity, but I do not have a right to the profits I derive from using it to steal other people's wallets. At best, if I have a right to something I have a right to the profits I **legitimately** derive from it. But Marxists believe that no one has a right to the profits his talents bring, and they would maintain that this is the case even if they allow, as they would be wise to allow, that everyone has a right to his talents in the sense that he ought to be secure from others' interference in his possession and enjoyment of them. I shall not consider whether the Marxists are right on this. For the sake of argument I shall assume that there are at least some cases where we have rights to profits we legitimately derive from things we have rights to.

If so, to compensate a person for transgressions against such rights we must restore to him whatever profits he would otherwise have acquired. If I steal money from a person who was on the point of investing it in a venture which would have made him $X, I do not compensate him until I give him $X. If I cripple a basketball player who earns $1,000,000 a year, I do not compensate him until I give him the money my action cost him.

So far I have pursued the line which emphasizes compensation as concerned primarily with making up for financial loss. But compensation is concerned with more than financial losses. Apart from compensation for financial loss an injured person must be compensated for any deterioration in the quality of his life. This indeed is the basic justification for compensating persons for financial losses. Thus a man who loses his sight or the use of his limbs is not adequately compensated by being assured of the salaries he would have receive had he not been injured. Compensation requires something more fundamental. But how should we think of it? One author writes that compensation requires that we make the injured party "whole again". This is suggestive but obviously imprecise. What does it mean, for example, to make someone "whole again"? Taken in one ordinary sense, if compensating a person meant making her whole, too many injuries would be incompensable. If a person has lost a leg, for example, how do you make her "whole again"? An acceptable definition of compensation need not make every loss compensable, but it must not make losses seem incompensable which we know are compensable.

Robert Nozick presents a definition of compensation which only appears to avoid this difficulty. According to Nozick, "Something fully compensates a person for a loss if it makes him no worse off than he otherwise would have been: it compensates person X for person Y's action A if X is no worse off receiving it, Y having done A, than X would have been without receiving it if

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Y had not done A." ¹ This seems to avoid the looseness of thinking of compensation as a "making whole." We cannot yet make a person who has lost a leg "whole" again, but it seems that we can often bring him to a position where he is, everything considered, no worse off than he would be with the leg. But without further explanation this really doesn’t work. Just as we often cannot make a person "whole again", it seems that we often cannot make him "no worse off." For example, if a person lives to experience the beauty in visible things, and loses his sight, how can we possibly make him no worse off than he was before his injury? Even a very large amount of money will not do it. Yet we know that such losses are often compensable.

The quality of a person’s life depends on the nature of his interests and how successfully he pursues them. But what exactly are interests? Sometimes an interest is defined as "anything which is the object of human desire." But this is both too broad and too narrow. It is too broad because there are some things some people desire that may not be in their interests, for example, cigarettes. And it is too narrow because there are some things that some people do not desire that may be in their interests, for example, nutritious food. But even if interests are not simply objects of desire, it may seem that they are still related and subservient to objects of desire. Thus, though X may not be among the things Mary desires, it may seem that X is in her interest only if it serves to make it more likely that she will get more of the things she deeply desires, and similarly though Y may be among the things Mary does desire, it may seem that it is not in her interests only if it serves to make it less likely that she will get more of the things she deeply desires. The trouble with this is that it makes it seem as if children cannot be as seriously harmed as adults. If our interests serve our deepest and most fixed desires, and if the desires of the young are unformed and impermanent, then it would seem that they have few or no interests, and hence, since harm is the invasion of an interest, that either children cannot be harmed or that they cannot be as deeply harmed as adults. And that is outrageous.

Interests are related, not only to actual desires, but also to possible desires. Though X may not help Mary to get more of the things that she deeply desires—if for no other reason than that Mary is still too young to have deep desires—X may yet be in her interest if it helps her to acquire desires for noble and challenging goals, and if it gives her the character and skill to be happy in the pursuit of these goals. Thus children have an interest in a good education, and are harmed if they do not get one.

Like adults’ interests, children’s interests vary. All children have an interest in a good education, but what amounts to a good education will be different for different children. It depends on

their proclivities and talents. But it may seem that adults' interests vary in a more radical way than children's interests. For whereas a child's interests serve to help him acquire worthy desires, it seems that an adult's interests simply serve to help him satisfy the desires he does have, be they worthy or unworthy. Consider, for example, a deep and fixed desire to count the blades of grass on a plot of land. If an adult had such a desire whatever helped him to satisfy it might be said to be in his interest. Yet, we would be reluctant to allow that whatever helps a child to acquire such a desire would be in his interest.

If a person's interests depend on what he is capable of, and harms are invasions of interests, then the ways in which we can harm a person depend on what he is capable of. Thus we harm a woman with an aptitude and liking for mathematics by locking her out of the mathematics library, but we do not similarly harm a mathematical dunce by locking him out of the mathematical library, though of course we similarly transgress on his freedom. Now given that an adult's desires are relatively fixed, typically the best life he is capable of is simply the life in which he pursues and satisfies the desires he does have, however trivial they may be. He may have intellectual, artistic or athletic talents such that, if he had different desires he would live a better and fuller life. But given the person he is, he may be incapable of living such a life. If so, his interests are whatever serves his admittedly trivial desires, and we harm him by invading these interests, not by invading the interests he might have had, had he acquired worthier desires commensurate with his talents.

With children it is very different. Given that their desires are relatively unfixed and their characters unformed, they are generally capable of acquiring the desires that would enable them to live lives worthy of their talents. Hence, their interests are whatever serves their acquisition of such desires, and we harm them by invading those interests.

The contrast between children and adults is, of course, overdrawn. Children are not completely malleable. Further, it is crucial for my analysis of compensation that adults can and do change. Sometimes, perhaps faced with a crisis, adults jettison their old desires, form new ones and make a fresh start. Thus it is possible for adults to change their interests by changing their desires.

This shows how it is possible to compensate a person for serious physical injuries, like the loss of sight, which detract from the quality of his life. The assumption that compensation for such injuries is well nigh impossible depends on the assumption that after the injury the person retains the very desires and interests he had before the injury. If all the rest of my desires are nothing compared to my desire to watch the sunset, and I lose my eyes, hardly anything anyone can do will bring me to the level of well-being I would have enjoyed had I not been injured, if my
desires remain as they were. But if my desires change, if I can disengage myself from desires I cannot satisfy and replace them with desires I can satisfy, perhaps I can be brought to the level of well-being I would have enjoyed had I not been injured. It will depend on whether my new desires are as worthy as my old desires. If they are, then in a sense, I have lost nothing and am indeed whole again.

Nozick mentions that an injured person can minimize his losses by rearranging his activities to limit his losses. But clearly this will, at best "limit losses," especially where the injury is the permanent loss of the ability to satisfy a dominant desire, and will not make the person no worse off than he would be had he not been injured. For that, a more radical procedure is necessary. The injured person must make himself like a child again so that he can reeducate himself to have a new set of desires.

This suggests a new way of looking at compensation. We cannot compensate a person for an injury by making him no worse off than he would have been had he not suffered the injury. We compensate him by making it possible for him to make himself no worse off than he would have been had he not been injured. Sometimes what he must do is relatively easy, but sometimes it is difficult. If a marathon runner loses his legs, we can compensate him by giving him the opportunity to make himself no worse off than he was before his injury. Perhaps we could do this by giving him a million dollars. However, if he is to be no worse off than he was, he cannot simply accept the money and become a playboy or wallow in self-pity. He must use it to re-educate himself to have desires he has a reasonable chance of satisfying and which are as worthy as the one he had before his injury.

However, the problem of compensation in such cases is even more complex than I have indicated. Just as compensation may require that we bring a person to the financial level he would have attained had he not been harmed, it may require that we bring him to the overall level of functioning he would have attained had he not been harmed. This may not be the level he was at when he was harmed. His powers may have been developing. If an injury for a long time interrupts the development of a child's ability to speak, he is not compensated if, as an adult, he is brought to the point where he can only speak as a child. This kind of case is less problematic than the case for compensation for losses of financial profit. For though it is controversial that we have rights to the profits we can derive from what we have a right to, it is not controversial that we have rights to the development of our faculties. Except in the case of projecting the normal development of children's faculties, however, it is probably usually more difficult to tell how a person's faculties would develop were he not harmed than it is to tell how his financial level would develop were he not harmed.
It may seem that a major difficulty in the view that compensation requires that we bring a person to the level he would have reached had he not been injured—and not merely to the level he was at when he was injured—is that the level he would have reached had he not been injured may be lower than the level he was at when he was injured. His fortunes at the time of injury could have been falling instead of rising. Suppose, for example, that X wrongfully or negligently injures Y and causes him to lose his sight, but it is discovered that Y would have lost his sight anyway. Is he owed any compensation? This can be given a further twist. Suppose that the injury causes Y to lose his sight in one eye, but as a direct result of the injury, his impending loss of sight in both eyes is discovered and arrested. Clearly he was injured, but equally, clearly he was benefited. If compensating him requires that we bring him to the level he would have reached had he never been injured, it seems that we must blind his remaining eye. But this is outrageous.

I have argued that if X transgresses against Y’s right to V and this prevents V from having or being W to which he also has right, then Y’s compensation must include his having or being W (or an equivalent). But this is loose. Despite careless statements to the contrary it is not the case that others must see to it that a person must have or be everything that he has a right to have or be. He must first claim it. This shows the way out of the above difficulty. If as a result of X’s injury to Y, Y’s impending blindness is discovered and arrested, it is true that X has prevented Y from being blind. But though Y has a right to be blind (setting aside standing responsibilities, he is morally free to blindness if he so chooses) it is unlikely that he would claim that condition.

But what if the harms are neither financial losses, nor injuries but pains, mental distress or embarrassment. If compensating a person for a harm is to bring him to the position he would have occupied but for the harm, then if X comes to suffer pain it may seem that he is compensated for that harm when he is freed from the pain. The proposal is not that this would compensate him for all the harms he might have suffered. If the pain was caused by an injury, for example a broken head, and that injury caused him financial losses, then to be fully compensated, he must be compensated for these two additional harms. But it seems that he is compensated for the pain as soon as he is freed of it.

But X freed of pain P is not quite in the same position as X would be had he not experienced P. For X freed of P is an X who has experienced P, and the experience of P places him in a different position than he would be had he not experienced P. The objection is not merely that X’s memories of P put him in a different position than if he had no memories of P. If that were the objection it could be met by stipulating that compensating X for the pain of P include freeing X from the memories of P. This would be practically, but not conceptually difficult. Neither is the
objection that either X's memories or experiences of P are dysfunctional. This is, of course, possible. Pain may cause neurosis which persists after the pain is gone, the bare memory of pain may be debilitating, and a person may be unable to stop dwelling on and resenting the pain he suffered and this may be both dysfunctional and a cause of further dysfunction. If these harms caused by either the memory or the experience of pain persist after a person is freed of pain, then he is not in the position he would be had he not experienced the pain, and they must be compensated for in the manner already indicated. The objection is that even after this compensation is made, the person is not where he would otherwise be because he now has the experience of pain he would not otherwise have. But, finally, the objection is not that compensation requires that we make a harmed person's experiences what they would be had he not been harmed. This would make all compensation impossible—for financial loss, injury or pain—because it would require that we change the past and, of course, that is impossible. The objection is rather that the balance of a person's satisfying experiences should be what they would be were it not for the wrongful harm and merely freeing a person of pain does not do this.

The balance of a person's satisfying experiences should be what they would be if his rights were not transgressed on because a person has a right that others not inflict pain on him by transgressing against his rights. Thus persons have rights to be compensated for pains wrongfully inflicted. If this seems severe, consider the following possibility: X injures Y when Y was a child of five. As a result Y remains an invalid until she is 70 years old when a cure is found. Surely she is not compensated by being given the powers of an average 70 year old woman. Her life has been diminished and, as far as possible, she must be helped to make up for the loss. Nothing can give her back the lost years, but something may be able to be done to make the years she has left more enjoyable than the average. This would partially make up for her losses.

The Effect of Consent

So far the case for saying that X has a right to compensation for a harm derived from the fact that the harm occurred in the process of a violation of X's rights. Though this is the most intuitively compelling kind of case where rights of compensation arise, it is not apparently the case where rights of compensation arise for subjects of medical experiments. In that case, there is no transgression against the subjects' rights. We all have rights that our bodies not be experimented on but if we agree to participate in medical experiments, those rights are not transgressed against. If subjects of a medical experiment had not agreed to participate in it, as for example in the notorious Tuskegee Syphilis study, or if they agree to participate but are kept ignorant of the risks of the
experiment then their rights are transgressed against, and the case for compensating them is exactly the same as the case for compensating people who are harmed when their rights are violated—for example, people who are assaulted or robbed. The question now is whether X has a right to compensation for a harm, or perhaps deserves compensation for a harm, when that harm did not occur in the process of a violation of his rights. This question would arise if X were harmed by an experiment he agreed to participate in knowing what the risks of harm were.

Of course X would have a right to compensation if he agreed to participate in the experiment only on the condition that he be compensated for any harms he suffered as a result of the experiment. But it does not follow that X fails to have a right to compensation if he agrees to participate in the experiment, but fails to stipulate that he participates only on the condition that he be compensated for any harms he suffers as a result of the experiment. Rights to compensation for harms may be generated in other ways than by extracting an agreement that harms be compensated.

The most appealing possibility is that a person has a right to be compensated for harms he suffers as a result of an experiment because this is only fair. The importance of fairness as a moral principle has been stressed in recent times by H. L. A. Hart and John Rawls. In particular they propose it as a way that special rights are generated other than by consents, promises and agreements. It is of particular concern to this essay because if considerations of fairness can give X a right to W from Y—without Y having promised or agreed to turn W over to X—then X may have a right to compensation for harms suffered as a result of an experiment he agreed to participate in, even if he did not extract a promise from those responsible for the conduct of the experiment that he be compensated. It depends on whether such compensation is fair.

The principle of fair play of Hart and Rawls may be summarized as follows: If there is a "mutually beneficial scheme of social cooperation," then "a person who has accepted the benefits of the scheme is bound by a duty of fair play to do his part and not to take advantage of the free benefits by not cooperating." Rawls and Hart meant this principle to be used to justify such arrangements as taxation and national defense. Those who pay taxes have rights that others pay taxes if these others accept the benefits of taxation; those who go to war to defend their country have rights that others do their part because they benefit from the country's defense. In neither case is it necessary that anyone promised to do anything. Similarly, it seems, the subjects of medical research have rights to compensation from society for

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the harms they suffer as a result of the research because society benefits from the enterprise of medical research.

But this was really too quick. Several problems must be resolved. First there is the question of the fair distribution of the benefits of medical research. If research is conducted primarily on male disorders, then fairness would not give men a right to expect women to contribute to the research. Or if the discoveries of research are so costly to implement that only the rich benefit from it, then it would not be fair that the rich have a right that the poor contribute. Similarly, if information about the benefits of research is so poorly disseminated that only the well educated stand to benefit from research it would not be fair that they have a right that the poorly educated contribute.

But even if all significant classes stand to benefit from research, whether it is fair for some to have rights that others contribute depends on whether these others accept, receive, or pay for the benefits. If X objects to a particular kind of research but cannot avoid receiving its benefits—perhaps because the benefit is some kind of treatment to the water supply—it is not clear that it is fair that others have a right that he contribute to that research. X must, in some significant sense, accept the benefits; for example, he must receive the benefits when he could without inconvenience refuse them, or even more clearly, he must go out of his way to enjoy the benefits.

Further, if the sponsors of the research are businessmen intending to make a profit on the research, it is not fair that they have rights that others "bail them out" when their ventures fail. The most popular defense of profits is that they are fair because businessmen take risks. If so, businessmen have no right to be bailed out when they fail. For then they would not be taking any risks, and the justification for their profits would disappear. Thus Chrysler Corporation may have benefited society, but it had no right to governmental support when it failed, even if government was wise to extend it such support.

This may seem so, not because Chrysler Corporation makes profits for its shareholders, but because we, the rest of the society, did not agree to sponsor Chrysler. This would make the principle of fairness collapse into the principle of agreement or consent—we are bound in fairness to help others, not because we accepted benefits from their sacrifices, but because we agreed, tacitly or explicitly, to help. I fear this would imply that society has no obligation to help compensate research-related injuries because though many or most people benefit from medical research, it seems strained to insist that they agree, even tacitly, to such research. So I tend to think that the principle of fairness does not collapse into the principle of consent and that if we accept the benefits of others' sacrifice, it is fair that they have rights to our help when it is needed. The principle of fairness seen as independent of the principle of consent does not commit us to "bail
out" every harebrained scheme for the general welfare that fails. For it does not say that the bare benevolent intentions of the sponsors of an enterprise entitle them to help. If the enterprise produces no general benefits, others cannot be bound by fairness to help the sponsors of the enterprise.

So far I have argued that if fairness dictates that society provide compensation for subjects of research who suffer research-related injuries such research must not be for profit and its benefits must be widely accessible. But other problems remain. It may be objected, for example, that the claim that the subjects of medical research have rights to compensation from society for research-related harms begs the question. Let us accept that everyone who is ready to accept benefits from medical research must shoulder a fair share of the costs of that research. But what are the costs of medical research? The claim in question assumes that these costs include the cost of compensating subjects for research-related harms. But isn't this the very question at issue?

People who are poor or altruistic, or just bored or self-destructive or foolish, may volunteer for medical research for nothing or for only a nominal fee. If so, the financial costs of medical research will be relatively small. Surely, however, the total costs of medical research would not merely be the nominal fees for subjects plus the salaries for researchers and the costs of materials and equipment. This would ignore the most important costs of all, viz., the injuries and harms to the subjects. The loss of sight or of health as the result of an experiment is a cost of that experiment. Subjects of experiments should not have to bear these costs alone. Fairness dictates that they have rights that the beneficiaries compensate them.

It may be objected that if the subjects of an experiment agree to participate they have no right to compensation. This must be suitably qualified before the difficult cases can be considered. First, the subjects must know what the risks of the experiment are, and if the risks are not known, must know this. Second, they must not have agreed to participate only on the condition that they be compensated if they are harmed. For if so, they do have rights to compensation even if they agreed to participate knowing the risks. Third, the subjects must have a realistic choice whether to participate or not. A parent with hungry children does not have a realistic choice to participate if he is offered money to do so, even if he knows the risks. These qualifications leave us with the following case: A person X is faced with the choice whether or not to participate in an experiment which promises substantial benefits to all segments of society. X knows and understands the risks but chooses to participate though he has many other attractive things he can realistically do. X is harmed as a result of the experiment. Should he be compensated if he did not agree to participate on the condition that he be compensated if he were injured?
Three possibilities must be distinguished. X agrees to participate but bargains for the highest fee he can get; X agrees to participate for a nominal fee; X agrees to participate because he knows he has a medical problem the research may help find a cure for. Take the first case. X knows he has a rare kind of blood which makes him the only one in the world who is a fit subject for the experiment. Moreover, he knows that the research could benefit millions who now lie in misery awaiting death. Finally he knows that though the injury the experiment can cause is substantial, the chances of his being injured are infinitesimal. Let us suppose that armed with this knowledge X now insists on an extremely large fee to be a subject of the experiment, even insisting that the sick who hope to benefit contribute extra amounts. If he is accepted as a subject of the experiment and, unluckily for him, suffers injury, I think it is clear that fairness gives him no rights of compensation. He is like a gambler who plays for great stakes and loses a bundle. If it is fair that he gets the profits he hopes for because he takes great risks, it is fair that he can demand no compensation for his losses. For otherwise there would be no risks and without the risks his profits would not be fair.

Equally clearly, it is fair that those who participate for a nominal fee have rights to at least some compensation for research-related injuries. If my previous argument is correct that person have rights to be helped by those who accept the benefits of their sacrifices—even if they have not extracted an agreement or promise of such help—subjects of research have rights to some compensation from society for injuries suffered in medical research even if there is no agreement to make such compensation. It is enough that all segments of society accept the benefits of medical research. The same goes for those who have a medical problem they hope the research will find a cure for. The benefit they hope to receive is no greater than the benefit others in the society stand to receive.

The Ethical Justification for Compensating Research Subjects

If subjects have rights to compensation for research-related injuries only if they have an agreement that they will be compensated for such injuries, then subjects who participate in research knowing or believing that compensation for research-related injuries is unavailable do not have rights to compensation for such injuries. If they know or believe compensation is not available, they clearly cannot, at least sincerely, agree that they will be compensated. That would be possible only if, contrary to what they know or believe, compensation is available. But, if my argument in the preceding section is correct, subjects of research may have rights to compensation for research-related injuries even if they have not secured an agreement that they will be compensated for such injuries. I argued, in particular, that they may have such rights because often it is fair that they do. If so, subjects who
agree to participate in research knowing or believing compensation for research-related injuries is not available may have rights to compensation for such injuries. Further, though a person who agrees to participate under these conditions cannot have agreed to participate only if his research-related injuries were compensated, he does not thereby waive his rights to such compensation. This I argued in the first section. A person does not waive his right to something just because he gets himself into a situation in which he knows or believes he will not get what he has a right to. If a person can have a right to something though he cannot have it, his knowing or believing that he cannot have it cannot constitute a waiver of his right to it.

We can now answer the question whether there is an ethical justification for compensating subjects for research-related injuries when these subjects know such compensation is not available. But first a comment on what this could mean. It could mean either that the subjects know or believe that funds for compensation are not available, or that they know or believe that the injuries they could suffer are so severe as to be incompensable, whatever the funds. This is possible. Death, for example, seems incompensable. In the second section, however, I showed how even very severe injuries are often (though, of course, not necessarily always) compensable. What is necessary is that the victim change his desires and interests, sometimes radically. For this funds are, of course, necessary and for severe injuries, probably large amounts. Thus, I shall assume in the following that what is believed or known to be unavailable is funding for compensation.

To return to the question, there is justification for compensating subjects who agree to participate in research believing compensation for research-related injuries is not available. But the kind of justification varies. The first is where the subjects have rights to compensation. This arises where, as I argued, in Section III, they participate in generally beneficial research for only a nominal fee. Since their agreement to participate under the stated conditions does not constitute a waiver of these rights, the justification for compensating them is the same as it is for giving persons what they have rights to: Usually, it amounts to an obligation. Sometimes, of course, rights may be overridden, and in particular, it may be impossible to give people what they have rights to. But we cannot know that we do not have the funds to give compensation to those subjects who have rights to it unless we try hard to find these funds. The fact that everyone sincerely, and on the best evidence, believed that these funds would be unavailable does not relieve us of the obligation to try and find them.

If funds prove to be indeed unavailable, then it is not the case that society has an obligation, everything considered, to compensate the subjects in question. Society cannot have an
obligation to do what it cannot do. This raises the question of whether society is justified in engaging in research when it is clear beforehand that subjects will be injured and that there will be no funds to compensate them with. There are two sides to the question: On the one hand there are the great benefits that are derived from medical research. On the other hand there is the fact that engaging in such research puts society in a position where it cannot do what it has compelling reasons to do. For subjects who engage in such research have rights to compensation for their injuries and society cannot, by assumption, honor these rights.

One way out is to secure from the subjects of research an explicit waiver of their rights to compensation. But this would only be a partial solution since there would still be reasons to compensate the injured subjects even if they had no right to compensation. Another possible solution is to decorate the victims of research-related experiments. Decoration is quite distinct from compensation. Decoration is a recognition of merit. Though an injured person may, of course, be decorated, he is decorated because of his merit, not because of his injury, and no effort may be made to make the quality of his life equal to what it was before his injury. That is, decoration need not involve compensation. Thus, injured soldiers may be compensated but not decorated, and decorated soldiers may not be compensated for the simple reason that they are not injured. Indeed decoration may be possible when there can be no question of compensation as, for example, when a dead soldier is decorated. The attractiveness of decorating subjects of medical research instead of compensating them is that decoration is much cheaper than compensation. If there are subjects willing to waive their rights to compensation, decorating them may be an acceptable substitute. But the matter has to be examined more thoroughly. The opportunity this offers for cynically exploiting the foolish or the desperate and then decorating them is too obvious to need comment.

Another way a society can pursue research when it has no funds for compensation is to encourage the case where the subjects have no rights to compensation because they had excellent choices to do otherwise but decided to participate in the research for personal profit. We can imagine a situation where there are no funds for compensation because the subject has insisted on getting beforehand, as his fee for participating, funds that would have been profitably invested and the proceeds saved for compensation. But though in such cases the subject has no right to compensation (unless of course he took the extra precaution of extracting an agreement that he would be compensated if he were injured), it does not follow that nothing can be said in justification of helping him. Such justification would flow from the duties of compassion, benevolence and humanity, not from the duty of justice. The help would therefore not be compensation, for compensation is a duty of justice.
Data on Risks of Biomedical and Behavioral Research
Demographic Notes on the Subjects of Biomedical and Behavioral Research

Robert A. Cooke, Ph.D.*

The purpose of this report is to summarize for the President's Commission (PCEMR) some basic information about the subjects of behavioral and biomedical research. Data are provided on selected demographic characteristics of subjects, the research procedures and interventions they experienced, and certain other features of the research projects in which they were involved. These data are based on interviews carried out with the principal investigators of over 2100 projects which passed through the review boards of their institutions during the period of July 1, 1974 to June 30, 1975. These interviews were conducted as part of the Survey Research Center's study for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Cooke, Tannenbaum, and Gray, 1978).

The Sample and Weighting of Projects for the National Commission

The study for the National Commission focused on 61 institutions out of a population of 424 which held general assurances of compliance with DHEW regulations concerning the protection of human subjects. This population consisted of universities, medical schools, hospitals, children's hospitals, institutions for the mentally infirm, and other types of institutions such as social research organizations. Probability sampling techniques were used to select the institutions from this population in consideration of their type, their size, and geographical location and to ensure that the final sample would meet certain criteria (e.g., that at least two institutions from each type/size/location cell would be selected). Additional sampling techniques were used to select

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projects within these institutions in a way that would enable us to interview as many investigators as possible even in those institutions where relatively little research was being conducted.

The use of these techniques produced a sample of projects in which certain types of institutions and projects were over-represented and other types were under-represented. It was therefore necessary to assign weights to each institution, and then to each project, for the National Commission study. Thus, when analyses were run, projects that were over-represented (i.e., included in the sample at a rate greater than their actual proportion in the population would justify) were "weighted down" and under-represented projects were "weighted up." An analysis showing, for example, the percentage of projects that were primarily biomedical rather than behavioral therefore would be properly adjusted in case either biomedical or behavioral studies were over-represented in the sample. (Details of the sampling procedure used in the National Commission study are presented in Cooke, Tannenbaum, and Gray, 1978, pp. 1.293-1.302).

The Sample and Weighting of Projects for the President's Commission

For the purposes of the analyses reported here, an additional weight was attached to each project in the sample. This new weight reflects the number of experimental group subjects that, according to investigators, were participating in their study. In the case of projects that were on-going, this weight also reflects the number of additional subjects that were expected to participate. The final weight used for the present analyses is a product of the original project weight and the new subject weight.

This complex weighting strategy permits the analyses to be sensitive to the number of subjects involved in each project. For example, a table showing the percent of biomedical versus behavioral projects would loosely translate into a table showing the percent of subjects involved in biomedical and behavioral studies. This weighting procedure, however, does not provide statistics that directly represent the national population of research subjects. Such statistics would require that subjects serve as a unit of analysis, or at least be considered, in the initial selection of the sample. Nevertheless, the data generated through the use of this weighting technique, if interpreted cautiously, can provide some general impressions about the characteristics and experiences of research subjects.

The data presented in the tables which follow are based on all the projects included in the National Commission sample with two general exceptions. First, studies which relied exclusively on secondary analysis techniques were excluded from the present analyses. Second, studies for which information on the number of experimental-group subjects was missing or incomplete could not be assigned a new weight and were filtered out
for these analyses. Despite these exclusions, the effective sample for the present analyses exceeded 2000 research projects.

Summary of the Analyses

The results of these new analyses are presented in ten separate tables. The first table focuses on the prevalence of 7 different research procedures and interventions. These data were obtained by asking investigators if their projects involved any of these procedures, either as an experimental intervention, as a procedure being evaluated, or as a means of collecting data for their study. The data are presented in two ways: (1) "percent of subjects," calculated using the new weights described above and (2) "percent of projects," calculated using only the weights developed for the National Commission study. The results show that the most prevalent research procedure was the "use of data from existing records." This procedure was used in 53.8% of the projects and experienced by 53.8% of the experimental subjects participating in the various projects (or, more accurately, used in 53.8% of the projects when weighted by the number of subjects).

The data included in this first table illustrate the effects of the new weight. For example, "self-administered questionnaires" were used in only 22.3% of the projects in the sample, but 43.3% of the subjects of all projects experienced this research procedure. This discrepancy indicates that projects using questionnaires involved relatively large numbers of subjects. In contrast, 34.7% of the projects entailed the "administration of a drug, chemical agent, fluid, or blood product," while only 13.6% of the subjects experienced the administration of a drug or some other substance. This discrepancy reflects the relatively small number of subjects involved in studies using this procedure.

Tables 2 through 6 provide more detailed information about five of the general procedures listed in Table 1. Additional information about the administration of drugs and other substances is summarized in Table 2. Among other things, the table shows that a very small percentage of all subjects were administered drugs or other substances which would have been administered if they had not been participating in the study. Supplementary information of this type is provided in the subsequent tables on the obtaining of bodily fluids, the obtaining of tissues, surgery, and anesthetic administration.

The next table (7) concerns the demographic characteristics of research subjects as reported by investigators. The figures in this table are based on the new weights; that is, the number of subjects in each project is taken into consideration. The percentages differ somewhat when calculated with the old weights, that is, when the number of subjects per project is not considered. For example, the percentage of females declines from 51.0% to 48.1% (old weight with project n = 2209), the percentage of Black subjects declines from 20.7% to 14.8%, and the percentage of
subjects between 3 months and 6 years old declines from 9.2% to 6.0%.

Risks and benefits to subjects are summarized in Table 8. All the percentages in this table are calculated with the new weight and are based on the estimates of investigators. Table 9 lists the main reasons why subjects agreed to participate in the research—again from the perspective of investigators. Table 10 summarizes information about the payment received by subjects for participating in the studies. Whether the old or new weights are used, it appears that in the large majority of cases either no payment or minimal payment was involved.

Finally, some analyses were run on the 59 Phase I and 281 Phase II, III, and IV studies included in the sample for the National Commission study. These analyses were carried out to provide a context for interpreting Arnold's (1980) report to the President's Commission on the incidence of injury during research at the Quincy Center. The results of these analyses—which are presented here in discussion rather than tabular form—do not reflect the new weights described above.

First, all new investigators conducting either FDA Phase I or Phase II, III, and IV drug studies were asked, "Is there any provision for giving treatment to subjects should they suffer any harmful effects due to this research?" Approximately 85% of the investigators conducting Phase I studies reported that there were such provisions and the remaining 15% did not know whether such provisions existed. Approximately 91% of the investigators conducting Phase II, III, and IV studies said there were such provisions, about 3% said there were no such provisions, and 6% were uncertain. (All percentages presented here were calculated by excluding missing data, that is, by omitting those projects whose investigators did not provide the necessary information.)

Second, investigators were asked "Is there any provision for giving financial compensation to subjects should they suffer any harmful effects due to the research?" Investigators conducting Phase I studies responded as follows: 13% reported such provisions; 25% said there were no provisions of this type; and 62% were not sure. In contrast, only 4% of the investigators conducting Phase II, III, or IV studies said that there were provisions for financial compensation while 78% said there were no provisions and 18% were uncertain.

Most of the investigators who conducted these drug studies provided information about the total number of experimental subjects involved, the number of subjects who dropped out, and the number of subjects experiencing harmful effects due to the research. On the average, the Phase I studies involved—or were expected to involve—23.9 experimental subjects (project n=59). Based on a somewhat smaller number of projects, it is estimated that on the average less than 1 (x=.68) subject dropped out of each of these studies and that an average of .7 subjects per study
experienced harmful effects. On the average, the Phase II, III, and IV studies involved—or were expected to involve—50.7 experimental subjects per study (project $n=272$). Again based on a somewhat smaller number of studies, it is estimated that an average of 1.25 subjects dropped out of each of these studies and that an average of 5 subjects per project experienced harmful effects. In the Phase I studies, the harmful effects were about twice as likely to be temporarily disabling than only trivial. The harmful effects in the remaining studies were about five times as likely to be trivial rather than temporarily disabling. The investigators reported permanently disabling effects and fatal effects were very rare.

REFERENCES
### TABLE 1
Prevalence of Research Procedures and Interventions**

<table>
<thead>
<tr>
<th>Research Procedure</th>
<th>Percent of Subjects</th>
<th>Percent of Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of data from existing records</td>
<td>53.8%</td>
<td>49.7%</td>
</tr>
<tr>
<td>Obtaining of medical history directly from patient</td>
<td>50.1</td>
<td>51.9</td>
</tr>
<tr>
<td>Questionnaires—self-administered interviews (other than medical history)</td>
<td>43.3</td>
<td>22.3</td>
</tr>
<tr>
<td>Obtaining of bodily fluids for analysis or experimental use</td>
<td>37.0</td>
<td>34.7</td>
</tr>
<tr>
<td>Behavioral observations or experimentation (including behavioral modification)</td>
<td>35.8</td>
<td>45.2</td>
</tr>
<tr>
<td>Psychological or educational testing</td>
<td>18.2</td>
<td>14.0</td>
</tr>
<tr>
<td>Administration of drug, chemical agent, fluid, or blood product (other than anesthetic)</td>
<td>13.8</td>
<td>34.7</td>
</tr>
<tr>
<td>Non-invasive measurement of bodily activity (e.g., temperature, blood pressure)</td>
<td>12.8</td>
<td>20.4</td>
</tr>
<tr>
<td>Counseling or advising of patient or client (excluding psychotherapy, psychological or social therapy)</td>
<td>11.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Obtaining of tissue for analysis or experimental use (biopsy)</td>
<td>10.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Measurement of electrical activity of body (EEG, EKG, GSR)</td>
<td>9.7</td>
<td>14.4</td>
</tr>
<tr>
<td>X-ray (fluoroscopy or scans</td>
<td>9.5</td>
<td>16.4</td>
</tr>
<tr>
<td>Psychological or social therapy (including psychotherapy)</td>
<td>6.8</td>
<td>4.1</td>
</tr>
<tr>
<td>Modification of an organization or a service delivery system</td>
<td>5.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Surgery (excluding oral surgery but excluding biopsy)</td>
<td>4.6</td>
<td>6.9</td>
</tr>
</tbody>
</table>
### TABLE 1
Research Procedures (Continued)

<table>
<thead>
<tr>
<th>Research Procedure</th>
<th>Percent of Subjects</th>
<th>Percent of Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary manipulation</td>
<td>3.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Administration of an isotope</td>
<td>3.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Examination of internal structures through natural orifices</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Dental care (other than surgery)</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Research on educational innovation(s)</td>
<td>2.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Use of ultrasound</td>
<td>2.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Radiosurgical technique</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Reproductive biology</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Examination of internal structures, not using natural orifices</td>
<td>1.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Obstetrical care</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Administration of anesthetic</td>
<td>1.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Prosthetic device</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Physical therapy or rehabilitation</td>
<td>1.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Administration of energy forms other than electricity</td>
<td>0.5</td>
<td>1.9</td>
</tr>
<tr>
<td>(e.g., heat, cold)</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>0.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Administration of electricity (e.g., shock defibrillation, paceremakers)</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Kidney dialysis</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Exchange transfusion</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Use of laser</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Extracorporeal circulation (excluding that for open-heart surgery)</td>
<td>...</td>
<td>0.7</td>
</tr>
<tr>
<td>Other type of intervention or procedure</td>
<td>0.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

* Less than 0.05%  
** Percent of projects that involved, or percent of experimental group subjects exposed to each of the procedures listed above—either as an experimental intervention, as a procedure being evaluated, or as a means of collecting data for the study. These data are based on information provided by the Principal Investigators of the projects.
### TABLE 2
Additional Information on the Administration of Drugs, Chemical Agents, Fluids, or Blood Products

<table>
<thead>
<tr>
<th>Number of drugs or substances being evaluated</th>
<th>Percent of All Subjects</th>
<th>Percent of All Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>86.9%</td>
<td>66.7%</td>
</tr>
<tr>
<td>1</td>
<td>7.0</td>
<td>19.0</td>
</tr>
<tr>
<td>2</td>
<td>1.9</td>
<td>6.1</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>2.8</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>2.1</td>
</tr>
<tr>
<td>5 or more</td>
<td>1.6</td>
<td>2.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substance being administered</th>
<th>Percent of All Subjects</th>
<th>Percent of All Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug or chemical agent</td>
<td>12.0</td>
<td>29.8</td>
</tr>
<tr>
<td>Vaccine</td>
<td>0.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Blood or blood product</td>
<td>0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Other</td>
<td>0.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route by which administered</th>
<th>Percent of All Subjects</th>
<th>Percent of All Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orally</td>
<td>8.0</td>
<td>17.7</td>
</tr>
<tr>
<td>Injection</td>
<td>5.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Topical</td>
<td>0.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Inhalation</td>
<td>0.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Other</td>
<td>1.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Would administration take place even if subjects were net participating in study?</th>
<th>Percent of All Subjects</th>
<th>Percent of All Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>6.3</td>
<td>12.9</td>
</tr>
<tr>
<td>No</td>
<td>1.7</td>
<td>17.6</td>
</tr>
<tr>
<td>Yes, for some subjects</td>
<td>...</td>
<td>1.7</td>
</tr>
<tr>
<td>Not ascertained</td>
<td>0.5</td>
<td>1.9</td>
</tr>
<tr>
<td>No administration involved</td>
<td>86.5</td>
<td>65.8</td>
</tr>
</tbody>
</table>
### TABLE 3
Additional Information on the Obtaining of Bodily Fluids

<table>
<thead>
<tr>
<th>Bodily fluid being used</th>
<th>Percent of All Subjects</th>
<th>Percent of All Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>33.2%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Urine</td>
<td>9.8</td>
<td>18.2</td>
</tr>
<tr>
<td>Saliva</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Amniotic (by amniocentesis)</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Pleural</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Abdominal</td>
<td>1.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Spinal</td>
<td>0.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Other</td>
<td>9.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Arterial, venous or capillary?</td>
<td>28.4</td>
<td>35.6</td>
</tr>
<tr>
<td>Venous</td>
<td>3.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Arterial</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Capillary</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Not ascertained</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Would fluid be obtained even if subjects were not participating in study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16.8</td>
<td>21.8</td>
</tr>
<tr>
<td>No</td>
<td>9.0</td>
<td>18.3</td>
</tr>
<tr>
<td>Yes, for some subjects</td>
<td>8.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Yes, but more is being taken</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Not ascertained</td>
<td>0.6</td>
<td>1.3</td>
</tr>
</tbody>
</table>
TABLE 4
Additional Information on the Obtaining of Tissue

<table>
<thead>
<tr>
<th>By biopsy, surgery, or other?</th>
<th>Percent of All Subjects</th>
<th>Percent of All Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>5.6%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Surgery</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Birth or abortion</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Autopsy</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Other</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Organ/port being biopsied</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Liver</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Brain</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Other</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Would procedure be used even if subjects were not participating in study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7.8</td>
<td>8.8</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Not ascertained</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No tissue obtained</td>
<td>91.1</td>
<td>89.3</td>
</tr>
</tbody>
</table>

TABLE 5
Additional Information on Surgery

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Percent of All Subjects</th>
<th>Percent of All Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast surgery</td>
<td>2.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Gynecological surgery</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Urological surgery</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>0.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Dental surgery</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Oral and maxillofacial surgery</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Vascular and cardiac surgery</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Other</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>No surgery involved</td>
<td>95.3</td>
<td>93.4</td>
</tr>
<tr>
<td>Would surgery take place even if subjects were not participating in study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.7</td>
<td>5.7</td>
</tr>
<tr>
<td>No</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Not ascertained</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>No surgery involved</td>
<td>95.3</td>
<td>93.4</td>
</tr>
</tbody>
</table>
### TABLE 6
**Additional Information on Anesthetic Administration**

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Percent of All Subjects</th>
<th>Percent of All Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local, topical</td>
<td>0.7%</td>
<td>2.5%</td>
</tr>
<tr>
<td>General</td>
<td>0.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Spinal</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Other</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Would procedure be used even if subjects were not participating in study?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.1</td>
<td>3.9</td>
</tr>
<tr>
<td>No</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Not ascertained</td>
<td>...</td>
<td>0.1</td>
</tr>
<tr>
<td>Anesthetic not involved</td>
<td>98.6</td>
<td>94.9</td>
</tr>
</tbody>
</table>

### TABLE 7
**Demographic Characteristics of Subjects**

<table>
<thead>
<tr>
<th>Sex:</th>
<th>Female</th>
<th>51.0%</th>
<th>Male</th>
<th>48.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race:</td>
<td>White</td>
<td>71.2%</td>
<td>Black</td>
<td>23.7%</td>
</tr>
<tr>
<td>Income:</td>
<td>Middle</td>
<td>51.3%</td>
<td>Lower</td>
<td>35.1%</td>
</tr>
<tr>
<td>Age:</td>
<td>Newborn</td>
<td>5.0%</td>
<td>3 months-6 years</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

*Percent of subjects in each group—based on the estimates of the principal investigators with their projects weighted in consideration of the number of experimental subjects in their studies.*
### Table 8
Probability of Risks and Benefits to Subjects*

<table>
<thead>
<tr>
<th>Benefits</th>
<th>None</th>
<th>Very Low</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>Unknown</th>
<th>Not Asscertained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>44.6%</td>
<td>2.6%</td>
<td>4.3%</td>
<td>25.6%</td>
<td>11.8%</td>
<td>1.9%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Psychological</td>
<td>51.3</td>
<td>10.0</td>
<td>5.4</td>
<td>13.2%</td>
<td>6.7%</td>
<td>4.2%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Other</td>
<td>76.7</td>
<td>0.4</td>
<td>2.0</td>
<td>7.6</td>
<td>8.1%</td>
<td>0.7%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Risks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Psychological Stress</td>
<td>39.0</td>
<td>39.5</td>
<td>10.2</td>
<td>4.8</td>
<td>0.4</td>
<td>1.4%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Complications</td>
<td>84.9</td>
<td>0.8</td>
<td>0.8</td>
<td>0.0</td>
<td>---</td>
<td>0.1%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Minor Medical Complications</td>
<td>60.6</td>
<td>22.3</td>
<td>2.9</td>
<td>1.9</td>
<td>1.2%</td>
<td>0.4%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Serious Medical Complications</td>
<td>63.8</td>
<td>8.7</td>
<td>1.3</td>
<td>1.1</td>
<td>0.1%</td>
<td>0.2%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Fatal Complications</td>
<td>88.0</td>
<td>6.1</td>
<td>1.0</td>
<td>0.1%</td>
<td>---</td>
<td>0.1%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Breach of Confidentiality -embarrassment</td>
<td>72.7</td>
<td>17.0</td>
<td>3.6</td>
<td>0.4</td>
<td>0.7%</td>
<td>---</td>
<td>4.7%</td>
</tr>
<tr>
<td>Breach of Confidentiality -legal problems</td>
<td>81.1</td>
<td>9.0</td>
<td>3.1</td>
<td>0.3%</td>
<td>0.1%</td>
<td>0.4%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Other Risks</td>
<td>91.8</td>
<td>2.4</td>
<td>0.9</td>
<td>0.1</td>
<td>---</td>
<td>0.1%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

* Percentages represent the percent of experimental subjects involved in the projects in the sample (with projects weighted in consideration of the number of experimental subjects involved). Probabilities reflect investigators' estimates of risks and benefits at the beginning of their projects.
TABLE 9
Main Reasons Why People Agreed to Participate in Research

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percent of Subjects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>To help their own disease/problem</td>
<td>16.0%</td>
</tr>
<tr>
<td>Other personal advantage</td>
<td>12.2</td>
</tr>
<tr>
<td>Enjoy the experience; interested; curious</td>
<td>9.5</td>
</tr>
<tr>
<td>To help the study; feel the project is worthwhile</td>
<td>9.4</td>
</tr>
<tr>
<td>Previous (positive) experience with research</td>
<td>4.1</td>
</tr>
<tr>
<td>To understand better disease or own condition</td>
<td>3.5</td>
</tr>
<tr>
<td>To learn something; educational experience</td>
<td>3.3</td>
</tr>
<tr>
<td>Money; financial reimbursement</td>
<td>2.7</td>
</tr>
<tr>
<td>Help others in general; help society</td>
<td>2.7</td>
</tr>
<tr>
<td>To help specific others (e.g., own children)</td>
<td>2.6</td>
</tr>
<tr>
<td>Future advantage in health care (e.g., check-ups)</td>
<td>2.5</td>
</tr>
<tr>
<td>Per recommendation of physician</td>
<td>1.7</td>
</tr>
<tr>
<td>To help science/research in general</td>
<td>1.6</td>
</tr>
<tr>
<td>To help others with same condition</td>
<td>1.5</td>
</tr>
<tr>
<td>No risk; study not seen as harmful</td>
<td>1.2</td>
</tr>
<tr>
<td>To help researcher; personal rapport with researcher</td>
<td>1.1</td>
</tr>
<tr>
<td>To get better care; more personal attention</td>
<td>1.0</td>
</tr>
<tr>
<td>Other</td>
<td>4.6</td>
</tr>
<tr>
<td>Don't know</td>
<td>0.8</td>
</tr>
<tr>
<td>Not ascertained/not applicable</td>
<td>16.9</td>
</tr>
</tbody>
</table>

* Percent of subjects in each group—based on the estimates of the principal investigators with their projects weighted in consideration of the number of experimental subjects in their studies.

TABLE 10
Payment to Subjects for Participation

<table>
<thead>
<tr>
<th>Amount of Payment**</th>
<th>Percent of Subjects</th>
<th>Percent of Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0 (no payment)</td>
<td>78.3%</td>
<td>74.5%</td>
</tr>
<tr>
<td>$1-5</td>
<td>5.9</td>
<td>3.1</td>
</tr>
<tr>
<td>$6-10</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>$11-15</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>$16-20</td>
<td>0.4</td>
<td>1.1</td>
</tr>
<tr>
<td>$21-25</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>$26-50</td>
<td>0.7</td>
<td>1.6</td>
</tr>
<tr>
<td>$51-100</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>$100-200</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>$200 or more</td>
<td>--*</td>
<td>0.5</td>
</tr>
<tr>
<td>Other payment (e.g., dollars per hour)</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Payment, but no information about amount</td>
<td>2.7</td>
<td>5.3</td>
</tr>
<tr>
<td>No information about payment to subjects</td>
<td>7.1</td>
<td>7.4</td>
</tr>
</tbody>
</table>

** Excluding reimbursement for expense of participating.
* Less than 0.05%.
Risk of Injury Associated with Twenty Invasive Procedures Used in Human Experimentation and Assessment of Reliability of Risk Estimates

Mary Harvey, M.D.*
Robert J. Levine, M.D.†

Objective
This study was designed to determine the risk of injury to human subjects which may result from the use of invasive procedures in medical research projects. Given the practical difficulties of evaluating the risk associated with all of the large number of procedures used in medical research, a representative sample of twenty invasive procedures was proposed for this study.

This project was not intended to generate new data with which to estimate risk of injury, but rather to evaluate data accumulated from previous experience with invasive procedures in medical research projects. Published reports of research projects in which the twenty procedures selected for evaluation had been used were selected as the source of data.

The risk of injury associated with any procedure performed in a controlled research environment has been assumed to be less than the risk of the same procedure performed on sick patients in a clinical setting. Although there are intuitively logical arguments to suggest that this is, in fact, the case, this assumption has not been shown to be correct by an actual comparison of the risks of procedures in the research setting and in the clinical setting.

The second objective of this study was, therefore, to compare the risks of the twenty selected procedures performed in both settings. Published reports of the complications associated with

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the routine diagnostic and therapeutic use of these procedures were selected as the source of data for this part of the study.

The third objective of the study was to make an assessment of the reliability of risk estimates in the publications reviewed for the first two parts of the study. The following approach was taken to accomplish this objective:

(1) Prospective and retrospective studies were compared for consistency of risk estimates for specific complications as well as for morbidity and mortality.

(2) Prospective studies on each complication were compared as in #1.

(3) When inconsistencies were detected, the studies with differences in estimate of risk were compared for differences in subject susceptibility to development of the complication, differences in method of performance of the procedure, differences in operator skill, differences in methods used to detect the complication, and differences in diagnostic criteria for when the complication had occurred.

(4) Criteria were developed for grading adequacy of assessment of risk and each study was evaluated according to these criteria.

The third objective was limited by the design of the study since in a survey study of the medical literature, the ability to accomplish this objective depends, in large extent, on the amount of information provided by the authors of the articles reviewed.

Certain epidemiological assumptions have been made in the design and execution of this project. The word “risk” is used in this study as a statement of probability. The risk of injury is then a question about the probability of injury occurring when a specific procedure is performed repeatedly under similar circumstances. In the situation in which we are interested, injury occurs as a result of one or more complications associated with the performance of an invasive medical or surgical procedure. Therefore, the questions which are asked in this study are “What is the probability of one or more complications occurring if procedure X is performed many times on a given population?” and “If a complication occurs, what is the probability that it will cause injury (morbidity) or death (mortality)?”

The probability of a complication resulting from a given procedure is determined by observing the number of occurrences of a given complication in a population exposed to the procedure. This is the incidence of the complication. Risk is therefore a measure of the incidence of the complication. Thus, if a patient is told that four out of 100 people who have procedure X will develop an injury (fatal or non-fatal), the statement is equivalent to saying that the risk of the procedure is 4%.

In this study the risk of injury associated with each procedure is determined, where possible, by calculating the inci-
Risk of Injury

Incidence of complications which occur in each study reported. The incidences calculated for each study are listed together for comparison. A combined incidence [the sum of all of the complications in all of the studies of a given procedure divided by the sum of all of the subjects in all of the studies for that procedure] is not calculated. This is avoided because the characteristics of the population at risk and the conditions surrounding the performance of a procedure greatly influence the incidence of complications in the subject population. Summing the results will not only provide an inaccurate assessment of the risk but will also obscure the important differences which can contribute to an understanding of factors which may increase or decrease the risk of injury from any procedure.

Throughout this text, the pronoun "he" has been arbitrarily used as the singular pronoun to refer to persons of either gender.

Materials and Methods

A list of procedures used in human experimentation was provided by the Institute for Social Research (ISR), Ann Arbor, Michigan (Attachment I). The list was developed during a study of Institutional Review Boards conducted by the ISR in 1976. For this study, a sample of 61 institutions representing 88 Institutional Review Boards was chosen by a modified random-selection process. A total of 2210 investigators whose research proposals had been reviewed by these Institutional Review Boards were interviewed to ascertain which procedures had been used in research projects involving human subjects during the period July 1, 1974, to June 30, 1975.*

The list of procedures assembled during the ISR study includes only the general categories of non-invasive and invasive procedures reported by those investigators. In order to study the risks associated with specific invasive procedures, the original ISR list was modified by excluding non-invasive procedures, and by including for consideration all specific procedures within each general category of procedure.

For example, the category "cardiac catheterization" was expanded to include right heart catheterization (Swan-Ganz catheter placement) and left heart catheterization. From the expanded list (Attachment II), twenty invasive procedures used in human experimentation were selected for evaluation (Attachment III). Selection criteria are presented in Attachment IV.

The published experience with the procedures selected for evaluation was obtained by means of an exhaustive Medline search. The search strategy called for key-word as well as title entries. The Medline file covering the period from 1970-1980 was searched for entries containing the names or synonyms of the twenty procedures and descriptors for "risk", "complication", *

* We are indebted to Mr. Robert A. Cooke, Associate Research Scientist, Institute for Social Research, Ann Arbor, Michigan, for providing us with the information on use of procedures in medical research.
Compensating for Research Injuries: Appendix E

"morbidity", "adverse effects", "human experimentation", and "research". In response to this strategy, the Medline file produced 1763 titles. All of these were read in abstract. Of this set, 600 were selected for detailed review on the basis of their apparent relevance to the purpose of this study.

In order to compile comparable data from a diverse literature, an extraction code was utilized (Attachment V). The code consists of ten items. Items 1 through 9 were used to assess the risk of the procedure in question and item 10 was used to gain access to relevant literature published before 1970.

Accuracy of the reported risks was judged by evaluating each study according to criteria developed to assess the adequacy of risk monitoring and risk reporting (Attachment VI).

Results

Review of the 1763 abstracts obtained in the literature search indicates that published data on the risk of injury to subjects in human experimentation are very limited.

There were two references to survey studies of the risk of injury to research subjects and no references to studies of the risk of injury due to performance of any specific procedure in a research project.

The survey studies include the 1975 report of the Secretary's Task Force on the Compensation of Injured Research Subjects, Department of Health, Education and Welfare, reported by Cardon, et al., in 1976 [47], and the Study of Institutional Review Boards, Institute for Social Research, Ann Arbor, Michigan, reported by Gray, et al., in 1978 [126]. Both studies provide an estimate of overall risk of injury to research subjects, but neither study analyzed risk as a function of exposure to specific interventions or procedures.

To estimate the risk of injury associated with each of the twenty procedures selected for evaluation in this study, we reviewed references to research projects in which these procedures were used. In 45% of these published reports, the occurrence of complications are not discussed. Complications are discussed in 55% of the research studies reviewed, but in one-third of these, non-quantitative descriptions of complications are given. For example, Gillquist, et al. report that some subjects experience "transient pain" in a project designed to test a new method of arthroscopy and Hartman, et al. describe an unknown number of occurrences of "areas of ecchymoses in the skin surrounding the point of insertion of the [bone biopsy] needle" [121, 138].

In the remaining studies, the number of occurrences of at least one complication is given. In many of these reports, however, only major complications are described. Less serious complications are cited as having occurred, but the incidence of these complications is not given.
The most thorough reporting of the incidence of complications occurred in research projects in which hemodialysis, lumbar puncture, exercise tolerance testing, anesthesia or experimental drugs were used. For the remaining 15 procedures, the published data were insufficient to allow estimation of risk of injury to research subjects.

Since most of the procedures selected for evaluation in this study are commonly used in patient care, there is considerable experience with complications following their use in the clinical setting. The incidence of these complications was ascertained by reviewing references to the reported complications of all twenty procedures when they are used as diagnostic or therapeutic interventions.

It is generally held that the risk of injury due to performance of a procedure in a controlled research environment is less than the risk of injury attending the performance of the procedure on a compromised patient in a clinical setting. In the absence of adequate data for the risk of injury in research, this assumption cannot be proved or disproved. However, if the assumption is accepted, then the complication rates reported for the clinical use of these procedures may be considered to be the expected maximum complication rate when the procedure is used in a research project.

In the following sections, the complication rates reported for each of the twenty procedures are presented. Complication rates reported in prospective studies are considered separately from complication rates reported in retrospective studies. For many of the procedures, the range of complications rates reported is extreme. When known, unusual circumstances which may account for these differences are discussed.

Risk of Injury to Research Subjects: An Overview. Literature which quantifies the risk of injury to human subjects in medical research is rare. The paucity of the literature on this subject reflects not the absence of such research, nor the lack of injuries in such research, but reflects instead its rather recent development as an important social and ethical concern.

The appearance in the 1960's of a large literature which discusses issues of ethics in medical research, as well as in general medical practice, reflects the increased social awareness which occurred in the medical community at that time, as well as in other segments of American society. Although medical literature is frequently considered to reflect only current issues in science, it almost always concurrently reflects the current concerns and conceptions (or misconceptions) of the society in which that science is practiced. An excellent example of this phenomenon is provided by Davenport who undertook, in 1939, an experiment to ascertain the types of reactions which resulted from lumbar puncture [65]. In a series of over 1000 patients he observed that 32.4% of his subjects had "reactions" (these were primarily headache, although an occasional vertigo developed). Since he also
observed that these "reactions" were more severe in women and Puerto Ricans and less severe in Blacks, he concluded not that the performance of lumbar puncture may result in considerable morbidity, but that the higher incidence among women and Puerto Ricans indicates a "neurotic trend," while the lower incidence among Blacks suggests that "the Negro is not as susceptible to pain as the White."

The general medical literature, as well as the research literature before the 1960's, is frequently remarkable for the absence of awareness of the concept of risk or complication to either patient or research subject. It is not uncommon during this period to read reports of research projects in which the occurrence of serious injuries are described by an author who does not indicate that he recognizes these as potentially avoidable complications of the procedure. For example, in 1960, Feer, et al. conducted the first experiment with hemodialysis as a treatment for schizophrenia (102). The authors meticulously describe the occurrence in four out of five cases of a "state of pre-collapse" or "collapse" (characterized by flushing, hypotension and occasional fever). The authors do not recognize these events as potentially life-threatening complications of hemodialysis but tend to interpret them as unusual physiologic responses of the schizophrenic to hemodialysis. Therefore, the authors are able to describe a patient with severe "collapse" who had inadequate blood pressure for three hours and observe, not that the patient was in cardiovascular or hypovolemic shock but that he was not his usual self, but was "catatonic" and withdrawn.

While physicians since Hippocrates have recognized the potential for iatrogenic disease, an increasing awareness of this problem occurs in the general medical literature about ten years before it appears in the medical research or medical ethics literature. In 1955, for example, Barr wrote the article Hazards of Modern Diagnosis and Therapy in which he anecdotally relates 50 occurrences of illness caused by diagnostic or therapeutic maneuvers in a population of approximately 1000 patients (18). This article has been used to cite a complication rate of 5% for medical therapy despite its informal, anecdotal nature.

Ten years later, Schimmel published The Hazards of Hospitalization which describes a prospective study of all complications occurring on the medical service of Grace-New Haven Community Hospital (teaching service) during a nine month period (256). The complications reported range from falling out of bed to fatal misadventure with diagnostic or therapeutic interventions. He identifies 240 complications occurring in 1252 hospitalizations (20.0% incidence of complications) with a 12.8% overall mortality rate.

In 1976 and 1978 the first and only articles on the overall risk of injury to research subjects appeared in the literature. Both were conducted as interview surveys of investigators who had conducted research involving human subjects. Information was
obtained about complications occurring in research conducted
1-3 years prior to the time of the study.

The first of these studies was done in 1975 by the Secretary's
Task Force on the Compensation of Injured Research Subjects,
Department of Health, Education and Welfare [47]. Its goal was
to estimate the incidence of research-related injuries. The survey
was conducted by telephone interview with investigators who
had been provided with a list of questions to be answered prior
to the telephone interview. Of 538 investigators invited to par-
ticipate in the study, 458 responded (response rate of 85%) and
adequate information was availab'e from 331.

In this study, complications were graded as trivial, tempo-
arily disabling, permanently disabling and fatal. Complication
rates were calculated for all research projects together as well as
for therapeutic and non-therapeutic research projects separately.
Therapeutic research was defined as that which was potentially
direct benefit to the subject while non-therapeutic research
was that not intended to be of direct benefit to the subject. Results
are reported as the number of occurrences of each injury in the
exposed population.

A total of 132,615 research subjects experienced 4957 in-
juries for an overall rate of occurrence of injuries of 3.7%. Of all
injuries reported, 79% were trivial, 19.6% were temporarily dis-
abling and less than 0.1% were permanently disabling or fatal.

When the results were evaluated independently for ther-
apeutic and non-therapeutic research projects, the incidence of
injuries was much larger in the therapeutic than in the non-
therapeutic group.

Approximately thirty percent of the total population of
research subjects reported in this study were involved in ther-
apeutic research projects. In this group there was a 10.8% inci-
dence of injuries. Of these injuries, 77% were classed as trivial,
22% as temporarily disabling, 0.3% as permanently disabling
and 1% as fatal.

In contrast, in the group participating in non-therapeutic
research projects, the incidence of injuries was 0.8%. Of the
injuries occurring, 94.7% were described as trivial, 5.2% were
considered temporarily disabling, less than 0.1% were perma-
nently disabling and nine were fatal.

This study suggests a low incidence of research-related in-
juries. Examination of the patterns of reporting in this study,
however, suggest that caution be used in interpreting the results.
For example, 65% of all reported therapeutic injuries were re-
ported by 8 investigators (2.6% of the investigators) each of whom
were involved in drug research and each of whom reported that
at least one complication occurred with each of their research
subjects.

Thirty-seven investigators (11.8% of investigators) reported
all of the injuries described as temporarily disabling and thirty-
four investigators (10.9% of investigators) reported all of the trivial injuries.

In the non-therapeutic research projects, all temporarily disabling injuries were reported by 12 investigators (3.8% of investigators) and the 673 trivial injuries were reported by 31 investigators (9.9% of investigators). Seventy-five percent of all injuries reported in non-therapeutic research were reported by only five investigators or 1.6% of all investigators.

These patterns of reporting may be interpreted to mean that a small number of investigators over-reported the occurrence of injuries in their research projects. However, they may also indicate that the majority of investigators under-reported the actual occurrence of injuries during their research. The latter is more likely since in this retrospective study investigators were asked to report on events which had occurred at least a year before the survey was done. This could only be done by reviewing the records available for the research project. Since a total of 132,615 subjects participated in the research projects of 313 investigators, this would mean that each investigator would have to review an average of 425 charts or records in order to provide a complete assessment of the injuries occurring to subjects in his or her research projects. This would be a herculean task for even the most dedicated investigator and it is unreasonable to assume that all of the investigators were able to provide a complete chart review.

Even if all investigators had been able to provide a complete account of injuries reported in the charts of their subjects or patient-subjects, differences in the initial definition or detection of injuries are likely to lead to under-reporting of the total number of injuries. For example, investigators are likely to differ in the frequency with which they report minor injuries such as mild pain, small hematomas or vasovagal reactions. Clearly, some will consider these occurrences worthy of a note in the chart and others will not. This type of discrepancy in recording injury is most likely to influence the incidence of trivial or temporarily disabling injuries since serious complications will almost always be recorded.

The second study of research-related injuries was done by the Institute for Social Research as part of a Study of Institutional Review Boards conducted in 1976. Determining the incidence of such injuries was not a major goal of this study and the information obtained on research-related injuries is much less complete than the information provided by the HEW study. In the ISR study, investigators whose research proposals had been reviewed by the Institutional Review Boards participating in the study were interviewed to ascertain the incidence of injury to research subjects.

In this report, complications are not grouped according to severity and results are not analyzed according to type of research done. This study reports only that injury occurred to
subjects in 3% of the projects reported. This figure gives no information about the incidence of injuries in these projects since it reports neither the number of injuries which occurred nor the number of patients at risk for these injuries. Although the authors suggest that their figure of 3.0% is comparable to the incidence of 3.7% reported in the HEW study, these two numbers are not in the least comparable. The HEW study reports the incidence of reported injuries in a known population of research subjects while the ISR study reports only the percentage of projects in which an unknown number of injuries has occurred. Similarity in the magnitude of these two numbers cannot, therefore, be used to conclude that both are accurate estimates of the risk of injury to research subjects.

Catheterization of the Urinary Bladder. Catheterization of the urinary bladder is used as a diagnostic procedure when it is desirable to obtain urine which has not been exposed to urethral flora. In these cases the catheter is removed immediately after the sample is obtained. Indwelling catheters are used with unconscious or critically ill patients whose urine output must be monitored on an hour to hour basis. They are also used with patients suffering from urinary obstruction, neurogenic bladder and incontinence secondary to neurological disease. The major complication associated with urinary catheterization is bacteruria and ascending urinary tract infection. Although mortality is not reported in any of the studies of catheter complications, bacteremia and death have certainly been associated with urinary tract sepsis.

The risk associated with catheterization of the urinary bladder is closely related to the length of time the catheter is in place. In and out catheterization, of the type that would be used in a research project, has been reported by Kass (1957) to have a risk of infection of 1%-2% (149). Turck and Petersdorf (1962) reported a risk of 1% for this procedure (292).

Six studies assessed the effects of long term, indwelling catheters attached to various types of drainage systems. Five of these addressed the problem of infection (116, 144, 158, 199, 289). The rates of infection in these studies was greater for females, and increased in both sexes with the number of days the catheter was in place. Overall, infection rates ranged from 7.3% (males catheterized four days) to 62% (both sexes, catheterized five days). Since different types of catheters, different drainage systems (open, closed and sterile vented) and patients with widely varying co-morbidity were used in these studies, they are not comparable. The sixth study (89) showed that among patients with catheters in place for greater than one month the bladder wall showed changes of polypoid cystitis in 85% to 95% of cases. No control patients without catheters had this condition. It is not clear whether this change in bladder wall morphology predisposes to infection.

Two studies assessed the effects of trans-catheter irrigation with antibiotics (307) or antiseptics (160) on infection rate. There
was no difference in the incidence of infection between patients who had been treated with antibiotic irrigation and their untreated controls (16% versus 18% infections). Instillation of cyclohexidine, a topical antiseptic, was followed by 38.7% infected urines, while a matched control group similarly catheterized but without cyclohexidine treatment developed 58.7% infections. The reason for the large difference in "control group" infection rate between these two studies is not clear, but may have been due to patient selection, catheterization technique or type of drainage system used.

An alternative to the indwelling catheter in patients requiring chronic urinary drainage is periodic "in and out" catheterization. Five studies approach this possibility. In two of these (292, 293) ambulatory patients were subjected to the procedure and cultured biweekly for six weeks. Among 200 patients of both sexes only one developed significant bacteruria. Similarly, Kass (149) performed the procedure once on each of 335 patients and found a 1%-2% infection rate.

Sterile intermittent catheterization technique was taught to 70 persons with neurological injury. These were studied with frequent cultures for 28 months or 5052 patient-days of self catheterization. During that time 38 patients developed 52 cases of infected urine, for a rate of 10.3 infections/1000 patient-days (238).

The last report of intermittent catheterization studied the use of clean (but not sterile) catheters by 218 patients who had previously been using long-term indwelling catheters. On entry into the study 91% of patients had infected urines. After varying times on the study technique, this number had decreased to 52% (Table 1).

Central Venous Catheterization. Venous cannulation with polyethylene catheters was first introduced in 1945. Initially, use of these catheters was restricted to peripheral veins where they were used to deliver intravenous fluids and medications. The use of polyethylene catheters in large central veins was introduced in 1949. Cannulation of the inferior vena cava, superior vena cava, axillary and jugular veins rapidly followed. Central venous catheterization is now a commonly used technique in both clinical practice and in medical research.

Recent advances in this technique include percutaneous catheterization rather than introduction of the catheter by cutdown on a vein and the introduction in the 1960's of Teflon catheters.

Cannulation of any central vein may cause complications associated with the insertion of the catheter. These complications include pain, infection and bleeding at the puncture site. For catheters introduced into the subclavian or jugular veins, proximity of these veins to the lung adds the additional complication of inadvertent lung puncture with resultant pneumothorax, hemothorax or hydrothorax. Additional complications of these
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Straight Cath</th>
<th>24 Hrs.</th>
<th>48 Hrs.</th>
<th>72 Hrs.</th>
<th>5 Days</th>
<th>7 Days or More</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kass (1957)</td>
<td>335</td>
<td>1.0-2.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0-2.0%</td>
</tr>
<tr>
<td>Turck &amp; Petersdorf (1962)</td>
<td>100</td>
<td>1.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0%</td>
</tr>
<tr>
<td>Turck, et al. (1962)</td>
<td>200</td>
<td>0.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td>Lapides, et al. (1976)</td>
<td>218</td>
<td>52.0%*</td>
<td>7(14.0%)</td>
<td>23(46.0%)</td>
<td>33(66.0%)</td>
<td>41(82.0%)</td>
<td></td>
<td>52.0%</td>
</tr>
<tr>
<td>Korbil &amp; Maher (1976)</td>
<td>100*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38(38.0%)</td>
</tr>
<tr>
<td>Tidd, et al. (1976)</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41(82.0%)</td>
</tr>
<tr>
<td>Islam &amp; Chapman (1977)</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 30.0%</td>
</tr>
<tr>
<td>Monson, et al. (1977)</td>
<td>251*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26.0%</td>
</tr>
<tr>
<td>Warren, et al. (1978)</td>
<td>187</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.0-18.0%</td>
</tr>
<tr>
<td>Kirk, et al. (1979)</td>
<td>125</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61(49.9%)</td>
</tr>
<tr>
<td>Keys, et al. (1979)</td>
<td>230</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29(12.0%)</td>
</tr>
</tbody>
</table>

a. Daily straight cath for neurogenic bladder
b. No antibiotic prophylaxis
c. Vented drainage only
d. Length of catheterization unknown
Catheters are related to function as a foreign body within a vascular structure. Thrombosis and systemic infection have both been frequent complications of this procedure.

Ten prospective studies of the complications associated with central venous catheterization are summarized in Table 2 (54, 96, 16, 29, 266, 304, 31, 196, 26). The studies report catheterizations of several different central veins, but do not include a study of femoral or inferior vena cava catheterization. Infectious and thrombotic complications are well-reported in all studies. Only three studies involve the subclavian or jugular veins and two of these report the incidence of pneumo-, hemo-, or hydrothorax. In this series, the incidence of local or systemic infection was 0.0% to 29%. The largest infection rate is reported by Miller, et al. (1980) for a study of hyperalimentation lines. The rate of infection associated with an in-dwelling catheter increases with the length of time the catheter is in place. Since hyperalimentation lines are intended to remain in place for as many months as possible, the high incidence of infection associated with this study is best explained by the long in-dwell time used with this type of catheter. If this study is excluded from consideration, the incidence of infection associated with the use of in-dwelling central venous catheters ranges from 0.0% to 3.4% (16, 29, 266, 304, 31).

Thrombosis or thrombophlebitis is reported as a complication in 6 studies with an incidence ranging from 3% to 69%. Cheney and Lincoln (1964) report the highest incidence of catheter-related thrombotic complications (54). They demonstrate the relationship between thrombotic complications and the length of time a catheter is in place by noting that at 24 hours their patients had a 9% incidence of thrombosis or phlebitis, while at 48 hours, the incidence had increased to 60%. With the exception of the hyperalimentation lines studied by Miller, et al. the catheters described in these five studies were in place from one to 45 days. Differences in in-dwelling time may account for some of the widely observed differences in the occurrence of thrombotic complications. All studies used clinical observation to detect these complications with the exception of Walters, et al. who used venography in twenty of their 240 patients and detected four asymptomatic axillary vein thromboses (304).

Of the three studies in which subclavian vein or internal jugular vein catheterization was done, two discuss the complications of pneumo- or hemothorax (26, 96). English, et al. report no occurrences of pneumo- or hemothorax in 200 procedures. Bellani, et al. report one pneumothorax and one hydrothorax occurring in 114 procedures, an incidence of 1.8%. The morbidity of central venous catheterization reported in these studies ranges from 1.5% to 82%. The highest morbidity rates are reported for studies in which the occurrence of thrombosis of the vein and occlusion of the catheter by thrombi were reported. Studies in which these complications were not specifically sought and were not reported have morbidity rates of 3.4% to 12.3%. The mor-
### Table 2
Complications of Central Venous Lines: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Local or Systemic Infection</th>
<th>Thrombosis or Phlebitis</th>
<th>Catheter Occlusion</th>
<th>Hemorrhage</th>
<th>Hydrothorax or Pneumothorax</th>
<th>Inadvertent Arterial Punctures</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheney &amp; Lincoln (1964)</td>
<td>137*</td>
<td>**</td>
<td>82(60.0%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>82(60.0%)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Elving &amp; Hrabacka (1967)</td>
<td>1049</td>
<td>**</td>
<td>262(25.0%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>262(25.0%)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>English, et al. (1969)</td>
<td>60</td>
<td>200*</td>
<td>0</td>
<td>3</td>
<td>3(1.5%)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Banks, et al. (1970)</td>
<td>118*</td>
<td>4(3.4%)</td>
<td>0</td>
<td>0</td>
<td>3(1.5%)</td>
<td>0</td>
<td>3(1.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bernard, et al. (1971)</td>
<td>98*</td>
<td>3%*</td>
<td>0.9%*</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>0.9%*</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Sketch, et al. (1972)</td>
<td>484*</td>
<td>0(0.0%)</td>
<td>3(7.8%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>7(14.5%)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Walters, et al. (1973)</td>
<td>240*</td>
<td>2(0.8%)</td>
<td>4(17.0%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>4(17.0%)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Bottino, et al. (1979)</td>
<td>67*</td>
<td>1(1.2%)</td>
<td>17(19.5%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>31(35.6%)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Miller, et al. (1980)</td>
<td>137f</td>
<td>40(29.0%)</td>
<td>5(3.6%)</td>
<td>14(10.2%)</td>
<td>**</td>
<td>**</td>
<td>21(16.8%)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Belani, et al. (1980)</td>
<td>114</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

(a) Basilic or cephalic vein  
(b) Access site not reported  
(c) Internal jugular vein  
(d) Subclavian vein  
(e) Antecubital  
(f) Hyperalimentation line

* Number of occurrences not given  
** Not reported
Compensating for Research Injuries: Appendix E

bidity in these studies results from local or systemic infection and from inadvertent arterial punctures. No mortality is reported in this group of prospective studies.

Retrospective studies of central venous catheterization are summarized in Table Three. Only two of seven studies in this group report the occurrence of infection in their catheterized patients (30, 148). Bogen (1960) reports a 5.1% incidence of local or systemic infection associated with femoral catheters placed by house-officers. James and Myers (1973) report a 0.6% incidence of infection associated with supraclavicular catheters placed by staff surgeons.

The incidence of thrombosis or phlebitis is examined in five of the seven studies and is 0.6% to 55%. Bansmer, et al. report a 55% incidence occurring in twenty patients with femoral catheters and Moncrief (1958) reports the next highest incidence of 14.8%, also occurring in patients with femoral catheters (17, 198). In the remaining three studies by Bogen (1960), Jernigan, et al. (1970), and James and Myers (1973), the incidence of thrombosis is reported as 4.3%, 0.1%, 0.06% respectively. The higher incidences reported by Bansmer, et al. and by Moncrief may result from the use of femoral catheters which tend to keep patients immobile and therefore predisposed to thrombotic complications. A comparison of thrombotic phenomena reported in retrospective and prospective studies shows a much lower reported incidence of thrombosis in retrospective studies. This is most likely to result from failure to detect thrombosis and phlebitis in retrospective studies due to poor reporting of these events.

In the retrospective series, a relatively large number of events are included in the category "other." These include a variety of complications such as air embolism, overhydration of a patient through a central venous catheter, mediastinal infiltrates, and lost catheter tubing. These less usual, but serious, complications of central venous catheterization are prominent in many retrospective studies because they represent somewhat unusual and grave complications which are likely to be recorded in a patient's chart and thus be preserved for detection in a retrospective study. In contrast, simple thrombosis without sequelae is more likely to be overlooked as a complication requiring documentation and thus, in retrospective studies, these types of events tend to be under-reported.

Swan-Ganz Catheter Placement. The Swan-Ganz catheter, introduced by Swan and Ganz in 1970, is a complex catheter which contains several lumens and a small, inflatable balloon at the distal end of the catheter. It is inserted into a large peripheral vein or a central vein and passed along the vein to the right side of the heart. From the right side of the heart, the catheter can be passed into the pulmonary artery. Use of the catheter allows measurement of pressures on the right side of the heart and, when the distal balloon is inflated in the pulmonary artery, measurement of the left ventricular end-diastolic pressure. The pro-
### TABLE 3
Complications of Central Venous Lines: Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Local or Systemic Infection</th>
<th>Thrombosis or Phlebitis</th>
<th>Catheter Occlusion</th>
<th>Hemothorax, Hydrothorax, or Pneumothorax</th>
<th>Other*</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moncrief (1958)</td>
<td>135*</td>
<td>**</td>
<td>20 (14.8%)</td>
<td>**</td>
<td>**</td>
<td>3 (2.2%)</td>
<td>20 (19.2%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Bansmer, et al. (1958)</td>
<td>29*</td>
<td>**</td>
<td>11 (55.0%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>11 (55.0%)</td>
<td>**</td>
</tr>
<tr>
<td>Bogen (1960)</td>
<td>234*</td>
<td>**</td>
<td>10 (4.3%)</td>
<td>**</td>
<td>**</td>
<td>12 (5.1%)</td>
<td>3 (14.5%)</td>
<td>**</td>
</tr>
<tr>
<td>Wilson, et al. (1962)</td>
<td>450*</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Jernigan, et al. (1970)</td>
<td>1000*</td>
<td>**</td>
<td>1 (0.1%)</td>
<td>**</td>
<td>**</td>
<td>2 (2.2%)</td>
<td>3 (0.3%)</td>
<td>**</td>
</tr>
<tr>
<td>James &amp; Myers (1973)</td>
<td>3000*</td>
<td>**</td>
<td>2 (0.6%)</td>
<td>**</td>
<td>56 (1.2%)</td>
<td>44 (1.5%)</td>
<td>177 (5.9%)</td>
<td>**</td>
</tr>
<tr>
<td>Feliciamo, et al. (1979)</td>
<td>1500*</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>4 (0.3%)</td>
<td>8 (0.5%)</td>
<td>2 (0.1%)</td>
</tr>
</tbody>
</table>

* Includes hematoma, air embolism, over-hydration
** Not reported
*** Occurred but number of occurrences not given

- [a] Femoral vein
- [b] Inferior vena cava
- [c] Subclavian vein
- [d] Axillary vein
- [e] Internal jugular vein
procedure is used extensively in the clinical practice of medicine in the management of critically ill patients. The procedural technique is relatively simple and a Swan-Ganz catheter can be placed at an intensive care bedside by a house-officer.

Swan-Ganz catheterization has also been frequently used for research purposes in studies of cardiovascular or pulmonary physiology of pharmacology.

The complications of the Swan-Ganz catheter result from several different technical aspects of the procedure.

Bleeding and infection may occur at the site of catheter insertion and venous thrombosis as well as systemic infection may result from the presence of the catheter as a foreign body in the venous system. If the catheter is introduced via the subclavian vein or internal jugular vein, pneumothorax or hemothorax may result from inadvertent puncture of the lung or perforation of a great vein. As the catheter passes through the right ventricle on its way to the pulmonary artery, irritation of the right ventricle may result in ventricular arrhythmias. Finally, the tip of the catheter or an inflated catheter balloon may cause infarction of the lung and/or hemorrhage.

These represent the major, most common complications of the Swan-Ganz catheter. A variety of unusual complications such as pulmonary artery-bronchial fistula, hemomediastinum, and pulmonary valve insufficiency have been reported in the case report literature [247, 125, 216].

Prospective studies of the Swan-Ganz catheter are summarized in Table 4. The first prospective studies designed to assess the incidence of complications occurring with use of the Swan-Ganz catheter were reported in 1979 [91, 233, 259]. Prospective studies before then report an investigator’s experience with the procedure, but these investigators do not monitor the procedure for specific complications. This reflects the fact that when a new procedure is introduced, the complications associated with the procedure are usually not well-defined until the procedure has been in clinical use for several years.

In their initial paper, introducing the catheter, Swan/Ganz, et al. (1970) noted a 15% incidence of ventricular ectopy occurring while the catheter passed through the right ventricle. No other complications were noted in the first 100 procedures performed by Swan and Ganz, but these authors do report the presence of a small clot on the tip of one catheter at the time it was removed. All of the catheters placed by Swan and Ganz were in place for less than 48 hours. The three other studies which note the occurrence of ventricular ectopy during placement of the catheter report an incidence of these events which ranges from 17% to 77.6% [151, 91, 259]. Elliot, et al. (1979) reports all occasions in which even a single ectopic beat was noted and reports the highest incidence, 77.6%. Shaw (1979), in contrast, reports only those occasions in which the ectopic beats occurred more
### TABLE 4

Complications of the Swan-Ganz Catheter: Prospective and Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Arrhythmias</th>
<th>Pneumothorax</th>
<th>Inflammation, Infection</th>
<th>Venous Thrombosis</th>
<th>Pulmonary Infarction, Hemorrhage</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swan, Ganz et al. (1970)</td>
<td>15(15.0%)</td>
<td>15(15.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15(15.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Steele &amp; Davies (1972)</td>
<td>103</td>
<td>*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Katz et al. (1977)</td>
<td>592</td>
<td>*</td>
<td>1(0.3%)</td>
<td>15(3.8%)</td>
<td>0</td>
<td>16(4.1%)</td>
<td>&gt;33(78.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Elliot et al. (1979)</td>
<td>110</td>
<td>90(72.6%)</td>
<td>0</td>
<td>2(1.7%)</td>
<td>0</td>
<td>2(1.7%)</td>
<td>6(5.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Primm et al. (1979)</td>
<td>57</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>7(12.3%)</td>
<td>7(12.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Shaw (1979)</td>
<td>73</td>
<td>27(37.0%)</td>
<td>**</td>
<td>0</td>
<td>**</td>
<td>**</td>
<td>27(37.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foote et al. (1974)</td>
<td>125</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>6(7.2%)</td>
<td>9(7.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Archer &amp; Cobb (1974)</td>
<td>86</td>
<td>4(4.7%)</td>
<td>0</td>
<td>1(1.2%)</td>
<td>0</td>
<td>0</td>
<td>5(5.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Occurred but number of occurrences not reported
** Not reported
(a) Includes 241 patients studied retrospectively
(b) Includes only patients with >1 in 4 ectopic beats
(c) Includes only ventricular tachycardia or fibrillation
frequently than one in every four beats. His reported incidence is 37.7%. Katz, et al. (1977) report an incidence of ventricular arrhythmias of 17% but more than half of the patients included in his prospective study were actually studied retrospectively. The occurrence of ectopy is often not recorded in a patient's chart unless it is sustained or requires treatment.

A single episode of pneumothorax was reported in this series. Katz, et al. (1977) recorded one such event in 392 procedures (0.3%). Elliot, et al. (1979) did not observe the occurrence of pneumothorax in their discussion of complications.

Five of the six studies report on the occurrence of infection associated with the Swan-Ganz catheter. The reported incidence ranges from 0.0% to 3.8%. The highest incidence is reported by Katz, et al. (1977) who noted five occurrences of local infection in his patients. Elliot, et al. (1979) report two episodes of systemic infection with S. aureus (1.7%) occurring after catheters were in place five or more days.

Venous thrombosis was not recognized in early studies by Swan/Ganz, et al. (1970) and Steele and Davies (1972) but Elliot, et al. (1979) noted two cases of subclavian vein thrombosis occurring in 115 patients (1.7%). Most of the catheters monitored for complications by Elliot, et al. (1979) were in place more than 48 hours.

Pulmonary infarction and hemorrhage was not observed in the early studies by Swan/Ganz et al. (1970) and Steele and Davies (1972). In later studies, the reported incidence ranges from 1.7% to 12.3%. The difference in reported incidences may result from the different methods used to detect this complication. Katz, et al. report an incidence of 4.1% which represents 16 patients with “suspected” pulmonary embolism. Four of these patients died of their underlying disease and were found to have catheter-related emboli at autopsy. Elliot, et al. report 2 cases (1.7%) detected by clinical and radiographic methods. Primm, et al. report 12.3% incidence which they detected by subjecting 57 patients to a ventilation-perfusion scan before and after a Swan-Ganz catheter was placed for routine cardiac catheterization. Seven of these patients developed new perfusion defects in the region of the catheter although the catheters had been in place only during the few hours required for cardiac catheterization.

The wide range of morbidity reported for these series, 0.0% to 82.6% is explained primarily by the differences between the studies in the report of ventricular arrhythmias. If this complication is excluded, the range reported for recent evaluations of the Swan-Ganz catheter would be 5.1% to 12.3%.

No fatalities were reported in any of the prospective studies.

Retrospective studies of the Swan-Ganz catheter are reported in Table 4 (110, 10). Foo et al. (1974) report only on the complication of pulmonary embolism, infarction or hemorrhage. They note 9 such episodes (2 pulmonary emboli and 7 infarctions)
occurring in 125 patients (7.2%). Methods of detecting these phenomena are not reported. Archer and Cobb (1974) cite an incidence of ventricular arrhythmias of 4.7%, but this includes only cases of ventricular tachycardia or fibrillation. Neither study reports any deaths due to the procedure.

Cardiac Catheterization. Cardiac catheterization has been used in many research studies designed to correlate the findings of exercise tolerance tests with presence of coronary artery disease. It has also been used to stage patients for long term prospective evaluations of coronary artery risk factors and to study the electrophysiology of the heart. Eight of these research studies were reviewed for this study. Eight of the eight studies failed to report any complications of the procedure in the published report of the project (150, 203, 231, 240, 248, 255, 291, 302).

The risk of injury during cardiac catheterization for diagnostic purposes has been extensively studied in the Cardiac Catheterization Co-operative Study reported by Swan, et al. (1968) (277). In this prospective study, 12,367 cardiac catheterizations performed by cardiologists at 16 institutions were studied between November 1963 and November 1965. The results of this study are summarized in Figure 1. Of the 300 clinical and research studies reviewed for this study, the co-operative study was the best designed evaluation of the complications of the procedure. It has been widely accepted as a reasonable evaluation of risk of injury during cardiac catheterization, even though it was completed over 15 years ago. No other major studies of the complications of cardiac catheterization have been performed since this study.

The Cardiac Catheterization Co-operative Study achieved this respectability by including the following elements of design in the study:

1. The complications to be identified by investigators were well defined prior to the study. Each investigator was required to complete a log of the occurrence of these complications at the end of each catheterization.

2. Each investigator was required to record full details about the patients' primary cardiac illnesses, other illnesses which a patient might have, medications or other factors which might increase the risk of the procedure.

3. Each investigator was required to keep a full record of the performance of the procedure and record any unusual events accompanying the performance of the procedure.

4. Each investigator was required to establish the outcome of any complication occurring and to provide follow-up of patients for the detection of any late-occurring complications.

5. During the conduct of the study, investigators were frequently monitored for their compliance with the study guidelines.
### FIGURE 1
Complications of 12,167 Cardiac Catheterizations: Cardiac Catheterization Co-operative Study, 1968.

<table>
<thead>
<tr>
<th>I. Arrhythmias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular Tachycardia</td>
<td>35</td>
</tr>
<tr>
<td>Bigeminy</td>
<td>1</td>
</tr>
<tr>
<td>Bundle Branch Blocks</td>
<td>2</td>
</tr>
<tr>
<td>Complete Heart Block</td>
<td>7</td>
</tr>
<tr>
<td>Ventricular Tachycardia</td>
<td>12</td>
</tr>
<tr>
<td>Ventricular Fibrillation</td>
<td>58</td>
</tr>
<tr>
<td>Asystole</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>153</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Perforation of Heart or Great Vessels</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Atrium</td>
<td>33</td>
</tr>
<tr>
<td>Right Ventricle</td>
<td>21</td>
</tr>
<tr>
<td>Aortic Root</td>
<td>17</td>
</tr>
<tr>
<td>Left Atrium</td>
<td>10</td>
</tr>
<tr>
<td>Left Ventricle</td>
<td>12</td>
</tr>
<tr>
<td>Extra-pericardial Aorta or Branch</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Arterial Complications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Thrombosis</td>
<td>37</td>
</tr>
<tr>
<td>Arterial Tears Dissections</td>
<td>16</td>
</tr>
<tr>
<td>False Aneurysm Formation</td>
<td>6</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. Nervous System Complications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Cerebral Disturbances</td>
<td>11</td>
</tr>
<tr>
<td>—(Loss of Consciousness, Seizures, Psychosis)</td>
<td></td>
</tr>
<tr>
<td>Focal Disturbances</td>
<td>13</td>
</tr>
<tr>
<td>—(Hemiparesis, Aphasia, etc.)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>V. Peripheral Nervous System Complications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial Plexus Injuries</td>
<td>8</td>
</tr>
<tr>
<td>Median or Ulnar Nerve Injury</td>
<td>2</td>
</tr>
<tr>
<td>Femoral Nerve Injury</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VI. Pulmonary Complications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Embolism, Infarction</td>
<td>11</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>2</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
</tr>
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</table>
### Risk of Injury

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII. Systemic Arterial Embolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral Emboli</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Emboli</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Emboli to Aortic Bifurcation</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Emboli to Legs</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>17</strong></td>
<td></td>
</tr>
<tr>
<td>VIII. Infection, Inflammation, Allergic Reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory Reactions</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Severe Local Infection</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>High Fever</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Post-pericardiectomy Syndrome</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Allergic Reactions</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>59</strong></td>
<td></td>
</tr>
<tr>
<td>IX. Hemorrhage</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>X. Severe Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Loss</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Vasovagal</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Catheter Through Narrow * Aortic Valve</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16</strong></td>
<td></td>
</tr>
<tr>
<td>XI. Equipment Failure</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Total Complications</td>
<td>444</td>
<td></td>
</tr>
<tr>
<td>Total Deaths</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td>3.2%</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.44%</td>
<td></td>
</tr>
</tbody>
</table>

*Less than the sum of listed complications because many complications above are listed in more than one category in order to show etiology.*

This study reports a 3.6% incidence of major complications for diagnostic cardiac catheterization in a population with known or suspected congenital or acquired heart disease. A 0.44% mortality was observed.

The results of the study show the influence of special characteristics of a subject population on the occurrence of complications of a procedure. Table Five shows the occurrence of major complications by age group. The largest number of complications occur in children under two months of age. This is due to the presence of congenital heart disease in this age group. Seventeen percent of all complications observed in this study occurred in this age group. For individuals over the age of one year, the incidence of major complications was 1.6% to 4.8%.

Table Six summarizes the incidence of complications according to risk group. Risk groups were determined on the basis of the patient's age, severity of cardiac disease and presence or absence of other major systemic or systemic diseases. Patients with
Compensating for Research Injuries: Appendix E

TABLE 5
Cardiac Catheterization Co-Op Study:
Complications by Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Patients</th>
<th>Number of Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d</td>
<td>325</td>
<td>50 (15.4%)</td>
</tr>
<tr>
<td>30-59 d</td>
<td>775</td>
<td>22 (19.0%)</td>
</tr>
<tr>
<td>2-11 mos</td>
<td>681</td>
<td>33 (4.8%)</td>
</tr>
<tr>
<td>1yr-1yr 11 mos</td>
<td>312</td>
<td>10 (3.2%)</td>
</tr>
<tr>
<td>2yr-4yr 11 mos</td>
<td>674</td>
<td>11 (1.6%)</td>
</tr>
<tr>
<td>5-14 yr</td>
<td>1903</td>
<td>30 (1.6%)</td>
</tr>
<tr>
<td>15-24 yr</td>
<td>1252</td>
<td>41 (3.3%)</td>
</tr>
<tr>
<td>25-49 yr</td>
<td>4141</td>
<td>137 (3.3%)</td>
</tr>
<tr>
<td>50-59 yr</td>
<td>2034</td>
<td>78 (3.8%)</td>
</tr>
<tr>
<td>&gt;60 yr</td>
<td>887</td>
<td>31 (3.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>1 (30.0%)</td>
</tr>
</tbody>
</table>

TABLE 6
Cardiac Catheterization Co-op Study:
% Complications by Risk Group

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>2.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.5%</td>
</tr>
<tr>
<td>High</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

low pre-procedure risk group status had a 2.3% incidence while patients with high pre-procedure risk group status had a 10.1% incidence of major complication. This distinction is obscured when only the overall incidence of major complications of 3.6% is cited.

Angiography. The major causes of injury from angiography result from the insertion of the catheter into an artery, the manipulation of the catheter in the artery and the injection of hypertonic contrast media. The complications of the procedure which are most often observed are pain, bleeding and local infection at the site of insertion of the catheter, tears, dissections or false aneurysms arising in the vascular wall due to manipulation of the catheter, and myocardial damage or renal failure resulting from intravascular volume changes caused by hypertonic contrast media. A spectrum of allergic reactions to contrast media may also be observed.

Table 7 summarizes the prospective studies of angiography (277, 281, 263, 217, 224, 88). The study by Eisenberg, et al. was intended to assess only the complication of renal failure in angiography and will be discussed with the retrospective studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Cardiac Complications</th>
<th>Vascular Complications</th>
<th>Renal Complications</th>
<th>Local Infection or Hemorrhage</th>
<th>Other†</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swan, et al. (1968)</td>
<td>3312*</td>
<td>34(1.0%)</td>
<td>15(0.5%)</td>
<td>**</td>
<td>1(0.03%)</td>
<td>10(0.4%)</td>
<td>63(1.9%)</td>
<td>3(0.09%)</td>
</tr>
<tr>
<td>Cardiac Catheterization Co-up Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandon, et al. (1973)</td>
<td>122†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigstedt &amp; Lunderquist (1978)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmo, et al. (1979)</td>
<td>100*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paterek &amp; Min., (1979)</td>
<td>83†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eisenberg, et al. (1980)</td>
<td>100‡</td>
<td>0</td>
<td>2(3.0%)</td>
<td>**</td>
<td>0(0.0%)</td>
<td>14(22%)</td>
<td>22(35%)</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 7
Complications of Angiography: Prospective Studies

** a. Coronary arteriography
b. Hepatic arteriography
c. All abdominal arteriography
d. Chemotherapy patients
e. Cerebral angiography
f. Includes all arteries
† Includes pain, nausea, vomiting, syncope, chest pain
** Not reported
Of the remaining 5 prospective studies, two do not report the occurrence of cardiac complications and three do not assess the renal complications of angiography. All studies report vascular complications as well as episodes of infection and hemorrhage and an array of other morbid events including pain, nausea, vomiting, vasovagal reactions, and relatively infrequent cerebral vascular accidents following the administration of contrast medium.

The range of cardiac complications is 0.0% reported by Paine, et al. to 1.0% reported by Swan et al., (217, 277). The study of Swan, et al. includes a series of 3312 coronary angiographies performed by cardiologists at 16 institutions and is remarkable for the thoroughness with which investigators monitored patients for the occurrence of complications, particularly those of the cardiovascular system. In contrast, Paine, et al. report a series of only 100 coronary angiographies performed for research purposes. The small number of procedures in Paine's study may not have allowed observation of a relatively uncommon event.

Vascular complications of angiography are reported with regularity and the range of complication rates reported in these studies is 0.5% from Swan, et al. to 3.0% from Petrak and Minton (224). Petrak and Minton report on a small series of cancer patients undergoing hepatic angiography prior to placement of an hepatic artery catheter for a research project assessing the efficacy of perfusion chemotherapy. The small number of subjects in this series and the significant co-morbidity of the subjects studies by Paine, et al. may explain the difference in observed incidence of vascular complications.

Sigstedt and Lunderquist report a series of 1804 abdominal angiographies. The overall rate of vascular complications observed in this study is 2.6%. The difference between this estimate and the lower estimate of 0.5% reported by Swan, et al. may result from the difference in the arteries cannulated in these studies. Since arterial wall damage is most likely to occur when a catheter must be frequently manipulated, the incidence of damage to the vascular structure can be expected to be greatest when arteries which are difficult to cannulate are studied. Sigstedt and Lunderquist demonstrate this phenomenon by analyzing their overall vascular complication rate in terms of the morbidity contributed by the study of specific arteries. In their study, specific vascular complications occurred with the following frequencies:

- Superior mesenteric artery 0.3%
- Renal artery 0.9%
- Celiac trunk 1.1%
- Splenic artery 4.4%
- Hepatic artery 5.6%
- Gastroduodenal artery 6.8%
- Left gastric artery 6.9%
- Inferior mesenteric artery 7.5%
When the results are analyzed for specific arteries, it is seen that with relatively accessible arteries such as the superior mesenteric or renal arteries, the incidence of vascular complications is much lower than with arteries which are more difficult to cannulate. For accessible arteries the results obtained by Sigstedt and Lundquist are comparable to those obtained by Swan, et al. for coronary arteries.

The renal complications of angiography are uniformly poorly reported in these studies. Renal complications of angiography occur 24 to 48 hours after the procedure is performed and can be detected, in most cases, only if specific blood tests are done within this time period. Since renal compromise may be mild to moderate and resolved without specific treatment, many cases may occur without detection unless they are specifically looked for during the 48 hours following the procedure. The absence of reporting of these complications in these studies may represent a failure of methods to detect these complications.

Local infections and hemorrhage at the site of catheter insertion are reported in all studies reviewed. The incidence of these events range from 0.0% in the study by Paine, et al. to 9.0% in the report by Petrik and Minton. As has been previously noted, the subjects reported in the latter study were all cancer patients receiving chemotherapy. Since chemotherapy often results in bone marrow suppression with resultant compromise of normal immunological and hemostatic mechanisms, a high incidence of bleeding and infection following catheter insertion in these patients is not remarkable.

Paine, et al. and Tandon, et al. report incidences of approximately 1.7% and 1.6% respectively. The incidence of 0.03% reported by Swan, et al. represents a single occurrence in the 3312 patients undergoing angiography in the Cardiac Catheterization Co-operative Study in 1963-65. The overall incidence of infection and hemorrhage in the 12,367 patients who underwent cardiac catheterization in this study was 0.02%.

The range of morbidity reported in these studies is 0.0% to 35%. The difference in incidence of the major complications discussed above accounts for some of the impressive difference in reported morbidity rates. The range of morbidity reported in these studies is also influenced by the reporting of complications which are listed under “other” in Table 7. For the most part, these include occurrences of injuries such as pain, nausea or vomiting, vasovagal episodes and chest pain. While most investigators carefully record all major or mortal complications, occurrences which are not life-threatening and which cause only patient discomfort are reported in great detail by some physicians and not at all for others. In this series, for example, the morbidity reported for the Sigestedt and Lundquist study includes the occurrences of backache, headache, tachycardia, and shivering. These events account for more than 50% of the 300 “other” complications
listed for this study. The Cardiac Catheterization Study, in contrast, reports only moderately severe to life-threatening complications, so that in the “other” category for this study there are only 16 occurrences noted.

Mortality for all these studies was low, ranging from 0.0% to 0.09%.

Retrospective studies of angiography are reported in Table Eight. The studies reported by McAfee (1957), Lang (1963), and Mortensen (1967) report estimates of each of the major complications associated with angiography, while the studies by Fitzgerald and Carr (1977), Ramirez (1978) and Byk (1979) report only a few of these complications (189, 174, 201, 187, 236, 42). Only the studies with complete data bases will be discussed.

The range of complication rates reported for the major complications in the three large retrospective studies presented here is relatively narrow. The major differences in these rates occur in reporting of vascular complications, local infection and hemorrhage, and “other” complications.

For vascular complications, the lowest incidence is reported by McAfee (0.05%) while Lang and Mortensen report incidences of 2.0% and 3.0% respectively. Local infection and hemorrhage also has the lowest incidence in the McAfee study (0.0%) compared to the 1.5% reported by Lang and 3.0% reported by Mortensen. These two types of complications result from insertion of the catheter and manipulation of the catheter within an artery.

The study reported by McAfee differs from the studies done by Lang and by Mortensen in that most of the procedures reported by McAfee were done using a translumbar needle approach while in the Lang and Mortensen reviews, the catheter was passed through a peripheral artery. Since vascular complications as well as infection and hemorrhage result from the insertion of the catheter and subsequent manipulation of the catheter, the different techniques employed for catheter insertion may explain the difference in observed complications.

The morbidity reported in these three studies ranges from 0.7% to 12.0% and reflects not only the above observed differences in catheter related complications, but also variability in the reporting of less serious complications such as pain and nausea. The overall mortality reported in these series is comparable, 0.06% to 0.1%.

The incidence of renal failure reported in the three major retrospective studies is 0.03%. Problems in detection and diagnosis of renal failure are more likely to occur in retrospective surveys, but the range reported in these large series is relatively small. In contrast, Schwartz et al., in a retrospective study, report a 12% incidence of renal failure which they defined as an increase in blood urea nitrogen of 50% or 20 mg/dl and/or an increase in creatinine of 50% or 1 mg/dl. In response to this study which was published in 1978, Eisenberg, et al. duplicated the
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Cardiac Complications</th>
<th>Vascular Complications</th>
<th>Renal Complications</th>
<th>Local Infection or Hemorrhage</th>
<th>Other</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>McAfee (1957)</td>
<td>13,207*</td>
<td>13(0.1%)</td>
<td>7(0.05%)</td>
<td>30(0.3%)</td>
<td>16(0.1%)</td>
<td>41</td>
<td>38(0.7%)</td>
<td>37(0.3%)</td>
</tr>
<tr>
<td>Lang (1963)</td>
<td>11,402b</td>
<td>**</td>
<td>224(2.0%)</td>
<td>2(0.02%)</td>
<td>167(1.5%)</td>
<td>403</td>
<td>4(0.06%)</td>
<td>7(0.06%)</td>
</tr>
<tr>
<td>Mortensen (1970)</td>
<td>3,195b</td>
<td>9(0.3%)</td>
<td>65(3.0%)</td>
<td>10(0.3%)</td>
<td>101(3.0%)</td>
<td>183</td>
<td>385(12.0%)</td>
<td>4(0.1%)</td>
</tr>
<tr>
<td>Fitzgerald &amp; Carr (1977)</td>
<td>2,100b</td>
<td>**</td>
<td>157</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Ramirez, et al. (1978)</td>
<td>71b</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Schwartz, et al. (1978)</td>
<td>105f</td>
<td>2(1.8%)</td>
<td>**</td>
<td>**</td>
<td>13(12.0%)</td>
<td>**</td>
<td>3(20.8%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>Bryk, et al. (1979)</td>
<td>82d</td>
<td>**</td>
<td>4(4.9%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>4(4.9%)</td>
<td>0(0.0%)</td>
</tr>
</tbody>
</table>

a. Abdominal aortogram
b. All angiotherapy
c. Excludes cerebral and coronary angiotherapy
d. Not specified
** Not reported
study done by Schwartz, et al. selecting a population with the same type and incidence of underlying disease and using the same definition of renal failure. The two studies differed in that Eisenberg, et al. hydrated patients with 250 cc of normal saline per hour while the cases reviewed by Schwartz, et al. had received only 80 cc of DSW per hour. The study by Eisenberg, et al. demonstrated that hydration, and not underlying disease, is the most important variable in occurrence of renal failure following angiography and demonstrates the significant effect which differences in performance of a procedure may have on the incidence of a given complication.

A summary of the reported mortality associated with the administration of contrast media is given in Table Nine. Estimates range from 1:33,000 to 1:300,000 with six of the eight reporting mortality rates between 1:33,000 and 1:60,000. Insufficient data are available on these studies to allow examination of the variability in reported mortality rates.

**TABLE 9**

<table>
<thead>
<tr>
<th>Radiographic Contrast Media: Mortality*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jungmichel [1940]</td>
</tr>
<tr>
<td>Pendergrass et al. [1942]</td>
</tr>
<tr>
<td>Coliez et al. [1955]</td>
</tr>
<tr>
<td>Wolf fromm et al. [1966]</td>
</tr>
<tr>
<td>Frommhold &amp; Braban [1960]</td>
</tr>
<tr>
<td>Tonolo &amp; Buia [1966]</td>
</tr>
<tr>
<td>Ansell [1970]</td>
</tr>
<tr>
<td>Witten et al. [1973]</td>
</tr>
</tbody>
</table>

* From: Shehadi, M.D. 1974

Placement of an Arterial Line. An arterial line is an indwelling Teflon catheter which may be placed in any peripheral artery for purposes of monitoring blood pressure or establishing an access for drawing blood samples. In clinical medicine it is used exclusively in the intensive care setting and the largest experience with its use has been accumulated by anesthesiologists. The arterial line is also frequently used in research studies to monitor blood pressure and arterial blood gases in studies of cardiopulmonary physiology and pharmacology.

Since an arterial line is essentially a resident foreign body within a vascular structure, the major complications associated with its use in either patient or research subject are bleeding from the vessel, thrombosis of the vessel with or without subsequent ischemia to dependent tissue and local or systemic infection.

Table Ten summarizes the major prospective studies of complications of the arterial line [38, 202, 23, 83, 114, 177, 159, 321, 24, 143, 25, 15]. The incidence of hematoma is not reported in 9 of these 12 studies. The incidence of hematoma is 0.0% to 45% in the three studies which report this complication.
### TABLE 10
Complications of Arterial Line Placement: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Hematoma</th>
<th>Thrombosis</th>
<th>Thrombosis with Ischemia</th>
<th>Infection</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. (1969)</td>
<td>110</td>
<td>49 (45.0%)</td>
<td>6 (7.0%)</td>
<td>0</td>
<td>**</td>
<td>57 (51.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Mosby et al. (1969)</td>
<td>70</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0</td>
<td>**</td>
<td>0</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Bedford et al. (1973)</td>
<td>105</td>
<td>**</td>
<td>40 (36.0%)</td>
<td>0</td>
<td>40 (38.0%)</td>
<td>0</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Downs et al. (1973)</td>
<td>72</td>
<td>**</td>
<td>22 (63.0%)</td>
<td>0</td>
<td>**</td>
<td>22 (63.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gardner et al. (1974)</td>
<td>530</td>
<td>50 (9.0%)</td>
<td>**</td>
<td>3 (0.0%)</td>
<td>53 (10.0%)</td>
<td>**</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Little et al. (1975)</td>
<td>41</td>
<td>**</td>
<td>9 (2.0%)</td>
<td>13 (3.0%)</td>
<td>22 (54.0%)</td>
<td>**</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Kim et al. (1975)</td>
<td>100</td>
<td>**</td>
<td>23 (2.0%)</td>
<td>0 (0.0%)</td>
<td>**</td>
<td>22 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Youngberg et al. (1976)</td>
<td>30</td>
<td>**</td>
<td>2 (7.0%)</td>
<td>0 (0.0%)</td>
<td>**</td>
<td>2 (7.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Bedford et al. (1977)</td>
<td>100</td>
<td>**</td>
<td>25 (2.0%)</td>
<td>0 (0.0%)</td>
<td>**</td>
<td>25 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Husum et al. (1979)</td>
<td>24</td>
<td>**</td>
<td>6 (3.0%)</td>
<td>0 (0.0%)</td>
<td>**</td>
<td>6 (3.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Bedford et al. (1979)</td>
<td>62</td>
<td>**</td>
<td>10 (2.0%)</td>
<td>**</td>
<td>**</td>
<td>16 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Bund et al. (1979)</td>
<td>130</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>5 (4.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

** Not reported

(a) Femoral arterial lines
(b) Dorsalis pedis arterial lines
The factors which would be most likely to influence the development of a hematoma include the skill of the operator, the hemostatic competence of the patient and the size of the needle used to cannulate the artery. In the studies by Brown, et al., Mosely, et al. and Gardner, et al. all lines were placed by skilled operators (38, 202, 114). The patients studied by Mosley, et al. and Gardner, et al. were all surgical patients and are likely to have been hemostatically competent. Unfortunately, in these two studies, the techniques used for performing the procedure are not well described, so that this possible source of the difference in incidence of hematoma formation cannot be evaluated.

Ten of the twelve prospective studies provide detailed accounts of the incidence of thrombosis of cannulated arteries. This event is reported to have an incidence between 0.0% and 63%. The single factor which explains most of this difference is the method used to detect arterial thrombi. For example, in the study by Mosley, et al., which reports a 0.0% incidence, clinical examination was used to detect arterial thrombosis. In contrast, in the study by Downs, et al., a 63% occurrence of arterial thrombosis is reported when these events are detected by angiography (83). Studies which used a Doppler to detect arterial thrombosis reported incidences in the middle of the range such as the 38% incidence reported by Bedford, et al. (23). When comparable methods of detection were used, differences in incidence of arterial thrombosis resulted from differences in the length of time the artery was cannulated.

The incidence of infection associated with arterial line placement is not reported in 9 of 12 studies. In the two studies which report an incidence of 0.0%, the arterial line was placed by an anesthesiologist or specially-trained nurse practitioner. In the study by Band, et al. which reports a 4% incidence of catheter-related infection, the arterial line was placed by house officers (15).

No mortality is reported for these studies. The range of morbidity, 0.0% to 63%, results from the differences in methods used to detect complications and from the difference in length of time in which an arterial line was allowed to indwell.

The major retrospective studies on complications associated with an arterial line are presented in Table Eleven. These studies provide almost no information on specific complications of arterial line. The morbidity which they report, which ranges from 0.25% to 12%, may reflect not only differences in methods of detection and length of cannulation, but also differences in the reporting of these events in medical records. The morbidity rate of 56% reported by Maki, et al. is excluded from consideration with the other retrospective studies since it represents 9 occurrences of S. aureus infection in immunocompromised patients receiving chemotherapy (182).
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Hematoma</th>
<th>Thrombosis</th>
<th>Thrombo-Ischemia</th>
<th>Infection</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortensen (1967)</td>
<td>120</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>3</td>
<td>**</td>
</tr>
<tr>
<td>Radial</td>
<td>148</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>18</td>
<td>**</td>
</tr>
<tr>
<td>Femoral</td>
<td>800</td>
<td>**</td>
<td>**</td>
<td>3</td>
<td>**</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Samaan (1971)</td>
<td>10</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>9*</td>
<td>9</td>
<td>**</td>
</tr>
<tr>
<td>Maki et al. (1979)</td>
<td>10</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

(a) All 10 patients were receiving chemotherapy, All 9 infections were S. Aureus.
* Incidence rates not calculated due to incomplete reporting of all complications
** Not reported
The single fatal complication reported in these studies resulted from a catheter embolus reported by Samaan, et al. [250].

**Exercise Tolerance Testing.** Exercise tolerance testing has been widely used for both research purposes and for the clinical evaluation of coronary artery disease. It also has increasing application as a method of assessing physical fitness.

In exercise tolerance testing, an individual performs exercise, commonly by walking on a graded treadmill. While the subject performs the test, an electrocardiographic tracing is continuously displayed on a cardiac monitor and the subject's blood pressure and pulse are monitored.

The subject is exercised in order to increase the work load of the heart and to determine whether evidence of ischemia develops either before or at maximal exercise for the subject. Evidence of ischemia would include chest pain, hypotension, arrhythmias, changes in the exercise electrocardiogram (ST-segment changes and T-wave changes), and even complaints of shortness of breath (dyspnea), fatigue or dizziness. The occurrence of dyspnea, fatigue or dizziness may simply imply poor physical fitness, but they are also symptoms associated with left ventricular failure.

Since subjects are constantly monitored during exercise tolerance testing, an exercise tolerance test can be stopped immediately if a patient develops hypotension, arrhythmias or any serious signs or symptoms of myocardial ischemia or left ventricular failure.

Due to the unique nature of the exercise tolerance test, it is more difficult to decide what constitutes a complication than with other procedures. An exercise tolerance test is performed to determine at what point in exercise evidence of ischemia or arrhythmias occurs. The test is then stopped. If evidence of ischemia and arrhythmias are considered as complications, then all positive exercise tolerance tests could be said to involve complications.

A reasonable way in which to evaluate the risk of exercise tolerance testing would be to consider as complications only those events which result in morbidity for the patient. These events might include symptomatic arrhythmias or arrhythmias requiring cardioversion, ischemic events or suspected ischemic events requiring hospitalization or loss of time from work, and so on.

Unfortunately, this distinction is made inconsistently by individuals reporting the risks of exercise tolerance testing. In studies which report the complications of exercise tolerance testing, there is wide variation in the definition of “complication.” Therefore, some investigators report all observed ST-segment changes as complications while others reserve complication for events leading to hospitalization or death.
A number of prospective and retrospective clinical studies as well as research studies were reviewed for this report. Dr. ... the difficulties noted, the "complications" reported in these studies are presented in the tables as they are reported by the authors of these studies. Morbidity calculated in these tables includes events as diverse as severe fatigue and myocardial infarction. The estimate of mortality, in this case, gives the only estimate of the risk associated with this procedure.

In Table 12, the first five studies listed represent prospective studies of the clinical use of exercise tolerance testing [39, 90, 40, 157, 74]. The last eight studies listed are research studies in which the exercise tolerance test was used as a procedure [11, 147, 13, 186, 156, 217, 78, 145]. An additional five research studies reviewed made no mention of complications.

In six of the eight research studies, the exercise tolerance test was used for research purposes only. In the remaining two studies, the test was used as an experimental diagnostic tool.

In the research projects, dyspnea, fatigue and dizziness were reported as complications in 2 studies. Dillahunt and Miller [1970] report an incidence of 2% in 100 patients exercised 2 weeks after a myocardial infarction and Paine, et al. [1978] report an incidence of 17.9% in 28 patients exercised approximately 4 months after infarction.

Angina is reported as a complication in 3 research studies. It is reported with an incidence ranging from 7% to 24%. The highest incidence is reported by Bailey, et al. [1977] in a study which involved 20 normal subjects and 63 subjects with angiographic evidence of coronary artery disease. None of the controls, but twenty of the diseased subjects experienced angina during this study. The lowest incidence is reported by Markiewicz, et al. [1977] who exercised subjects 3, 5, 7, 9 and 11 weeks after myocardial infarction.

Arrhythmias were observed in 7 of the eight research studies. They were not observed by Aronow and Cassidy [1975] who exercised only normal, healthy subjects. In the other seven studies, coronary artery disease or congenital heart disease was known to be present in at least some of the subjects studied. The observed incidence of arrhythmias ranged from 3.8% to 21.4%. The highest incidence occurred in the study by Dillahunt and Miller [1979] in which the subjects were two weeks post-myocardial infarction. If this study is not considered, the range of incidence of observed arrhythmias was 3.8% to 7.8%. Although several cases of ventricular tachycardia were reported, most were asymptomatic and none required cardioversion.

Myocardial infarction as a result of the exercise tolerance test was not reported in any research study and there were no fatal complications in any research study.
### TABLE 12

Complications of Exercise Tolerance Tests: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Fatigue, Dizziness</th>
<th>Angina</th>
<th>Arrhythmia or Conduction Disturbance</th>
<th>Infarction</th>
<th>Other</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruca, et al. (1983)</td>
<td>1060</td>
<td>**</td>
<td>**</td>
<td>1 (0.1%)</td>
<td>0</td>
<td>1(0.1%)</td>
<td>1(0.1%)</td>
<td>1(0.1%)</td>
</tr>
<tr>
<td>Ellesstad, et al. (1969)</td>
<td>4028</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Bruce, et al. (1974)</td>
<td>2332</td>
<td>**</td>
<td>**</td>
<td>7 (0.2%)</td>
<td>0</td>
<td>12(0.5%)</td>
<td>10(0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Korber, et al. (1975)</td>
<td>140</td>
<td>**</td>
<td>**</td>
<td>14(10.0%)</td>
<td>0</td>
<td>0</td>
<td>14(10.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Dotry, et al. (1975)</td>
<td>0</td>
<td>**</td>
<td>**</td>
<td>4(6.6%)</td>
<td>0</td>
<td>0</td>
<td>4(6.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Aronow &amp; Cassidy (1975)</td>
<td>10</td>
<td>**</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>James, et al. (1976)</td>
<td>152</td>
<td>**</td>
<td>**</td>
<td>10 (6.6%)</td>
<td>0</td>
<td>0</td>
<td>10 (6.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Bailey, et al. (1977)</td>
<td>83</td>
<td>**</td>
<td>20(24.0%)</td>
<td>5 (6.0%)</td>
<td>0</td>
<td>0</td>
<td>25(30.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Markiewicz, et al. (1977)</td>
<td>210</td>
<td>**</td>
<td>15 (7.0%)</td>
<td>8 (3.8%)</td>
<td>0</td>
<td>0</td>
<td>23(11.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Kennedy, et al. (1977)</td>
<td>90</td>
<td>**</td>
<td>**</td>
<td>7 (7.8%)</td>
<td>0</td>
<td>0</td>
<td>7 (7.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Paine, et al. (1978)</td>
<td>103</td>
<td>2 (2.0%)</td>
<td></td>
<td>7 (7.0%)</td>
<td>0</td>
<td>2(2.0%)</td>
<td>11(11.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Dillahun &amp; Miller (1979)</td>
<td>28*</td>
<td>5 (17.9%)</td>
<td>5(17.9%)</td>
<td>6(21.4%)</td>
<td>0</td>
<td>0</td>
<td>16(57.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Ivanova, et al. (1980)</td>
<td>144</td>
<td>**</td>
<td>**</td>
<td>7 (4.9%)</td>
<td>0</td>
<td>0</td>
<td>7 (4.9%)</td>
<td>0</td>
</tr>
</tbody>
</table>

(a) Test done 2 weeks after myocardial infarction
(b) Patients with Printzmetal's angina
** Occurred but number of occurrences not given
The prospective clinical studies of the complications of exercise tolerance testing do not report incidence of fatigue, dyspnea, dizziness or chest pain as complications. The incidence of arrhythmias reported in this series has a range of 0.1% to 66.6%. The incidence of 66.6% was reported by Detry, et al. [1975] in a group of six patients known to have Printzmetal's angina. An incidence of 10% is reported for the 140 patients with known or suspected coronary artery disease who were studied by Kerber, et al. [1975]. In the two large series reported by Bruce, et al. [1963, 1974] the observed incidence of arrhythmias was 0.1% and 0.3% respectively.

Myocardial infarction due to exercise tolerance testing was not observed in any prospective study. The single death in this series was reported by Bruce, et al. [1963] and involved a patient with mitral stenosis who developed pulmonary edema during the test and died two days later.

Retrospective studies of exercise tolerance testing are reported in Table 13 [90, 243, 311]. Ellestad, et al. [1969] report the occurrence of two myocardial infarctions in 1000 exercise tolerance tests (0.2%), but no fatalities in this series. Welch, et al. [1975] reviewed 1000 exercise tolerance tests performed on women under the age of fifty who complained of chest pain. Subjects with congenital or valvular heart disease or with idiopathic hypertrophic sub-aortic stenosis were not included in this review. One fatal myocardial infarction (0.1%) occurred in a 26 year old woman with unsuspected disease of the left main coronary artery.

Rochblis and Blackburn [1971] report the results of a questionnaire survey which had a response rate of 25%. In 270,000 tests, there were 50 morbid events reports (0.037%) and 16 deaths associated with the performance of these tests. The reported mortality rate is, therefore, 0.009% or 1:10,000. The incidence of deaths and morbid events reported in this study is 0.04% or 4:10,000. The retrospective design of this study and the low response rate of the survey should be taken into consideration before generalizing these results.

Liver Biopsy. Percutaneous liver biopsy has been used as a research tool to assess the effect of drugs and physiological states on the architecture of the liver. Its major use is in the diagnosis of hepatic disease, and assessments of the risks associated with the procedure have been made in a diagnostic setting.

Complications associated with this procedure are considered "major" if surgery is required to correct them. These include hemorrhage, major bile leaks and peritonitis. Minor, nonsurgical, complications include lesser hemorrhage, hypotension and post-biopsy pain requiring analgesics for control.

Three studies employed liver biopsy purely in a research setting [242, 275, 308]. Two of these make no mention of complications or their absence. A 5% incidence of minor complications is noted in the third [242].
TABLE 13
Complications of Exercise Tolerance Testing: Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Fatigue, Dizziness, Dyspnea</th>
<th>Angina</th>
<th>Arrhythmias or Conduction Disturbance</th>
<th>Infarction</th>
<th>Other</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellestad, et al. (1969)</td>
<td>1000</td>
<td>**</td>
<td>**</td>
<td>12 (1.2%)</td>
<td>2 (0.2%)</td>
<td>0</td>
<td>14 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Rochnis &amp; Blackburn (1971)</td>
<td>170,000</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Welch, et al. (1975)</td>
<td>1000</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>1</td>
<td>**</td>
<td>16 (0.009)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

* Includes angina, arrhythmias, hypotension
** Not reported
Among prospective studies of the procedure as a diagnostic tool no mortality or major complication was encountered. Five of the six studies (5, 104, 128, 163, 215) had fewer than 200 patients (range 29 to 198) and one (223) observed 1000 patients. Only three of the six studies systematically discussed complication rates. Overall the minor complications occurred with a rate of 3.0 to 14.5%. Pain accounted for 1.5 to 9.2% of these complications, with bleeding and episodes of hypotension accounting for 3.6 to 4.8%. These are shown in Table 14.

Retrospective studies include reviews of the literature (283, 320, 322) and of collected single-institution experience (4, 163, 283). Studies of work prior to 1952 show a mortality rate of 0.12 to 0.17%. More recent studies show a range of zero to 0.45%.

The occurrence of complications requiring surgery is reported in retrospective studies with a frequency ranging from 0.1 to 0.45%. Five out of six studies do not discuss non-surgical complications such as hypotension and pain because, as one author points out, "regrettably the clinical records in many cases were incomplete regarding the occurrence of complications" (4). The data from retrospective studies may be seen in Table 15.

It is generally held that the mortality and morbidity of the procedure is higher in older studies than in newer ones because more recent workers use smaller gauge needles (1.9 mm outside diameter) and better techniques. Review of Table 14 and 15 shows no such trend. Mortality is lower in the two oldest reviews than in the most recent large study. Further, in a prospective study of this question, Greenwald (128) used a large bore Jamshidi needle, and found a zero mortality rate. His reported morbidity rate is also not significantly different from other careful studies.

Bone Biopsy. Biopsy of bone has had a major application in medical research where it has been used for studies of inherited as well as acquired disorders of bone metabolism. Clinically, bone biopsy is being used with increasing frequency to establish a histologic diagnosis for bone lesions detected radiographically.

Complications of bone biopsy are pain, infection and hemorrhage in all biopsies and pneumothorax in biopsies of the ribs or vertebrae.

Seven research projects in which the bone biopsy was used were reviewed for this study (111, 86, 241, 234, 224, 69, 2). Seven of the seven provided no report of complications.

Prospective studies reporting complications associated with the diagnostic use of bone biopsy are reported in Table 16. Only the studies reported by Gladstein and Grantham (1974) and Debnam and Staple (1975) report the occurrence of infection in their series (122, 66). They report an incidence of 0.5% and 1.5% respectively. The same two authors report the occurrence of hemorrhage due to bone biopsy and again report incidences of 0.5%
### TABLE 14
Complications of Percutaneous Liver Biopsy: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Mortality</th>
<th>Documented Bleeding</th>
<th>Hypotension</th>
<th>Pain*</th>
<th>Other*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warin, et al. (1975)</td>
<td>25</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Villeneuve, et al. (1976)</td>
<td>31</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Greenwald, R., et al. (1977)</td>
<td>146</td>
<td>0</td>
<td>1(0.7%)</td>
<td>4(2.8%)</td>
<td>13(9.3%)</td>
<td>2(1.4%)</td>
</tr>
<tr>
<td>Ali, et al. (1978)</td>
<td>67</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(1.5%)</td>
<td>1(1.5%)</td>
</tr>
<tr>
<td>Knaur, G., et al. (1978)</td>
<td>175</td>
<td>0</td>
<td>1(0.6%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Okuda, K., et al. (1978)</td>
<td>198</td>
<td>0</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Ferrault, J., et al. (1978)</td>
<td>1000</td>
<td>0</td>
<td>34(3.4%)</td>
<td>14(1.4%)</td>
<td>88(8.8%)</td>
<td>6(0.9%)</td>
</tr>
<tr>
<td>Ferrucci, J., et al. (1980)</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>**</td>
</tr>
</tbody>
</table>

a. Pain requiring analgesia  
** Not reported  
b. Includes hemobilia, arteriovenous fistulae and presence of non-hepatic tissue in biopsy specimen

### TABLE 15
Complications of Percutaneous Liver Biopsy: Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Mortality</th>
<th>Documented Bleeding</th>
<th>Hypotension</th>
<th>Pain*</th>
<th>Other*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terry, R. (1952)</td>
<td>7,532</td>
<td>9(0.12%)</td>
<td>16(0.21%)</td>
<td>**</td>
<td>**</td>
<td>8(0.11%)</td>
</tr>
<tr>
<td>Zamcheck, N. et al. (1953)</td>
<td>20,016</td>
<td>34(0.17%)</td>
<td>0.24%</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Work Group XII (1975)</td>
<td>**</td>
<td>(0.02%)</td>
<td>0.24%</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Knauer, G. (1978)</td>
<td>999</td>
<td>0</td>
<td>3(0.5%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Ali, M. &amp; A. Fayemi (1979)</td>
<td>731</td>
<td>3(0.45%)</td>
<td>16(2.2%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Robinson, J. et al. (1980)</td>
<td>43</td>
<td>0</td>
<td>1(2.3%)</td>
<td>**</td>
<td>**</td>
<td>1(2.3%)</td>
</tr>
</tbody>
</table>

a. Pain requiring analgesia  
** Not reported  
b. Includes hemobilia, arteriovenous fistulae, and presence of non-hepatic tissue in biopsy specimen
and 1.5% respectively. Johnson, et al. (1977) note a 2.2% incidence of hemorrhage.

Pneumothorax occurring with rib or vertebral biopsy occurs with a reported incidence of 1.0% to 7.0%. The highest incidence is from a study by Hanafee and Tobin (1969) in which only 14 patients are reported (131). If this series is excluded, the incidence of pneumothorax ranges from 1.0% to 2.8%. Again, the higher figure occurs in a small series (35 patients) reported by Nordenstrom (1971) (211). In studies with more than 60 patients, the reported incidence of pneumothorax is 1.0% to 1.5% (122, 66, 285).

The reported morbidity in this series ranged from 0.0% to 17.8%. If the small series by Hanafee and Tobin is excluded, there are three studies with reported morbidity rates greater than 2.8%. These are the studies by Gladstein and Grantham (1974), Debnam and Staple (1975), and Johnson, et al. (1977). In all three studies, the major portion of the reported morbidity is derived from the occurrence of complications listed as "other." These include pain and vasovagal responses. The studies with lower overall morbidity did not report these events.

No mortality was reported in any prospective study.

Retrospective studies of the complications of bone biopsy are summarized in Table 17. They are remarkable for presenting large numbers of patients in whom no apparent complications occurred. Of the seven studies reviewed, only the study by Ellis, et al. (1964) of 1445 bone biopsies reports the occurrence of a complication (93). Ellis, et al. report two cases of infection, an incidence of 0.1%.

Since over 6,000 bone biopsies are reported in the retrospective studies, the absence of complications in these series is surprising. It may result from incomplete recording of occurrences of local infection and bleeding in a patient's chart when these are not severe.

Endoscopy and colonoscopy. Endoscopy is a procedure in which a flexible tube equipped with an optical system is inserted into the esophagus, stomach or duodenum. Endoscopy allows visualization of the internal surfaces of these structures as well as directed biopsy of any abnormalities seen. Endoscopy was first performed by Kussmaul in 1866 in Freiburg, Germany (174). Kussmaul's first patient was, appropriately, a sword swallower. However, endoscopy remained a curiosity until the introduction of fiberoptics in the 1950's. In the late 1960's and early 1970's, a flexible endoscope was developed, and endoscopy performed with a flexible, fiberoptic endoscope is now one of the most frequently used procedures in medicine. In the 1970's the method has been modified to allow endoscopic visualization of all parts of the gastrointestinal tract. The two most commonly used procedures are upper gastrointestinal endoscopy and colonoscopy.

Endoscopy. The complications of endoscopy include perforation of the intestinal lining with the endoscope or biopsy
### TABLE 1a—Complications of Bone Biopsy: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Infection</th>
<th>Hemorrhage</th>
<th>Pneumothorax</th>
<th>Other**</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartman &amp; Sombeck (1962)</td>
<td>42</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hanafee &amp; Tobin (1969)</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>1 (7%)</td>
<td>0</td>
<td>1 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Duursma, et al. (1969)</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smirnov &amp; Baranov (1971)</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nordenström (1971)</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>1 (2.8%)</td>
<td>0</td>
<td>1 (2.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Gladstein &amp; Grantham (1974)</td>
<td>188</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
<td>2 (1%)</td>
<td>6 (3%)</td>
<td>10 (5.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Debnam &amp; Staple (1975)</td>
<td>60</td>
<td>1 (1.5%)</td>
<td>1 (1.5%)</td>
<td>2 (3%)</td>
<td>6 (3%)</td>
<td>8 (7.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Thomsen &amp; Fredericksen (1978)</td>
<td>85</td>
<td>0</td>
<td>0</td>
<td>1 (1.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Johnson, et al. (1977)</td>
<td>45</td>
<td>0</td>
<td>0</td>
<td>1 (2.2%)</td>
<td>0</td>
<td>1 (1.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Occurred with vertebral or rib biopsy  ** Includes pain and vasovagal responses

### TABLE 17—Complications of Bone Biopsy: Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Infection</th>
<th>Hemorrhage</th>
<th>Pneumothorax</th>
<th>Other**</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis, et al. (1964)</td>
<td>1445</td>
<td>2 (0.1%)</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
<td>2 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Cramer, et al. (1964)</td>
<td>79</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schajewicz &amp; Derqui (1968)</td>
<td>3717</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peco &amp; Laul (1970)</td>
<td>58</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parfit, et al. (1970)</td>
<td>200</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mathews, et al. (1979)</td>
<td>500</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DuSantos, et al. (1979)</td>
<td>34</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Rib or vertebral biopsies only  ** Pain, vasovagal episodes
forceps, bleeding, cardiovascular complications and complications associated with the sedation or anesthetic used during the procedure. Infection is an unusual complication which has resulted from contaminated endoscopes.

Although thousands of these procedures are performed every month in the United States, there have been no large-scale prospective evaluations of the occurrence of complications associated with its use. Six prospective studies with small numbers of patients are summarized in Table 18 (175, 7, 32, 113, 176, 319). Only two of the six report the incidence of any specific complication. Bough and Meyers (1978) used a cardiac monitor on 51 patients undergoing endoscopy and observed arrhythmias or electrocardiographic changes in 9 patients. These events occurred more frequently in patients with known cardiac disease than in normal patients. In the remaining five studies, cardiac monitoring was not used during the procedure. Liguory and Loriqa (1978) studied 155 patients and observed 3 perforations (1.9%), and 15 episodes of bleeding (9.7%), however, 144 patients in this series underwent sphincterotomy at the time of the procedure. The complications observed by Liguory and Loriqa are more likely to have resulted from the sphincterotomy than from the esophagoduodenoscopy.

The morbidity reported by the six studies ranges from 0.0% to 17.6%. Liguory and Loriqa report a 17.6% morbidity in their study of sphincterotomy and endoscopy. And Bough and Meyers report a 12.9% morbidity in their study of cardiac arrhythmias during endoscopy. If these two studies are not considered, the reported morbidity for the remaining four studies is 0.0% to 3.7%. The nature of complications which occurred in these studies is not reported. No author reports any fatalities in this series.

There have been two large retrospective studies of the complications of esophagastroduodenoscopy. These are summarized in Table 18 along with a smaller series and a report by XII Work Group of the NIAMDD Evaluation Effort on the Future of Digestive Disease Research (320). In 1975, Work Group XII was given the task of assembling information on the risk of procedures used in gastroenterology. Their report, published in 1975, states "after diligent effort it became apparent that it was virtually impossible from the existent medical literature to derive meaningful numbers from which to calculate risk factors which may be encountered by individual subjects or patients in a specific study" (320). As an interim measure, they reviewed the literature reporting complications of procedures used in gastroenterology and calculated morbidity and mortality rates by adding the total number of morbid or fatal events reported in the literature and dividing by the total number of endoscopies reported in the literature reviewed. Using this method they report a morbidity of 0.49% for endoscopy. A mortality rate is not reported.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Perforation</th>
<th>Bleeding</th>
<th>Cardiovascular</th>
<th>Anesthetic Complications</th>
<th>Other</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROSPECTIVE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lieberman (1976)</td>
<td>44</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>1(2.3%)</td>
<td>1 (2.3%)</td>
<td>**</td>
</tr>
<tr>
<td>Ament &amp; Christie (1977)</td>
<td>163</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>6(3.7%)</td>
<td>6 (3.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Dough &amp; Meyers (1975)</td>
<td>51</td>
<td>**</td>
<td>**</td>
<td>8(17.6%)</td>
<td>**</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liguory &amp; Loriga (1970)</td>
<td>155*</td>
<td>3 (1.9%)</td>
<td>15 (9.7%)</td>
<td>**</td>
<td>**</td>
<td>2(1.3%)</td>
<td>20(12.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Gaisford (1978)</td>
<td>71</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Woodliff (1979)</td>
<td>176</td>
<td>0</td>
<td>0</td>
<td>**</td>
<td>0</td>
<td>2(1.1%)</td>
<td>2 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>RETROSPECTIVE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiller, et al (1972)</td>
<td>23,500</td>
<td>95 (0.4%)</td>
<td>0</td>
<td>0</td>
<td>6(0.02%)</td>
<td>101</td>
<td>(0.4%)</td>
<td>23 (0.09%)</td>
</tr>
<tr>
<td>&quot;Work Group XII (1975)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levy &amp; Jacobsohn (1976)</td>
<td>700</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>7(1.0%)</td>
<td>17 (2.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Mandelstam, et al. (1978)</td>
<td>211,410</td>
<td>70(0.03%)</td>
<td>63(0.03%)</td>
<td>129(0.06%)</td>
<td>50(0.02%)</td>
<td>215</td>
<td>507 (0.2%)</td>
<td>13(0.006%)</td>
</tr>
</tbody>
</table>

* Review of literature prior to 1975
(a) Sphincterotomy done in 144
(b) All patients monitored for any arrhythmia

** Not reported
The two large retrospective series which have been published report similar incidences of major complications and similar morbidity and mortality rates. Schiller, et al. (1972) reviewed 23,500 endoscopies and reported 95 perforations (0.4%), no episodes of bleeding or cardiovascular complications, and 6 anesthetic complications (0.02%). The morbidity for this series was 0.4% and the mortality was 0.09%.

Mandelstam, et al. (1976) report the results of a retrospective survey conducted by the American Society for Gastrointestinal Endoscopy (A/S/G/E) in 1974 (184). This study was a questionnaire survey which had a 64% response rate. Complications occurring with 211,410 endoscopies were reported. Complications included 95 perforations (0.03%), 63 episodes of bleeding (0.03%), 129 cardiovascular complications (0.06%), approximately 50 anesthetic complications (0.02%), and 215 other complications (0.1%). The morbidity for the series was 0.2% and the mortality rate was 0.006%.

Colonoscopy. The complications of colonoscopy include perforation of the intestine, bleeding due to trauma from the colonoscope or from a biopsy site, and cardiovascular complications. Bacteremia resulting from colonoscopy has also been considered a complication of this procedure.

All available studies of the complications of colonoscopy are retrospective. These are summarized in Tables 19 & 20 (1, 63, 117, 244, 246, 269, 270, 320). The complications associated with colonoscopy alone are shown separately from those associated with colonoscopy with biopsy.

The incidence of perforation in colonoscopy alone ranges from 0.0% to 0.9% and in colonoscopy with biopsy 0.0% to 1.0%. For colonoscopy alone, the incidence of perforation in studies reporting more than 1000 procedures ranges from 0.03% to 0.3%. The extremes at both ends of the overall range are reported in series with less than 1000 procedures.

The incidence of bleeding reported for colonoscopy alone is 0.0% to 0.3% but for colonoscopy with biopsy, the incidence of bleeding ranges from 0.1% to 3%.

Cardiovascular complications are uncommonly reported in these retrospective studies. Only three of the eight studies reviewed considered cardiovascular complications in their evaluation of colonoscopy. Work Group XII (1975) detected 10 cardiovascular complications in their literature review of 25,298 procedures and calculated an incidence of 0.05%. Rogers, et al. (1975) report an incidence of cardiovascular complications of 0.05% for colonoscopy alone and 0.03% for colonoscopy with biopsy in their report of the results of the A/S/G/E Study in 1975 (244).

The morbidity reported for colonoscopy alone in this series ranges from 0.0% to 0.9% and for colonoscopy with biopsy the reported range is 0.5% to 3.8%. If the small series of 133 pro-
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Perforation A</th>
<th>Perforation B</th>
<th>Bleeding A</th>
<th>Bleeding B</th>
<th>Cardiovascular A</th>
<th>Cardiovascular B</th>
<th>Other A</th>
<th>Other B</th>
<th>Mortality A</th>
<th>Mortality B</th>
<th>Morbidity A</th>
<th>Morbidity B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roseman (1972)</td>
<td>627</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td></td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Geiser, et al. (1974)</td>
<td>614</td>
<td>252</td>
<td></td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>23</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Work Group XII (1975)</td>
<td>25,298</td>
<td>6214</td>
<td></td>
<td>35</td>
<td>18</td>
<td>12</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Rogers, et al. (1973)</td>
<td>25,298</td>
<td>6214</td>
<td></td>
<td>5</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>A/S/G/C/L: Study</td>
<td>6290</td>
<td>1609</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Smith &amp; Navaonga (1975)</td>
<td>12,740</td>
<td>7393</td>
<td></td>
<td>33</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Delegel, et al. (1975)</td>
<td>12,740</td>
<td>7393</td>
<td></td>
<td>33</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Smith (1979)</td>
<td>12,740</td>
<td>7393</td>
<td></td>
<td>33</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Albus (1977)</td>
<td>12,740</td>
<td>7393</td>
<td></td>
<td>33</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

A = Diagnostic colonoscopy
B = Colonoscopy with biopsy or polypectomy
* = Review of literature prior to 1975
* = Not reported
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Perforation</th>
<th>Bleeding</th>
<th>Cardiovascular</th>
<th>Other</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roseman (1973)</td>
<td>627 49</td>
<td>0.08% 0.0%</td>
<td>0.0% 0.0%</td>
<td>** **</td>
<td>** **</td>
<td>0.08% 6.0%</td>
<td>0.0% 0.0%</td>
</tr>
<tr>
<td>Geenan, et al. (1974)</td>
<td>814 292</td>
<td>0.09% 0.07%</td>
<td>0.0% 1.7%</td>
<td>** **</td>
<td>** **</td>
<td>0.09% 2.4%</td>
<td>** **</td>
</tr>
<tr>
<td>Work Group XII (1975)*</td>
<td>25,298</td>
<td>0.2%</td>
<td>0.0% 0.3%</td>
<td>** **</td>
<td>** **</td>
<td>0.07%</td>
<td>0.4% **</td>
</tr>
<tr>
<td>Rogers, et al. (1975)</td>
<td>25,268 0.214</td>
<td>0.2% 0.3%</td>
<td>0.05% 1.0%</td>
<td>** **</td>
<td>** **</td>
<td>0.3% 2.3%</td>
<td>0.0008% 0.0%</td>
</tr>
<tr>
<td>Smith &amp; Nivatvongs (1975)</td>
<td>8,290 1,669</td>
<td>0.08% 1.0%</td>
<td>0.02% 2.0%</td>
<td>** **</td>
<td>** **</td>
<td>0.1% 3.0%</td>
<td>0.02% 0.0%</td>
</tr>
<tr>
<td>Depradi, et al. (1975)</td>
<td>100</td>
<td>0.0% 0.0%</td>
<td>0.0% 1.0%</td>
<td>** **</td>
<td>** **</td>
<td>0.0% 0.0%</td>
<td>0.0% 0.0%</td>
</tr>
<tr>
<td>Smith (1970)</td>
<td>12,740 7,393</td>
<td>0.3% 0.1%</td>
<td>0.3% 1.0%</td>
<td>** **</td>
<td>** **</td>
<td>0.04% 0.04%</td>
<td>0.0% 0.03% 0.01%</td>
</tr>
<tr>
<td>Abrams (1977)</td>
<td>63 133</td>
<td>1.0% 0.8%</td>
<td>0.0% 3.0%</td>
<td>** **</td>
<td>** **</td>
<td>0.0% 3.8%</td>
<td>0.0% 0.0%</td>
</tr>
</tbody>
</table>

a. Diagnostic colonoscopy
b. Colonoscopy with biopsy or polypectomy
* Review of literature prior to 1973
** Not reported
Compensating for Research Injuries: Appendix E

Procedures reported by Abrams [1977] is excluded, the range of morbidity for colonoscopy with biopsy is not significantly narrowed, but remains 0.5% to 2.8%.

In Table 21, five studies reporting the incidence of bacteremia during and following endoscopy and colonoscopy are summarized [77, 133, 175, 212, 235]. The study by Lieberman (1976) reports the incidence of bacteremia after upper gastrointestinal endoscopy and the remaining four studies report the incidence of bacteremia after colonoscopy. In all studies blood cultures were drawn at various times after the procedure. In the studies by Rafoth, et al. (1975), Hartong, et al. (1977) and Dickman, et al. (1976), blood cultures were also drawn at different times during the procedure. The timing of intra-procedure and post-procedure blood cultures varied in all studies. Timing of blood cultures may affect detection of bacteremia since bacteremia induced by disruption of a mucosal surface is usually transient in healthy subjects. Positive blood cultures on at least one occasion were reported in all studies following colonoscopy. In two studies, the organism isolated was felt to represent a skin contaminant. Subsequent blood cultures were negative in all cases but one. Follow-up on the patient with persistent bacteremia was not available.

The range of morbidity reported for colonoscopy alone was 0.0% to 0.9% and colonoscopy with biopsy, 0.5% to 3.8%. The range for mortality was 0.0% to 0.03% for colonoscopy alone and 0.0% to 0.01% for colonoscopy with biopsy.

### TABLE 21
Risk of Bacteria in Colonoscopy: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Number of Blood Cultures</th>
<th>Bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rafoth, et al. (1975)</td>
<td>52</td>
<td>156</td>
<td>0</td>
</tr>
<tr>
<td>Lieberman (1976)</td>
<td>20</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>Norfleet, et al. (1978)</td>
<td>40</td>
<td>200</td>
<td>1*</td>
</tr>
<tr>
<td>Hartone, et al. (1977)</td>
<td>15</td>
<td>**</td>
<td>2*</td>
</tr>
<tr>
<td>Dickman, et al. (1976)</td>
<td>52</td>
<td>202</td>
<td>3</td>
</tr>
</tbody>
</table>

* Considered contaminant  ** Not reported

Bronchoscopy. Prior to the development of the flexible, fiberoptic bronchoscope by Ikeda in the mid-60's, bronchoscopy was performed primarily in the operating room, by surgeons, using a rigid instrument which required that the patient or subject be anesthetized.

Since the introduction of the fiberoptic bronchoscope in the United States in 1969, however, bronchoscopy has become a bedside procedure performed many hundreds of times a year in most hospitals.
Bronchoscopy has its greatest use as a diagnostic or therapeutic procedure. Its use in research is generally in experimental diagnostics or therapeutics. However, the passage of a bronchoscope allows biopsy of lung tissue through the bronchial wall and this aspect of bronchoscopy has had a more important role in research than has the procedure of bronchoscopy alone.

The complications of bronchoscopy should be considered separately from the complications of a biopsy performed with bronchoscopy, whether the biopsy is a brush biopsy or a transbronchial biopsy.

Complications of bronchoscopy alone may be pulmonary or cardiac complications and include hypoxemia, aspiration, pneumonia, laryngospasm, bronchospasm, myocardial ischemia, infarction or cardiac arrhythmias.

The only complication associated with brush biopsy alone is bleeding from the site of biopsy. With transbronchial biopsies, bleeding (often significant) and pneumothorax are the major complications.

Table 22 summarizes eleven prospective studies of the complications of bronchoscopy and biopsy (267, 305, 8, 323, 237, 173, 222, 239, 324, 93, 134).

The complications of bronchoscopy alone are not reported by five of these studies. Of the remaining six studies, five report that no pulmonary or cardiac complications occurred which were due to the bronchoscopy alone. The sixth study by Pereira, et al. (1974) reports 3 occurrences of pulmonary complications, a 6.9% incidence. Many of the complications associated with bronchoscopy require special methods for detection (such as a cardiac monitor for arrhythmias or arterial blood gases for hypoxemia) or follow-up beyond the time of procedure. While most of the studies reported in this series used cardiac monitoring during the procedure, special attention to detection of complications such as hypoxemia or pneumonia are not well enough described in these studies to allow assessment of the reported incidences of 0.0% for cardiac and pulmonary complications.

The reported incidence of bleeding following brush biopsy varies from 0.0% to 7.5% (237, 173, 323, 239). The highest incidence is reported by Richardson, et al. and represents 14 events occurring in 200 bronchoscopies. In this study the procedure was performed by the senior authors and there are no special characteristics of the patient population or performance of the procedure which explain the higher incidence. Hemoptysis is not a difficult event to detect and it is unlikely to be overlooked by physicians performing a prospective evaluation of the complications of the procedure.

The reported incidence of bleeding after transbronchial biopsy ranges from 1.0% to 12.0% while the reported incidence of
Complications of Bronchoscopy: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Complications Due to Bronchoscopy</th>
<th>Complications Due to Brush Biopsy</th>
<th>Complications Due to Transbronchial Biopsy</th>
<th>Mortality</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smiddy, et al. (1971)</td>
<td>270</td>
<td>0</td>
<td>0</td>
<td>**</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Wanner, et al. (1972)</td>
<td>285</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Anderson &amp; Fontana (1972)</td>
<td>450</td>
<td>0</td>
<td>0</td>
<td>**</td>
<td>6(1.3%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Zavala, et al. (1973)</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>1(1.3%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rath, et al. (1973)</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Levin, et al. (1974)</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td>4(12%)</td>
<td>0</td>
</tr>
<tr>
<td>Pereira, et al. (1974)</td>
<td>72</td>
<td>[6.9%]</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td>4(12%)</td>
</tr>
<tr>
<td>Richardson, et al. (1974)</td>
<td>200</td>
<td>**</td>
<td>**</td>
<td>14(7%)</td>
<td>N/A</td>
<td>4(12%)</td>
</tr>
<tr>
<td>Zavala (1975)</td>
<td>600</td>
<td>**</td>
<td>**</td>
<td>6(1%)</td>
<td>N/A</td>
<td>14(7%)</td>
</tr>
<tr>
<td>Ellis (1975)</td>
<td>111</td>
<td>**</td>
<td>**</td>
<td>9(8%)</td>
<td>1(0.2%)</td>
<td>7(1%)</td>
</tr>
<tr>
<td>Hanson, et al. (1976)</td>
<td>184</td>
<td>**</td>
<td>**</td>
<td>15(9%)</td>
<td>7(4%)</td>
<td>22(1.3%)</td>
</tr>
</tbody>
</table>

**Not reported**
pneumothorax is 0.2% to 13.8%. A higher incidence of bleeding in a given study is not associated with a higher incidence of pneumothorax in that study. In all studies, the procedure was performed by the senior author but the experience of these authors with transbronchial biopsy is not known. No special patient groups were selected for these studies. All biopsies were performed under direct vision or under fluoroscopic direction if direct vision was not possible. The discrepancy in the incidence rates reported in these studies is most likely due to differences in the skills of the operators and differences in the susceptibility of the patient population for these events.

The morbidity reported for bronchoscopy alone is 0.0% to 5.6%. The mortality for the procedure alone in this series is 0.0% to 1.4%. The death reported in this group of studies resulted from a pulmonary complication of bronchoscopy.

The morbidity for bronchoscopy with brush or transbronchial biopsy ranges from 1.0% to 14.9% and reflects the different incidences of bleeding and pneumothorax in these studies. The mortality associated with bronchoscopy and biopsy was 0.0% to 0.2%. The single death in this group of studies was due to pneumonia following bronchoscopy.

Two major retrospective studies of bronchoscopy are summarized in Table 23. Credle, et al. (1974) report 24,521 bronchoscopies and Suratt, et al. (1976) report 48,000 bronchoscopies (60, 276). These studies report only the complications of bronchoscopy and of the anesthesia required to perform bronchoscopy. The results reported by Credle, et al. are from a questionnaire survey which had a 76.8% response rate. The results cited by Suratt, et al. are from a questionnaire survey with a 31% response rate. It is difficult to compare the incidence of either cardiovascular or pulmonary complications in these two reviews because Suratt, et al. report only complications they consider "life-threatening." There is some overlap between complications considered "life-threatening" by Suratt, et al. and those classified as "minor" by Credle, et al. For example, Suratt, et al. lists T-wave changes and syncope as "life-threatening" events but does not explain whether they were actually serious enough to be "life-threatening" or whether they were just considered potentially serious complications.

The morbidity for the series reported by Suratt, et al. is 0.2% and includes only serious complications. The morbidity for the series reported by Credle, et al. is 0.3% and includes all major and minor complications. The reported mortality rates for the two series are 0.03% (Suratt, et al.) and 0.01% (Credle, et al.).

Laparoscopy. Isolation of complications due specifically to the performance of laparoscopy is particularly difficult because of the variety of settings and associated procedures which often accompany it. Laparoscopy, the act of inserting a hollow tube into a small abdominal incision, is performed for diagnostic and ther-
### TABLE 23

Complications of Bronchoscopy: Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Cardiovascular Complications</th>
<th>Pulmonary Complications</th>
<th>Anesthesia Complications</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Major</td>
<td>Minor</td>
<td>Major</td>
<td>Minor</td>
<td>Major</td>
</tr>
<tr>
<td>Credle, et al. (1974)</td>
<td>24,521</td>
<td>3(0.01%)</td>
<td>0(0.03%)</td>
<td>9(0.04%)</td>
<td>39(0.01%)</td>
<td>11*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Life-Threatening**</td>
<td>Life-Threatening</td>
<td>Life-Threatening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suratt, et al. (1976)</td>
<td>48,000</td>
<td>27(0.06%)</td>
<td>52(0.1%)</td>
<td></td>
<td></td>
<td>25*</td>
</tr>
</tbody>
</table>

* Questionnaire Surveys
** Suratt, et al. report only complications which they considered life-threatening.
There is some overlap between complications considered life-threatening by Suratt, et al. and complications considered minor by Credle, et al.

- a. Total number who received anesthesia = 3850
- b. Total number who received anesthesia not reported
Diagnostically the procedure is used to assess causes of infertility in women. It is also used in assessing gastrointestinal disease, but is in this case almost always accompanied by biopsy under direct visualization. Further variation in this regard occurs because the biopsy may be obtained percutaneously through a site other than that used for introducing the laparoscope, or may be made directly through the instrument.

The major therapeutic use of the laparoscope is in elective female sterilization. Again, techniques vary widely. A single incision or multiple incisions may be used, and the fallopian tubes may be cut, clipped or electrically cauterized.

In all of these procedures two additional factors must be noted. First, in all uses of the laparoscope carbon dioxide or other inert gas is introduced into the abdomen to induce pneumoperitoneum. Secondly, all of the procedures require anesthesia. Different groups of clinicians have used local, spinal and general (inhalational or intravenous) anesthetics. In general, the reporting of procedure-associated complications has not taken these independent risk factors into account.

Only one report [94] was found in which diagnostic laparoscopy unaccompanied by biopsy was studied. There is no mention of procedure-associated complications in this prospective study. Four other prospective studies of the procedure were found, and biopsies were taken in all of them. Complications are defined as "major" if they necessitated emergency surgical intervention, and "minor" if conservative management was sufficient. Major complications include hemorrhage, perforation of bowel, and peritonitis. Minor complications include hemorrhage (resolving spontaneously), subcutaneous emphysema, transient cardiac arrhythmias and small bile leaks.

One of the prospective studies merely notes that there were no complications [112]. In the other three [27, 19, 207], the rate of minor complications ranged from 0.3% to 7.1%. Major complications reported in these three studies range from zero to 2.9%. It is likely that variations in reporting account for the wider range among minor complications. In all of these studies, a single death is reported associated with the procedure. The study [207] which reports a major complication rate of 2.9% used laparoscopy to perform tubal sterilization. All but 0.6% of the major complications were directly due to the operative part of the procedure. Taking this into account, the range of major complications due to laparoscopy alone is zero to 0.6% (Table 24).

Two major retrospective studies of diagnostic and operative (sterilizing) laparoscopy depended on questionnaires. In one [225] questionnaires regarding the number of procedures performed and the incidence of complications were sent to 21,936 physicians identifying themselves as obstetricians/gynecologists.
### TABLE 24—Complications of Laparoscopy: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Major Complications*</th>
<th>Minor Complications*</th>
<th>Pregnancies*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>Morbidity</td>
<td>Mortality</td>
</tr>
<tr>
<td>Borst, et al. (1973)</td>
<td>70</td>
<td>0</td>
<td>0</td>
<td>5(7.1%)</td>
</tr>
<tr>
<td>Nilson &amp; Jervo (1976)</td>
<td>1012</td>
<td>0</td>
<td>29(2.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Friedman &amp; Wolff (1977)</td>
<td>55</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>El-Minawal et al. (1978)</td>
<td>352</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Barry, et al. (1978)</td>
<td>238</td>
<td>1(0.4%)</td>
<td>1(0.4%)</td>
<td>4(1.7%)</td>
</tr>
</tbody>
</table>

a. Cardiovascular problems, or conditions requiring laparotomy
b. Conditions not requiring surgical intervention
c. Laparoscopy for sterilization only
** Not reported

### TABLE 25—Complications of Laparoscopy: Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Major Complications*</th>
<th>Minor Complications*</th>
<th>Pregnancies*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>Morbidity</td>
<td>Mortality</td>
</tr>
<tr>
<td>Wheless &amp; Thompson (1973)</td>
<td>3,600</td>
<td>0</td>
<td>0(0.25%)</td>
<td>70(2.2%)</td>
</tr>
<tr>
<td>Work Group XII (1975)</td>
<td>4,404</td>
<td>0</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Phillips, et al. (1977)</td>
<td>96.464</td>
<td>5(0.01%)</td>
<td>755(0.5%)</td>
<td>**</td>
</tr>
<tr>
<td>Phillips, et al. (1978)</td>
<td>201,565</td>
<td>5(0.003%)</td>
<td>482(0.24%)</td>
<td>**</td>
</tr>
<tr>
<td>Phillips, et al. (1978)</td>
<td>31,656</td>
<td>0</td>
<td>17(0.54%)</td>
<td>**</td>
</tr>
<tr>
<td>Phillips, et al. (1978)</td>
<td>77,183**</td>
<td>0</td>
<td>205(0.27%)</td>
<td>**</td>
</tr>
<tr>
<td>Cunnanan, et al. (1980)</td>
<td>5,018</td>
<td>0</td>
<td>25(0.0.5%)</td>
<td>**</td>
</tr>
</tbody>
</table>

a. Cardiovascular problems, or conditions requiring laparotomy
b. Conditions not requiring surgical intervention
c. Laparoscopy for female sterilization only
** Not reported
4,354 replies were received, a response rate of 19.9%. A total of 96,464 diagnostic and 201,565 operative laparoscopies had been performed. The mortality rate for diagnostic procedures was 0.01% and for operative procedures 0.003%. Major complications occurred with a rate of 0.8% in diagnostic laparoscopies, and 0.24% when tubal sterilization was performed. Minor complications were not included in the study.

In the second study (226) a similar group of 2,800 physicians received a similar questionnaire, and 964 (34.4%) replied. Complication rates were similar to those found in the larger study with the exception that zero mortality is reported for diagnostic laparoscopy.

Other smaller retrospective studies (62, 313) also found no mortality associated with either diagnostic or operative laparoscopy.

The overall range of major morbidity in retrospective studies is 0.2-0.8%. Minor morbidity is only reported in three of five studies, and ranges from 0.5 to 2.2% (Table 25).

Prospective studies (Table 24) found an overall major morbidity range of 0.4 to 2.9%, a markedly higher value than that reported in retrospective work. This discrepancy may result, in part, from the low response rate to questionnaires. Responses of 19.9 and 34.4% of questionnaires do not permit reliable complication rates to be calculated.

Arthroscopy. Arthroscopy is a procedure which involves insertion of a tube which is approximately one-quarter inch wide into a joint via a small incision in the skin. The procedure is done to allow visualization of the bony and synovial components of a joint. Its application in research has been in the study of the rheumatic diseases. Its most common use, however, is in the diagnosis of structural damage to joints in orthopedic medicine.

The procedure was introduced in 1931 but did not gain widespread clinical acceptance until the 1950's when smaller, more manageable arthoscopes became widely available.

Complications which might be expected to develop from use of this procedure include infection, bleeding into the knee (hemarthrosis), and mechanical damage to the internal structures of the joint.

Table 26 summarizes the prospective studies of arthroscopy. Eleven studies reported over 40 years failed to show any occurrences of infection (6, 43, 119, 120, 50, 106, 146, 214, 191, 172). In all of these studies the occurrence of infection was specifically sought. Failure of infection to develop may result from the fact that arthroscopy has been considered a surgical procedure until very recently. Therefore, it has almost always been performed in the sterile environment of the operating room or a minor procedures room by orthopedic surgeons or surgeons in training. With development of small, flexible, fiberoptic arthoscopes, the
procedure will become a bedside or outpatient procedure. The incidence of infection may increase in these circumstances.

Hemarthrosis is reported only by Casscells (1971).

Damage to cartilage is observed in 2.7% of cases by Casscells (1971) and 0.5% of cases by Jackson (1972) (50, 146). In both studies, most of the individuals who had arthroscopy had subsequent arthrotomy so that the opportunity to detect these complications was roughly equal. The senior authors performed all procedures used in both studies. Performance of procedure cannot be compared because Casscells does not describe the method used in his study.

The overall morbidity for this procedure ranged from 0.0% to 2.7%, the higher value resulting from minor cartilage damage reported by Casscells (1971).

Retrospective studies of arthroscopy are summarized in Table 27. Over 5,000 arthroscopies are reported in these three studies. No incidences of infection or hemarthrosis are observed.

Dick et al. report 75 cases of cartilage damage without serious sequelae occurring in 3714 arthroscopies, an incidence of 2.0% for this complication as well as for total morbidity.

No deaths are reported in prospective or retrospective studies.

Amniocentesis. Diagnostic amniocentesis is used to assess fetal maturity late in pregnancy and to discover genetic abnormalities in the fetus during the middle of the first trimester of gestation. The latter use has increased remarkably in recent years. In a report of 3,000 amniocenteses done at a single clinic between 1970 and 1978 one-half of the procedures were performed in the last 1.3 years of the study (123).

Three major multi-institution prospective studies have been performed to assess the fetal and maternal safety of mid-trimester amniocentesis. Two of these were case-controlled (197, 294) and the third used historical controls (263). The experience at a single institution was studied prospectively by Manganiello, et al. (185). One historically controlled (52) and one uncontrolled (140) prospective study used ultrasound placental localization in an effort to reduce the risk of fetal injury (Table 28).

Two of the three multi-institutional studies found no significant difference in rate of fetal loss between patients undergoing amniocentesis and controls. The third found a 1% rate of loss in controls and a 2% rate in amniocentesis subjects. Maternal mortality was specifically mentioned in one study, and noted to be zero. Minor maternal complications, such as amniotic fluid leaks, superficial hematomas and abdominal tenderness were reported in 1.8 to 2.6% of subjects.

Overall, among prospective studies fetal loss rates range from 1% to 3.9%. Although none of the series shows a statistically significant increase in fetal wastage over case-matched or histor-
### Table 26
Complications of Arthroscopy: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Infection</th>
<th>Hemarthrosis</th>
<th>Damage to Cartilage</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finkelstein, et al (1971)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Burman, et al. (1974)</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Jayson &amp; Dixon (1968)</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Casscells (1971)</td>
<td>150</td>
<td>0</td>
<td>0</td>
<td>4(2.7%)</td>
<td>4(2.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Jackson (1972)</td>
<td>200</td>
<td>0</td>
<td>0(0.5%)</td>
<td>4(2.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>O'Conner (1974)</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alm, et al. (1974)</td>
<td>124</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gillquist (1976)</td>
<td>245</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leslie, et al. (1977)</td>
<td>76</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>McGinty &amp; Matza (1978)</td>
<td>297</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gillquist &amp; Hagberg (1978)</td>
<td>135</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 27
Complications of Arthroscopy: Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Infection</th>
<th>Hemarthrosis</th>
<th>Damage to Cartilage</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dick, et al. (1976)</td>
<td>3714</td>
<td>0</td>
<td>0</td>
<td>75(2.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gillquist, et al. (1979)</td>
<td>1232</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Huang, et al. (1970)</td>
<td>400</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### TABLE 28
Complications of Amniocentesis: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects</th>
<th>Maternal Complications</th>
<th></th>
<th>Fetal Complications</th>
<th></th>
<th>Procedure Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Morbidity</td>
<td>Mortality</td>
<td>Morbidity</td>
<td>Morbidity</td>
<td>Dry Tap</td>
</tr>
<tr>
<td>Turnbull, et al. (1978)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>2428</td>
<td>37(1.5%)</td>
<td>**</td>
<td>**</td>
<td>40(2.0%)</td>
<td>**</td>
</tr>
<tr>
<td>Controls</td>
<td>2428</td>
<td>12(0.5%)</td>
<td>**</td>
<td>**</td>
<td>25(1.0%)</td>
<td>**</td>
</tr>
<tr>
<td>Simpson, et al. (1978)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>1223</td>
<td>44(3.6%)</td>
<td>**</td>
<td>**</td>
<td>48(3.9%)</td>
<td>**</td>
</tr>
<tr>
<td>NICHD Study Group (1970)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>1040</td>
<td>27(2.6%)</td>
<td>0(0.0%)</td>
<td>**</td>
<td>36(3.5%)</td>
<td>**</td>
</tr>
<tr>
<td>Controls</td>
<td>992</td>
<td></td>
<td></td>
<td></td>
<td>32(3.2%)</td>
<td>**</td>
</tr>
<tr>
<td>Manganiello, et al. (1978)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>252</td>
<td>1(0.4%)</td>
<td>**</td>
<td>**</td>
<td>5(2.0%)</td>
<td>1</td>
</tr>
<tr>
<td>Hohler, et al. (1978)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients*</td>
<td>133</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Chandra, et al. (1978)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>179</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>7(3.0%)</td>
<td>**</td>
</tr>
<tr>
<td>Patients*</td>
<td>715</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>7(1.0%)</td>
<td>**</td>
</tr>
</tbody>
</table>

a. Includes all spontaneous abortions and stillbirths in the pregnancies studied
b. Includes only fetal loss known to be due to amniocentesis
* Ultrasound used
** Not reported
Risk of Injury

critical controls, several notations of amnionitis or fetal demise secondary to cardiac puncture do appear. Thus, even though the number of subjects in these studies is large (133 - 2428), and direct evidence for amniocentesis-related fetal death exists, the numbers may not be large enough to provide precise risk data for these rare events.

Procedural complications of unknown importance include “dry” taps and taps producing blood stained fluid. Only two of the six prospective studies deal specifically with this issue. It has been suggested (52) and denied (140) that bloody taps are related to fetal mortality and morbidity.

Two of the three retrospective studies of amniocentesis make no reference to maternal morbidity. The one which does consider this risk notes only a 0.09% incidence of minor hematoma and localized pain (229). This figure is markedly lower than that reported in prospective work. This could be due to variations in reporting or, more likely, to the fact all the amniocenteses in this study were performed late in pregnancy. Only one of the retrospective studies of early amniocentesis reports on fetal mortality (123), and these workers note a rate of 1.4%, not different from historical controls.

Fetal morbidity was assessed by inviting all women who had amniocentesis at a single institution over a 5-year period to bring the child born of that pregnancy in for a medical examination (67). Of 274 letters sent, 201 replies were received. Of these, 75 women refused to bring in their children and 19 had not yet delivered. Thus, 107 or 38.3% of potential subjects were examined. Among these, 10 amniocentesis-associated lesions were found. These ranged in severity from “depressed dimples” to disruption of patellar ligament. Reference to the mothers’ charts showed that all of the mothers of affected children had amniocentesis requiring two or more needle passes.

Dialysis. Dialysis, whether it be hemodialysis or peritoneal dialysis, is a procedure which is usually performed when the only other alternative is death or a significant chance of death. Perhaps for this reason, evaluations of the procedure of dialysis focus almost exclusively on estimates of the life expectancy of a patient on dialysis, rather than a quantification of the rate of complications of the procedure. The complications of dialysis are many, but one uncommonly decides not to do the procedure because of them. A patient facing death without dialysis, who is giving informed consent for the initiation of the procedure, may not be as interested in the rate of complications which can occur with the procedure as he may be in the number of years he can expect to live with the procedure and all its complications. This is particularly true for acute hemodialysis and acute peritoneal dialysis where the procedure is an intervention performed to preserve life. While there is a great deal of data on expected survival following initiation of chronic dialysis and some information of the effectiveness of acute dialysis in specific clinical
TABLE 29
Complications of Amniocentesis: Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Maternal Complications</th>
<th>Fetal Complications</th>
<th>Procedure Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Morbidity</td>
<td>Mortality</td>
<td>Morbidity</td>
</tr>
<tr>
<td>Picker, et al. (1979)</td>
<td>2093</td>
<td>2(0.09%)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>Gallus, et al. (1979)</td>
<td>3000*</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Epley, et al. (1978)</td>
<td>274</td>
<td>**</td>
<td>**</td>
<td>10(3.7%)</td>
</tr>
</tbody>
</table>

* 1500 with ultrasound
** Not reported
[a] Of the 274 procedures, follow-up was available for 107 only
situations, there is almost no information available on the incidence of the well-known complications of either acute or chronic hemodialysis or acute or chronic peritoneal dialysis. Table 30 summarizes two prospective and two retrospective studies of chronic hemodialysis and acute and chronic peritoneal dialysis. Chan (1978) studied the incidence of complications in 19 patients receiving 3129 dialyses over 59 months (51). During this time he observed 19 morbid events (0.6% incidence) which included eight episodes of sepsis, three seizures, and 7 other infectious complications. He also noted multiple complications with thrombosis and extrusion of AV shunts but does not report the exact number of these occurrences and does not include them in his estimate of incidence of morbidity. The 0.6% incidence of morbidity reported by Chan also does not include episodes of hypotension which occurred at least once in all 19 patients. Chan reports a mortality during this period of 25% but does not report how many deaths were due to underlying renal disease and how many were due to complications of dialysis.

TABLE 30
Complications of Hemodialysis and Peritoneal Dialysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Dialyses</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPECTIVE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaamonde, et al. (1975)</td>
<td>184</td>
<td>154(84.0%)</td>
<td>7(3.8%)</td>
</tr>
<tr>
<td>Chan (1978)</td>
<td>3129</td>
<td>19*(0.6%)</td>
<td>25**</td>
</tr>
<tr>
<td>RETROSPECTIVE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maher, et al. (1965)</td>
<td>1093</td>
<td>6%</td>
<td>***</td>
</tr>
<tr>
<td>Maher, et al. (1965)</td>
<td>228</td>
<td>11%</td>
<td>***</td>
</tr>
</tbody>
</table>

* Excludes hypotension which occurred at least once in all 19 patients in the study.
** Deaths may have been due to underlying renal disease, not dialysis.
*** Not reported.

In a retrospective study of complications of 1093 hemodialyses, Maher, et al. (1965) reported a 6% incidence of complications causing morbidity (181). These complications included all the well-recognized complications of hemodialysis, but the exact number of occurrences of each type of complication are not given.

In a prospective study of acute peritoneal dialysis, Vaamonde et al. (1975) report on the occurrence of complications in a population of critically ill patients requiring acute peritoneal dialysis (297). These procedures were performed by renal attendings, renal fellows or senior house officers under supervision. A total of 154 major complications and 7 deaths attributable to acute peritoneal dialysis are reported. The morbidity in this series was 84.0% and the mortality from procedure-related deaths was 3.8%.
Maher, et al. (1965) also report a retrospective survey of the complications observed with chronic peritoneal dialysis in renal failure patients (181). In 119 patients who received 228 peritoneal dialyses, an 11.0% incidence of morbid complications is reported. No deaths are reported in this series.

The incidences of complications reported in these studies are clearly affected by the co-morbidity of the populations studied as well as by the extensiveness with which complications were monitored and reported. They do not help to establish an estimate for the incidence of complications of dialysis in the general population of patients receiving this treatment.

While it is difficult to imagine the use of hemodialysis for research purposes, several research projects have used hemodialysis as an experimental treatment for schizophrenia and for psoriasis (102, 300, 301, 296, 167, 208, 262). The results of these studies are summarized in Table 31. All of these studies report hemodialyses performed on individuals with normal renal function. In most cases, the subjects received arterio-venous shunts for performance of the procedure. Subjects participating in the study by Nissenson, et al. were dialyzed using a femoral access (208).

Since the number of subjects in each study is very small, incidences or reported events are not given. Table 31 shows the incomplete reporting of common hemodialysis complications which characterizes all of these research studies. Of the complications which are reported, most are major, life-threatening events. From the data available from these research studies, the risk of injury to research subjects can not be estimated other than to note that serious complications can occur with a reasonably high frequency. No mortality was reported in any of these research projects.

Plasmapheresis. Plasmapheresis involves the extracorporeal separation of a patient's blood into its components, and the subsequent return to the patient of all his blood minus a specific fraction. Formed elements, platelets or cells, may be removed for donation. In the therapy of certain diseases whose basis is felt to be immunological, plasma is removed and replaced volume for volume by normal plasma, a protein solution, or normal saline. At the present time all therapeutic uses of plasmapheresis are considered experimental.

Since patients are maintained in euvolemia during the procedure, no procedure-associated deaths have been reported. The major complications result from infection at the access site, electrolyte imbalance, and reaction to the replacement fluid, most commonly donor plasma.

Three of the 18 research studies using plasmapheresis involved normal subjects. One study noted 9 instances of minor complications in 150 procedures (41). Of the other two, one
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Nausea, Vomiting, Malaise, Insomnia</th>
<th>Hyponatremia</th>
<th>Hypotension</th>
<th>AV Shunt Infection or Thrombosis</th>
<th>Acute Renal Failure</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feur, et al. (1980)</td>
<td>5</td>
<td>**</td>
<td></td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>\geq 4</td>
<td>0</td>
</tr>
<tr>
<td>Wugemarker &amp; Coyle (1977)</td>
<td>10</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td>\geq 1</td>
<td>\geq 1</td>
<td>0</td>
</tr>
<tr>
<td>Wugemarker &amp; Coyle (1978)</td>
<td>10</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td>\geq 1</td>
<td>\geq 1</td>
<td>0</td>
</tr>
<tr>
<td>Twaniowski, et al. (1980)</td>
<td>4</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td>\geq 3</td>
<td>\geq 3</td>
<td>0</td>
</tr>
<tr>
<td>Kroll, et al. (1978)</td>
<td>2</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>\geq 3</td>
<td>0</td>
</tr>
<tr>
<td>Nissenson, et al. (1979)</td>
<td>4</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>\geq 3</td>
<td>0</td>
</tr>
<tr>
<td>Sidorowicz, et al. (1980)</td>
<td>4</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>\geq 3</td>
<td>0</td>
</tr>
</tbody>
</table>

* Complications are those reported by investigators. Other well known complications of hemodialysis were not mentioned in these studies.

** Complications occurred, but number of occurrences not reported.

a. Psoriasis
specifically noted no morbidity (161) and the other does not discuss problems (108).

The remaining 15 studies utilize plasmapheresis as experimental therapy for a wide variety of diseases. Nine of the 15 studies do not list complications. Several refer to "shunt infections" and "symptoms of hypocalcemia" without giving incidence data. Among the remaining five studies the incidence of untoward effects ranged from 1.7% to 36% (Table 32).

Six studies noted that certain laboratory values predictably turned abnormal with plasmapheresis. Three studies noted marked prolongation of blood coagulation times in subjects undergoing plasmapheresis (108, 154, 274). Four series remarked on significantly decreased post-plasmapheresis platelet counts (41, 64, 154, 161), and two studies noted hypercoagulability of blood due to loss of anti-thrombin III activity (108, 274). All of the subjects studied in these series remained asymptomatic in spite of the abnormal laboratory values.

It is most likely that the wide variation in reported complication rate is a result of at least 3 factors. First, sample size in all of these studies is small (range = 1–25 patients, mean = 7.6). Secondly, investigators use different definitions for complications and different criteria for diagnosing these complications. Third, complications are inconsistently reported.

General Anesthesia. Evaluating the risk of general anesthesia is complicated by the intimate association between anesthesia and the surgical procedures which always accompany it. The challenge to anesthesiologists has been the separation of anesthesia morbidity and mortality from surgical morbidity and mortality.

Assessment of the risk of anesthesia may be approached in several different ways. Deaths occurring in the pre-operative and post-operative period can be reviewed to ascertain the contribution of anesthesia to the death. This approach gives an estimate of the overall mortality associated with general anesthesia.

An assessment of morbidity due to anesthesia is more difficult, however, because many of the morbid events which might be considered complications of anesthesia may also result from major surgery. For example, aspiration might follow prolonged respiratory depression due to anesthesia but might also result if pain due to a surgical incision prevents a patient from coughing or getting up out of bed. This problem has been approached by studying the minor complications occurring in patients undergoing minor surgical procedures under general anesthesia on either an outpatient or short-stay basis.

Finally, since both morbidity and mortality associated with anesthesia depend in some measure on the type of anesthetic used, the morbidity and mortality associated with specific anesthetics can be studied. These studies are initially designed as research studies, occasionally on normal volunteers. After the
<table>
<thead>
<tr>
<th>Study</th>
<th>Number Of Patients</th>
<th>Number Of Procedures</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kliman, et al. (1964)</td>
<td>25*</td>
<td>&gt; 25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duchholz, et al. (1975)</td>
<td>6*</td>
<td>25</td>
<td>0(36.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Powles, et al. (1971)</td>
<td>11</td>
<td>48</td>
<td>4(36.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Punching, et al. (1970)</td>
<td>3</td>
<td>50</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Lockwood, et al. (1977)</td>
<td>9</td>
<td>b</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Marran, et al. (1977)</td>
<td>2</td>
<td>b</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Buskard, et al. (1977)</td>
<td>2</td>
<td>b</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Dau, et al. (1977)</td>
<td>5</td>
<td>61</td>
<td>2(2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Simons, et al. (1978)</td>
<td>4</td>
<td>54</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sultan, et al. (1979)</td>
<td>7</td>
<td>18</td>
<td>2(11.0%)</td>
<td>**</td>
</tr>
<tr>
<td>McKenzie, et al. (1979)</td>
<td>17</td>
<td>270</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Taft (1979)</td>
<td>4</td>
<td>23</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Wallace, et al. (1979)</td>
<td>12</td>
<td>240</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Keller, et al. (1979)</td>
<td>18</td>
<td>179</td>
<td>3(1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Holdstock, et al. (1979)</td>
<td>5</td>
<td>40</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Flinn, et al. (1979)</td>
<td>3</td>
<td>b</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>McLeod &amp; Sassetti (1980)</td>
<td>3</td>
<td>b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Evans, et al. (1985)</td>
<td>1</td>
<td>7</td>
<td>1(14.3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Normal volunteers
** Not known
--- Not reported
initial clinical trial of the anesthetic agent, anesthesiologists usually try to evaluate the agent by using it on patients undergoing the same types of surgery and by comparing its use in this setting with the use of other, well-known agents in a similar setting.

During the past ten years, most of the research and clinical studies conducted by anesthesiologists have been of the latter type. The major assessments of overall mortality in anesthesia were published in the 1960's and the major studies of the minor complications of anesthesia were published in the 1960's and early 1970's.

Major retrospective and prospective studies of mortality associated with general anesthesia are summarized in Table 33 (20, 81, 227, 84, 57, 194, 135). The range reported for deaths in which anesthesia was the primary cause is 1 in 536 to 1.3 in 10,000. The range reported for deaths in which anesthesia was contributory, but not the primary cause is 1 in 259 to 2.7 in 10,000.

The lowest incidence in this series is reported by Phillips, et al. (1960) (227). This study was conducted by the Baltimore Anesthesia Study Committee during a five and one-half year period in the late 1950's. During this period, there were 1024 post-operative deaths which were reviewed by the study committee.

Using information provided by the principals in these cases, the study committee ascertained that 64 deaths were due to anesthesia alone and in 196 deaths, anesthesia was a contributing cause. In order to determine a mortality rate, the number of anesthetics performed in the city of Baltimore during the five and one-half period of the study was calculated in the following manner: National Health survey data on the incidence of operative procedures was extrapolated to the Baltimore City Health Department's estimate of the city population during the study period. This number formed the denominator of the mortality rate calculated in this study. The national incidence of operative procedures is the number of reported operations occurring in the United States during a given time period divided by the population of the United States as given by the last census count. There are many problems relating to the accuracy of this number alone, but for purposes of this study it is sufficient to observe that there is no reason to assume that the national incidence of operative procedures is similar in magnitude to the incidence of operative procedures occurring in Baltimore in any given year. Moreover, when this number is applied to an estimate of the city's population, any error present in the first number will be compounded by the error present in the second number. These problems in statistics make these data unreliable. The most useful piece of information to be obtained from this study is the assessment made by the study committee that 51% of the deaths due to anesthesia alone resulted from mismanagement of the anesthetic and not from properties of the anesthetic agent itself.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Anesthetics</th>
<th>Incidence of Death</th>
<th>Anesthesia-Primary</th>
<th>Anesthesia-Contributory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beecher &amp; Toold</td>
<td>599,581</td>
<td>1:2680</td>
<td>1:1500</td>
<td></td>
</tr>
<tr>
<td>(1954)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dormette &amp; Orth</td>
<td>63,150</td>
<td>1:2429</td>
<td>1:1344</td>
<td></td>
</tr>
<tr>
<td>(1956)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phillips et al.</td>
<td>**</td>
<td>1:3:10,000</td>
<td>2:7:10,000</td>
<td></td>
</tr>
<tr>
<td>(1960)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driggs et al.</td>
<td>14,487*</td>
<td>1:536</td>
<td>1:259</td>
<td></td>
</tr>
<tr>
<td>(1961)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clifton &amp; Hotten</td>
<td>205,640</td>
<td>1:1208</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>(1963)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory (1965)</td>
<td>62,291*</td>
<td>1:2660</td>
<td>1:833</td>
<td></td>
</tr>
<tr>
<td>Harrison (1968)</td>
<td>177,928</td>
<td></td>
<td>3:3:10,000</td>
<td></td>
</tr>
</tbody>
</table>

* Only general anesthetics reported
** Not reported
(a) Certain studies may include spinal anesthesia but investigators do not always calculate mortality rates for spinal and general anesthesia independently.
In Table 34, the mortality of anesthesia is summarized according to pre-operative physical status of the patient. Class I represents a normal, healthy patient with no underlying disease, while Class V represents patients with severe systemic disease which is a threat to life. Classes II through IV include patients with increasing severity of systemic disease. Using this classification, mortality was 0.0% for Class I patients and increased with severity of underlying disease to 4.2% (42/10,000) for Class V patients. Increasing risk with increasing comorbidities has also been noted in the studies by Beecher and Todd (1954) and Memery (1965).

Several studies reporting the incidence of minor complications in general anesthesia are presented in Table 35. The minor complications which occur with relatively high frequency in most of the five studies shown are nausea and vomiting during the 24 to 72 hour period following anesthesia, sore throat (this occurred with high frequency in patients who had not been intubated as well as in intubated patients), pain due to positioning during anesthesia or other aspects of anesthesia, headache and a variety of other complaints including prolonged drowsiness, dizziness, dental trauma, and minor lacerations. The range of incidence of all occurrences of minor complications is 28% to more than 100%. All studies were done on otherwise healthy individuals undergoing minor elective surgical procedures and the anesthetics used in these procedures were comparable. The difference in reported incidence is most likely due to the thoroughness with which investigators pursued these complaints. The striking aspect of these prospective studies is their overall agreement that the incidence of minor, but unpleasant, complications of general anesthesia is relatively high.

### Table 34

<table>
<thead>
<tr>
<th>Physical Status</th>
<th>Number of Patients</th>
<th>Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>6028</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Class II</td>
<td>5365</td>
<td>5 (0.1%)</td>
</tr>
<tr>
<td>Class III</td>
<td>2477</td>
<td>7 (0.3%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>546</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Class V</td>
<td>71</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>14,487</td>
<td>27 (0.2%)</td>
</tr>
</tbody>
</table>

*From Dripps et al. (1961)*

Insufficient information is given in the remaining studies to allow assessment of the data from which these mortality figures are derived.

The data from Dripps et al. (1961), however, demonstrate how mortality from anesthesia can be influenced by the characteristics of the population receiving the anesthesia. Table 34 summarizes the anesthesia mortality observed in this study according to pre-operative physical status of the patient. Class I represents a normal, healthy patient with no underlying disease, while Class V represents patients with severe systemic disease which is a threat to life. Classes II through IV include patients with increasing severity of systemic disease. Using this classification, mortality was 0.0% for Class I patients and increased with severity of underlying disease to 4.2% (42/10,000) for Class V patients. Increasing risk with increasing comorbidities has also been noted in the studies by Beecher and Todd (1954) and Memery (1965).
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>Nausea, Vomiting, Malaise</th>
<th>Sore Throat</th>
<th>Other Pain</th>
<th>Bruises, Lacerations</th>
<th>Other</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmonds-Seal &amp; Eve (1962)</td>
<td>513</td>
<td>113 (22.0%)</td>
<td>72 (14.0%)</td>
<td>94 (18.0%)</td>
<td>85 (16.6%)</td>
<td>92 (18.0%)</td>
<td>356 (69.0%)</td>
</tr>
<tr>
<td>Thomas (1963)</td>
<td>100</td>
<td>**</td>
<td>7 (7.0%)</td>
<td>21 (21.0%)</td>
<td>**</td>
<td>**</td>
<td>28 (28.0%)</td>
</tr>
<tr>
<td>Fahy &amp; Marshall (1969)</td>
<td>408</td>
<td>60 (14.8%)</td>
<td>**</td>
<td>55 (13.5%)</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Steward (1973)</td>
<td>264 *b</td>
<td>15%</td>
<td>~11%</td>
<td>**</td>
<td>**</td>
<td>173 (42.4%)</td>
<td>286 (70.0%)</td>
</tr>
<tr>
<td>Thompson et al. (1972)</td>
<td>180 *b</td>
<td>54%</td>
<td>13.5%</td>
<td>32%</td>
<td>**</td>
<td>83.5%</td>
<td>**</td>
</tr>
<tr>
<td>Brindio &amp; Soliman (1975)</td>
<td>500</td>
<td>148 (29.6%)</td>
<td>80 (16.0%)</td>
<td>137 (27.4%)</td>
<td>**</td>
<td>301 (60.2%)</td>
<td>&gt;100%</td>
</tr>
</tbody>
</table>

* Includes drowsiness, dizziness, dental trauma
** Not reported
(a) Children
(b) Report gives percentages only
Spinal Anesthesia. Spinal anesthesia is accomplished by the injection of a local anesthetic into subarachnoid or epidural space. In the first case the anesthetic acts directly on the spinal cord, and the desired extent of anesthesia is achieved by tilting the patient, allowing the drug to flow cephalad. In epidural anesthesia the nerve roots are affected, and the anesthetic may be administered through a catheter that is left indwelling for the duration of surgery. Spinal anesthesia was introduced long after general (inhalational) anesthesia had become widely accepted. Being free of the complications associated with general anesthesia, and leaving the patient alert but pain-free, spinal anesthesia enjoyed tremendous popularity at first. By 1940, however, anecdotal reports of irreversible paralysis, spinal hematomas and chemical meningitis had appeared [reviewed by Kennedy, et al., 1950] and the procedure fell into disfavor. Since that time several large, prospective studies have appeared attempting to document the actual incidence of procedure-associated problems.

Three of the four prospective studies have greater than 10,000 patients [71, 85, 228]. The fourth comprises 200 patients anesthetized by a single physician (315). Among the 35,000 patients included in all of these studies there was one intraoperative death (post-mortem showed no neurological damage) and two respiratory arrests, both resuscitated. It is not clear whether these are examples of morbidity associated with the procedure or with the attendant surgery.

No major, irreversible central nervous system complications were observed in any of the studies. The incidence of peripheral nerve problems ranged from 0.1% to 1.3%. These included paresthesias with decreased sensation, anesthetic, external rectus muscle paresis and weakness of one or more extremities. All are reported to have resolved completely within one month to one year.

In these series cardiopulmonary complications, most frequently hypotension and respiratory depression due to inadvertent high spinal block, are reported with a range of zero to 3%. Hypotension is variously defined as a systolic pressure of less than 80 torr (315) and as a drop in systolic pressure of 25 torr from pre-operative levels (228). This difference in definition may account in part for the range of incidence of the complication. In all cases the hypotension was readily reversible.

As with diagnostic lumbar puncture, invasion of the spinal canal is associated with post-puncture headache. Three of the four studies report this complication with an incidence ranging from 3.5% to 14%. Vandam and Dripps (85) demonstrated that the headache was indeed due to the spinal tap by using two sets of controls. One set was matched for age, sex, and operative procedure but received inhalational anesthesia. The other set, similarly matched, received inhalational anesthesia and then were given a spinal. This group "never knew that they had been
given spinal anesthesia" and had the same incidence of headache as the experimental group. Headache was not noted among patients receiving general anesthetic only. No correlation exists between needle size and frequency of headache. Vandam and DiArps (85) and Phillips, et al. (228) used 24 gauge needles and noted 14% and 3.5% incidence of headaches respectively. Wilkinson (315) used a 20 gauge needle and noted a 12% rate of post-procedure headache.

With the exception of the Beying study (71), which does not report the incidence of headache, the range of reported rates of complication with this procedure is small (Table 36). This is probably due to the extensive and careful charting which is a routine part of the anesthesiologist's standard practice, similarity in the general group of surgical patients, and perhaps greater similarity in the performance of the procedure than is seen with other procedures. The studies reported by anesthesiologists are frequently outstanding for detail in describing procedures, skill of the operator, co-morbidity of the subject population and target complications which are to be monitored.

**Lumbar Puncture.** Lumbar puncture has been a valuable adjunct to the diagnosis of central nervous system disease since its introduction in the early years of this century. By providing access to fluid protected by the "blood-brain barrier" it has also been used in research to follow the distant effects of metabolic manipulation.

The most frequent complication of lumbar puncture is headache, ranging in severity from moderate discomfort to debilitating pain. Vertigo, nausea and vomiting have also been noted. Unusual complications, including subarachnoid, subdural, and epidural hematomas occur with great rarity and were not noted to occur in any of the large, prospective series.

In eight prospective studies reported between 1930 and 1950 the incidence of post-spinal tap headache ranges from 0.45% to 47%. Two of the eight studies do not discuss the problem. Three of the studies attempt to prevent or control headache by means of a maneuver. In two of these (37, 205) the incidence of headache in the "control" group (17.4% and 36.5%) is significantly higher than in the experimental group (4.8% and 0.43%). If these last numbers are omitted as possible examples of observer bias, the overall range of post-tap headache varies from 2.5% to 47.1%. This range takes into account that some investigators distinguish between "mild" and "severe" headaches, some count them all, and some only report those requiring strong analgesics (Table 37).

It has been suggested that frequency and severity of post-tap headache is directly related to needle size. A study in which spinal taps were performed on paid volunteers under carefully controlled conditions (290) using 18, 20 and 22 gauge needles showed a 36% overall incidence of headache, and also indicated
### TABLE 36
Complications of Spinal Anesthesia: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Procedures</th>
<th>CNS Complications</th>
<th>Peripheral Nerve Complications</th>
<th>Cardiac-Pulmonary Complications</th>
<th>Epidural Hemorrhage</th>
<th>Other</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dripps &amp; Vandam (1954)</td>
<td>10,998</td>
<td>0</td>
<td>66(0.6%)</td>
<td>0</td>
<td>0</td>
<td>14%**</td>
<td>~1.466</td>
<td>0</td>
</tr>
<tr>
<td>Wilkinson (1963)</td>
<td>2,000</td>
<td>0</td>
<td>2(0.1%)</td>
<td>0</td>
<td>0</td>
<td>240(12.0%)</td>
<td>24(12.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Phillips, et al (1969)</td>
<td>10,440</td>
<td>0</td>
<td>131(1.3%)</td>
<td>32(3.0%)</td>
<td>0</td>
<td>0.06(8.3%)</td>
<td>1,317(12.6%)</td>
<td>1(0.0009%)</td>
</tr>
<tr>
<td>Department of Anesthesiology, Beijing Medical College (1989)</td>
<td>10,978</td>
<td>2(0.2%)</td>
<td>124(1.0%)</td>
<td>27(0.2%)</td>
<td>41(0.4%)</td>
<td>100(0.9%)</td>
<td>320(3.0%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- b. Headache, backache, nausea, vomiting.
- c. Headache not reported.
- d. Only percentages reported.
### TABLE 37
Complications of Lumbar Puncture: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Post-Puncture Headache</th>
<th>Other Problems*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Nelson, M. (1930)</td>
<td>102</td>
<td>16(17.4%)</td>
<td>5(4.8%)</td>
</tr>
<tr>
<td>Davenport, K. (1939)</td>
<td>705</td>
<td>137(19.4%)</td>
<td>64(9.1%)</td>
</tr>
<tr>
<td>Noon, Z. B. (1949)</td>
<td>621</td>
<td>84(13.5%)</td>
<td>116(18.7%)</td>
</tr>
<tr>
<td>Brocker, B. (1958)</td>
<td>456</td>
<td>107(23.5%)</td>
<td>107(23.5%)</td>
</tr>
<tr>
<td>Tourtellotte, W., et al.  (1964)</td>
<td>894</td>
<td>4(0.45%)</td>
<td>60(36.5%)</td>
</tr>
<tr>
<td>Hansen, P. &amp; J. Hansen (1979)</td>
<td>351</td>
<td>11(3.2%)</td>
<td>37(25.2%)</td>
</tr>
<tr>
<td>McGaha, E., et al. (1979)</td>
<td>19</td>
<td>11(21.6%)</td>
<td>13(25.5%)</td>
</tr>
<tr>
<td>Lorber, J. (1980)</td>
<td>304</td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

* Includes vertigo, traumatic tap, death from cerebellar contig
b. This includes one tap-related fatality
* Severity not graded
** Not discussed

* Problems:
- **: Significant
- **: Very Significant
- **: Critical
no difference in the frequency with which headache occurred regardless of needle size used.

Factors Influencing Reliability of Risk Estimates
Three hundred studies were selected for evaluation in this project. These included 107 reports of research projects in which one of the twenty procedures was used and 193 studies in which the complications of one of the twenty procedures was reported.

Of the 107 research project reports reviewed, 48 (45%) did not include a discussion of complications. Fifty-nine project reports (55%) did include a discussion of complications, but in twenty of these reports (34%) the number of occurrences was not given.

TABLE 38
Literature Review for Procedure Risk Evaluation:
Number and Type of Studies Reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Studies</th>
<th>Complications Discussed</th>
<th>Complications Not Discussed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td>231</td>
<td>124</td>
<td>0</td>
</tr>
<tr>
<td>Non-Research</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies*</td>
<td>124</td>
<td>59/107 (55%)</td>
<td>48/107 (45%)</td>
</tr>
<tr>
<td>Research Studies*</td>
<td>107</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td>Retrospective</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>300</td>
<td>262</td>
<td>48</td>
</tr>
</tbody>
</table>

* All studies classified as Type A or Type B
** All studies classified as Type A, B, C, or D.

Complications were discussed in all prospective clinical studies and in all retrospective studies. In many instances investigators in these studies reported only one or two of several possible common complications without indicating that the complications not discussed had not occurred.

For most of the procedures evaluated, the incidence reported for specific complications and for morbidity was unexpectedly large. Mortality for all procedures was relatively infrequent and the range of incidence of deaths due to complications of procedures was not as large as that for morbidity. In some cases, the differences in incidences of reported complications could be explained by the following differences in the studies compared:

(1) Differences in the population with respect to susceptibility to those complications known to occur with a given procedure.
(2) Differences in the performance of the procedure, either in the techniques used or in the skill of the operator.
(3) Differences in definition of what constitutes a complication of a given procedure.
(4) Differences in criteria used to determine when a complication has occurred.

(5) Differences in methods used to detect complications.

In many instances, the information reported in a study was insufficient to allow assessment of these factors.

Prospective and retrospective studies of the same procedure frequently reported very different incidences for complications, morbidity and mortality. Figure 2 summarizes this information.

Each of the 231 prospective studies (includes research studies) reviewed was evaluated for compliance with the criteria developed to assess quality of risk reporting. Fifty-six (24%) of these studies met all nine criteria. Six or more criteria were met by 128 studies (55%). This 55% includes the 56 studies which met 9 out of 9 criteria (Table 39). In studies meeting 6 out of 9 criteria, the criteria most often not met were those requiring a description of the skill of the operator, a description of the method of performance of the procedure, a description of the characteristics of the population studied, a description of the sequelae of complications and recommendations for the prevention of future complications.

<table>
<thead>
<tr>
<th></th>
<th>Number Meeting Six or More Criteria</th>
<th>Number Meeting Nine Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>128(55%)</td>
<td>56/231(24%)</td>
</tr>
</tbody>
</table>

Discussion

Although there is a rich literature discussing the ethical issues of human experimentation, informed consent and theoretical aspects of the problem of potential injury to human research subjects, there is little literature which quantifies the overall risk of injury to human research subjects and there is no literature which quantifies the risk of injury resulting from the use of specific invasive procedures in research projects. Moreover, the reporting of complications in published research projects is so inconsistent and incomplete that the risk of these procedures can not be calculated even by reviewing a large series of projects in which the procedure has been used.

Using information available in the medical literature, it would be theoretically possible to determine the risk associated with the routine clinical use of these procedures and use these estimates as rough estimates of the maximal risk of injury to which a research subject might be exposed. However, review of the medical literature reveals a confusing array of conflicting incidences reports for many of the procedures evaluated in this study.
## FIGURE *

Range of Complication Rates for Selected Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary bladder catheterization</td>
<td>0.5% - 82%</td>
<td>**</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous catheterization</td>
<td>3.4% - 60%</td>
<td>**</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>0.3% - 55%</td>
<td>0.1% - 1.5%</td>
</tr>
<tr>
<td>Swan-Ganz catheter placement</td>
<td>8.2% - 57.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>2.3% - 10.1%*</td>
<td>0.44%</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>1.9% - 35%</td>
<td>0.0% - 0.09%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.7% - 26.7%</td>
<td>0.06% - 0.3%</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial line placement</td>
<td>4% - 63%</td>
<td>0%</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise tolerance testing</td>
<td>0.1% - 66.8%</td>
<td>0.0% - 0.1%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.03% - 1.4%</td>
<td>0.0009% - 0.1%</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>0.6% - 14.5%</td>
<td>0.02% - 0.45%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.32% - 4.6%</td>
<td></td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone biopsy</td>
<td>1.2% - 17.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.0% - 0.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopy</td>
<td>1.1% - 17.6%</td>
<td>0%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.2% - 2.4%</td>
<td>0.0% - 0.09%</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>1.0% - 14.9%</td>
<td>0.0% - 1.4%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.2% - 0.3%</td>
<td>0.01% - 0.03%</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>2.1% - 7.1%</td>
<td>0.0% - 0.4%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.2% - 2.4%</td>
<td>0.0% - 0.01%</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthroscopy</td>
<td>1.0% - 2.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.0% - 2.0%</td>
<td>0%</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amniocentesis*</td>
<td>0.4% - 3.6%</td>
<td>0%</td>
</tr>
<tr>
<td>Prospective</td>
<td>0.0% - 9.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>1.7% - 36%</td>
<td>0%</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anesthesia</td>
<td>28.0% - 100%</td>
<td>1:33,000 - 1:300,000</td>
</tr>
<tr>
<td>Spinal Anesthesia</td>
<td>3.0% - 12.6%</td>
<td>0.0% - 0.009%</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>0.4% - 47.0%</td>
<td>0%</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Represents a single study. Complication rate reported by cardiac risk group
b. Maternal morbidity only
** Not reported
Not surprisingly, the risk estimates calculated from prospective and retrospective studies for the same procedure are often very different. In general, the estimate given by retrospective studies is lower than that from prospective studies. The retrospective study is often compromised by low response rates if it is a questionnaire survey. It is almost always characterized by under-reporting whether it is a questionnaire survey or a direct review of medical records. Non-responders to questionnaires may be the very physicians who have had a high incidence of complications. Under-reporting will occur if the individuals who kept the original records failed to record all complications of interest and if the respondent to a questionnaire survey has himself kept incomplete records or if he has not had time to review his records adequately for response to the survey.

Well-designed prospective studies should provide better estimates of risk. However, for most of the procedures we evaluated, prospective studies reported impressive, and occasionally extreme, ranges of risk estimates.

This phenomenon reflects the lack of co-ordinated risk assessment procedures in many areas of medical practice.

All risk estimates are derived from experience. An estimate of risk is a statement of statistical probability. The magnitude of the probability of a procedure complication occurring is determined by observing how many times that complication occurs when the procedure is repeated many times under similar circumstances. The important words here are "under similar circumstances". Much of the information available on the complications of invasive procedures in routine clinical practice represents a single investigator's unique experience. Because of differences in the patients, the procedure or in the definition and detection of complications, the "circumstances" of these studies are rarely similar. The risk estimates derived from these studies are difficult to generalize. At best, they are risk estimates only for situations which are similar to those from which the risk estimate was derived.

If it is difficult to generalize this data to the routine clinical practice of medicine, it is impossible to extrapolate it to estimate the risk of injury in the research setting. To do so would be equivalent to informing a bettor at the race track that the chance of a certain horse winning a race is between 26% and 78% depending on whether it is a healthy horse or a sick horse, on whether the track is wet or dry and on whether the finish is judged by "eyeball" technique or by electronic camera.

At present, the best information on the risk of a procedure which an investigator can give a research subject is an estimate of risk based on the investigator's own experience with the procedure. This information is, of course, anecdotal until it is documented in a scientific manner and made available to the research community.
In medical research the opportunity does exist for developing reliable risk data which may be used to evaluate research proposals, to give informed consent, and to develop adequate compensation schemes for subjects who do sustain injury during research. Individuals conducting medical research often conduct their experiments in situations in which complications can be easily monitored. They are trained to observe and record in great detail the events which occur during a research project and could apply these skills of observation and accurate reporting to the monitoring of complications as they perform their projects.

However, in order to avoid a situation in which a meaningless collection of isolated experiences is accumulated, a cooperative effort in which the experience of individuals at several institutions is collected under similar circumstances is required. In clinical medicine, an example of such an effort is provided by the Cardiac Catheterization Co-operative Study reviewed in this paper. Such a co-operative effort might use criteria similar to those developed for assessment of quality of risk-reporting in this study to ensure that the subject populations studied are well-defined, the techniques used to perform procedures are similar, the complications are well-defined and the methods used for detecting them are similar. In this manner, reliable risk estimates for the unique situation of medical research might be developed.
Attachment I

The procedures listed are those reported to have been used in human experimentation by investigators who responded to an interview survey conducted by the Institute for Social Research, Ann Arbor, Mich., in 1976. The procedures were employed (1) to collect data for a research project; (2) to evaluate the feasibility of the procedure; or (3) to evaluate the effectiveness of the procedure as a diagnostic or therapeutic intervention.

A total of 2340 projects were reported. The percentage of the 2340 projects in which each procedure was used is indicated in the right-hand column.

### PROCEDURES USED IN HUMAN EXPERIMENTATION

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraction of data from medical records</td>
<td>50.5%</td>
</tr>
<tr>
<td>Obtaining a medical history</td>
<td>50.4%</td>
</tr>
<tr>
<td>Conducting an interview</td>
<td>34.3%</td>
</tr>
<tr>
<td>Psychological or educational testing</td>
<td>13.8%</td>
</tr>
<tr>
<td>Psychological or social therapy</td>
<td>4.2%</td>
</tr>
<tr>
<td>Other forms of counseling*</td>
<td>11.1%</td>
</tr>
<tr>
<td>Testing educational innovations</td>
<td>4.2%</td>
</tr>
<tr>
<td>Modifying an organizational or service delivery system</td>
<td>4.0%</td>
</tr>
<tr>
<td>Physical therapy or rehabilitation</td>
<td>3.1%</td>
</tr>
<tr>
<td>Use of prosthetic device</td>
<td>1.4%</td>
</tr>
<tr>
<td>Dietary manipulation</td>
<td>6.3%</td>
</tr>
<tr>
<td>Non-invasive measurement of other body activities (e.g., temperature, blood pressure)</td>
<td>25.3%</td>
</tr>
<tr>
<td>Measurement of electrical activity of body (e.g., ECG, EKG, EMG)</td>
<td>13.8%</td>
</tr>
<tr>
<td>Aspiration of Body Fluids</td>
<td></td>
</tr>
<tr>
<td>*Blood</td>
<td>41.6%</td>
</tr>
<tr>
<td>*Urine</td>
<td>17.8%</td>
</tr>
<tr>
<td>*Pleural fluid</td>
<td>1.5%</td>
</tr>
<tr>
<td>*Abdominal fluid</td>
<td>1.6%</td>
</tr>
<tr>
<td>*Spinal fluid</td>
<td>2.1%</td>
</tr>
<tr>
<td>*Synovial fluid</td>
<td>1.4%</td>
</tr>
<tr>
<td>*Amniotic fluid</td>
<td>0.5%</td>
</tr>
<tr>
<td>*Other</td>
<td>6.0%</td>
</tr>
</tbody>
</table>
### Tissue Biopsy

<table>
<thead>
<tr>
<th>Tissue</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>0.7%</td>
</tr>
<tr>
<td>Kidney/bladder</td>
<td>0.7%</td>
</tr>
<tr>
<td>Liver</td>
<td>2.0%</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.7%</td>
</tr>
<tr>
<td>Skin</td>
<td>3.2%</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.9%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>2.5%</td>
</tr>
<tr>
<td>Other</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

### Administration of drug, chemical agent, fluid or blood product (other than anesthetic)

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug or chemical agent</td>
<td>29.4%</td>
</tr>
<tr>
<td>Blood or blood products</td>
<td>0.1%</td>
</tr>
<tr>
<td>Other</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

### Administration of anesthetic

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local or topical</td>
<td>2.5%</td>
</tr>
<tr>
<td>Spinal</td>
<td>0.2%</td>
</tr>
<tr>
<td>General</td>
<td>2.9%</td>
</tr>
<tr>
<td>Other</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

### Acupuncture

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

### Administration of an isotope

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

### Administration of electricity—

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroshock, defibrillation</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

### Administration of other energy forms—

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat, cold</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

### Roentgenography

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of laser</td>
<td>0.4%</td>
</tr>
<tr>
<td>Use of ultrasound</td>
<td>3.9%</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

### Examination of internal structures

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using natural orifices</td>
<td>7.6%</td>
</tr>
<tr>
<td>Not using natural orifices</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

### Exchange transfusion

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>0.5%</td>
</tr>
<tr>
<td>Extracorporeal circulation</td>
<td>0.2%</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

### Procedures in reproductive biology

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraception</td>
<td>0.1%</td>
</tr>
<tr>
<td>Sterilization</td>
<td>0.05%</td>
</tr>
<tr>
<td>Diagnostic methods for infertility</td>
<td>0.1%</td>
</tr>
<tr>
<td>Artificial insemination</td>
<td>0.5%</td>
</tr>
<tr>
<td>Other</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

### Surgical procedures (including oral surgery)

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental procedures (other than surgery)</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

† Not Specified
Attachment II

EXPANDED LIST OF PROCEDURES USED IN HUMAN EXPERIMENTATION

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary bladder catheterization</td>
<td>Angiography</td>
</tr>
<tr>
<td>Central venous catheterization</td>
<td>General anesthesia</td>
</tr>
<tr>
<td>Peripheral venous catheterization</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Arthrocentesis</td>
<td>Spinal anesthesia</td>
</tr>
<tr>
<td>Gastro-duodenal aspiration</td>
<td>Local anesthesia</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>Infiltration</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Nerve blocks</td>
</tr>
<tr>
<td>Kidney biopsy</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Muscle biopsy</td>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>Bone biopsy</td>
<td>Plasmaphoresis</td>
</tr>
<tr>
<td>Lung biopsy</td>
<td>Exchange transfusion</td>
</tr>
<tr>
<td>Intestinal biopsy</td>
<td>Administration of blood products</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Rossetography</td>
</tr>
<tr>
<td>Placement of Swan-Ganz Catheter</td>
<td>Exercise tolerance testing</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>Roentgenography</td>
</tr>
<tr>
<td>Placement of arterial line</td>
<td>Administration of a contrast agent</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>Computerized axial tomography</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Ultrasonography</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td></td>
</tr>
</tbody>
</table>

Attachment III

LIST OF TWENTY INVASIVE PROCEDURES SELECTED FOR RISK EVALUATION

(1) Catheterization of the urinary bladder
(2) Central venous catheterization
(3) Placement of Swan-Ganz catheter
(4) Cardiac catheterization
(5) Angiography
(6) Placement of arterial line
(7) Exercise tolerance test
(8) Liver biopsy
(9) Bone biopsy
(10) Endoscopy
(11) Colonoscopy
(12) Bronchoscopy
(13) Laparoscopy
(14) Arthroscopy
(15) Amniocentesis
(16) Dialysis
(17) Plasmapheresis
(18) General anesthesia
(19) Spinal anesthesia
(20) Lumbar puncture
Attachment IV.

SELECTION CRITERIA FOR PROCEDURES AND EXAMPLES OF IMPORTANT EXCLUSIONS

1. The procedure is invasive.
   (For the purposes of this study, ultrasound and roentgenography were considered to be invasive procedures since sound waves and X-rays penetrate the body surface.)

2. The procedure has well-recognized complications.
   (Exclusion examples: Ultrasonography excluded because complications of the procedure, if any, are not yet well-defined. Therefore, rate of complications cannot be reasonably determined.)

3. The complications associated with the procedure can be monitored by the investigator.
   (Exclusion examples: Roentgenography and radiotherapy excluded because important complications may occur only many years after exposure to the procedure. An investigator is unlikely to have adequate follow-up to be able to determine complication rates.)

4. The procedure is associated with more than minimal risk to the subject.
   (Exclusion examples: Skin biopsy and peripheral venous phlebotomy excluded since only minimal risk is associated with these procedures.)

5. Selection preference is given to procedures which are more likely to be used in research projects than in non-experimental diagnostic or therapeutic settings.

Attachment V

EXTRACTION CODE FOR RISK EVALUATION STUDY

1. Type of study
   a) Prospective
   b) Retrospective

2. Name of procedure

3. Purpose of procedure
   a) Diagnostic
   b) Therapeutic
   c) Experimental diagnostic procedure
   d) Experimental therapeutic procedure
   e) Research only (Procedure is not subject of research project)
   f) Research only (Procedure is subject of research project)

4. Describe expertise of the operator

5. Describe the method used for the performance of the procedure
6. Description of subjects
   a) Number
   b) Age (Range and mean or median)
   c) Physical status
7. List other procedures done concurrently
8. Complications
   a) Type
   b) Number
   c) Outcome
   d) How did it present?
   e) How managed?
   f) Reversible?
9. Recommendations made for preventing future complications
   a) Yes
   b) No
10. List relevant references

Attachment VI

CRITERIA FOR ADEQUACY OF RISK ASSESSMENT AND RISK REPORTING

The following criteria were used to evaluate the adequacy of published reports of complications associated with the 20 invasive procedures examined in this report.

1. The investigator should describe the primary purpose for which the procedure was performed. The statement should indicate which of the following situations applied:

   a) The procedure was performed as a diagnostic or therapeutic intervention in the normal course of the care of the patient. Performance of the procedure allowed opportunistic research to be done. (Example: Research with cell cultures prepared from amniotic fluid obtained during diagnostic amniocentesis.)

   b) The procedure was performed as an extreme measure to diagnose or to treat a patient who had failed all other diagnostic or therapeutic modalities. However, the procedure is not yet accepted as standard medical practice within the community and may, in fact, still be considered experimental. (Example: Use of plasmapheresis in rheumatoid arthritis.)

   c) The procedure was performed solely for research purposes but the procedure itself is not the subject of the research. (Example: Placement of an arterial line for arterial blood gas monitoring in a lung water study.)
d) The procedure was performed solely for research purposes and is itself the object of the research project. (Example: Early experimental trials of Swan-Ganz catheter placement in human beings.)

2. The investigator should describe in detail the method by which the procedure was performed. This statement should include a description of the techniques used for patient preparation, the type and route of administration of anesthetic or any other drug used, technical aspects of the performance of the procedure, and intra-procedure and post-procedure methods used for monitoring the patient.

3. The investigator should describe the level of expertise of all individuals performing the procedure and should report whether the procedure was performed by one or by several different individuals during the research project.

4. The investigator should list all known complications which will be specifically monitored during the performance of the research project.

5. The investigator should describe the patient population in which the procedure was performed. This statement should include a description of any known pre-existing disease, all current medications, and known risk factors which might increase the risk of the procedure to individual subjects. The investigator should also describe the screening process done before an individual is accepted as a research subject.

6. The investigator should report the number of research subjects on whom the procedure was performed.

7. The investigator should describe all complications associated with the procedure. This statement should include a description of the following:
   a) Type of complication
   b) Presentation of the complication
   c) Recognition and management of the complication
   d) If the complication was reversible, describe the actions which were successful in reversing the complication.
   e) Outcome of the complication. Unless the complication is fatal, the investigator should describe the severity and duration of resultant morbidity.

8. The investigator should report the number of cases of each type of complication occurring and the number of fatal outcomes.

9. The investigator should provide a statement which describes those steps which he believes might prevent further occurrences of any complications associated with the procedure.
REFERENCES


Compensating for Research Injuries: Appendix E


71 Department of Anaesthesiology, First Teaching Hospital, Beijing Medical College. 1980. Major complications in continuous epidural anesthesia, CHINESE MED. J. 93:194-200.


Risk of Injury

81 Dornette, W. H. L., and Orth, O. S. 1958. Death in the operating room. ANESTH. ANALG. (Clev.) 33:545-569.
Compensating for Research Injuries: Appendix E


Risk of Injury


Compensating for Research Injuries: Appendix E


coronary artery disease and left ventricular dysfunction, Am. J. CARDIOL. 48:717-723.
Risk of Injury


309 Welch, C. C., Proudfoot, W. L., and Sheldon, W. C., 1975. Coronary arteriographic findings in 1,000 women under age 50, **Am. J. Cardiol.** 35:211.


Perspectives on Compensating Accident Victims

John G. Fleming, D. Phil, D.C.L.*
Stephen D. Sugarman, J.D.†

Introduction
In the United States accident victims are currently compensated for their losses in quite diverse ways. Broadly speaking four main sources of compensation are available: the torts system, private first-party insurance and other private sources (e.g., sick leave), general public income maintenance programs and tailored public accident compensation plans (e.g., auto no fault and workers’ compensation).

Some victims draw from multiple sources, others from none. All of the sources have objectives in addition to compensating accident victims. For example, tort law also purports to deter socially undesirable behavior; private health insurance is also concerned with the allocation of health care resources; workers’ compensation is also concerned with rehabilitation.

As a result, if one focuses on the compensation objective alone our patchwork of sources is not readily defensible. Why are some innocent victims treated differently from others? Why does victim culpability sometimes count and sometimes not? Why do some victims pay for their accident loss protection while others don’t?

Some would defend the patchwork in terms of the other objectives served by the various compensation sources. Some would argue that our complex system is better viewed as in transition, not fairly judged at any one instant but rather over time as it inches toward an integrated coherent scheme. Some would defend the current inequalities in terms of careful judgments about whether the victim deserves each source. Others, of course, find the patchwork either merely bewildering or else positively unjust.

These tensions within the current American solution cannot be ignored by those concerned about how victims of any particular class of accidents should be treated. In short, since it is important to have a context in which to place the Commission's

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December 1980

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attention to victims of human experimentation, there is no avoiding the examination of the complex ways American accident victims generally are treated. The aim of this essay is to provide an overview and critique of our present system. We discuss in turn: tort liability for negligence (including defenses such as assumption of risk), strict liability in tort, tailored compensation plans and general compensation schemes. Our goal is not to tell the Commission members how to solve their accident compensation problem; but rather to help them to think about it.

Negligence.

Prior to the modern industrial age the social problem of allocating losses caused by accident was not considered serious, and the jurisprudence of what we now call tort law was correspondingly underdeveloped. The machine age dramatically escalated the toll of human injury on the roads, rails and workplace. At the same time, legal scholars and judges began to turn their minds to an appropriate philosophy of tort law. As a result, by the middle of the Victorian era the fault principle became firmly established as the fundamental basis of legal responsibility for accidents.

The Fault Principle

In the 1880’s Oliver Wendell Holmes gave an important series of lectures in the course of which he developed a theory of torts that offered both an interpretation of and a justification for fault-based liability for unintentional harms. Holmes first considered and rejected a contrasting theory—liability for any harm caused by voluntary conduct. His strongest criticism was that it would be unfair to hold a person liable for a harm he could not have anticipated. In short, moral values demanded liability based on fault. Recognizing that this would leave some innocent victims uncompensated, Holmes asserted that private or state accident insurance would far better serve that function. The expensive machinery of private litigation should be reserved, he argued, for cases in which more than mere misfortune has occurred.

Does this mean that personal (subjective) blameworthiness should be a precondition of tort liability? Holmes rejected that theory as well. Rather, liability for tort should rest upon objectively unreasonable conduct. Put simply, in unintentional injury cases, fault means negligence and negligence is to be defined in this objective manner.

Holmes gave two rather different justifications for the appropriateness of an objective test of negligence. First, ease of administration demanded that negligence law not be saddled with having to evaluate and take into account claims of awkwardness, foolishness, immaturity, inexperience and the like that might cause one to hurt another despite one’s very best efforts. Second,
Compensating Accident Victims

society (the community) fairly demands of its members that they control their conduct so as not to behave in an unreasonably dangerous manner—or else pay for the harm done.

Tort law in action captured the idea of objectively unreasonable conduct in the symbolic "reasonable man." The judicial process would find the defendant (or defendant's employer) negligent if the defendant failed to act as a reasonable person would have acted under the circumstances.

Plainly this formulation took care of the main category of injurers whom Holmes wanted to protect from liability: if an accident was not foreseeable, no reasonable person could be expected to avoid it. But if not obvious at the outset, it soon became clear that by limiting liability to negligence, defendants might also be relieved of paying for some injuries they knowingly cause. Railroad crossing accidents provide a good example. Although railroad officials knew well that their trains were injuring and killing people at crossings in large numbers, his alone did not suffice to impose liability. Rather the plaintiff had to show what specific action the defendant reasonably should have taken that would have avoided the harm. Railroads could, of course, build bridges over or tunnels under every road crossing; but the expense would obviously be so great that it was reasonable not to take such drastic prevention efforts—at least for every little rural crossing. Victims might have challenged railroading itself as unreasonably dangerous (a German statute imposed strict liability on railroads as early as 1838), but this would have failed as did similar attempts regarding automobiles.

In short, the judicial process was soon embroiled in deciding just how many safety precautions were necessary to escape liability. Put differently, the heart of the negligence system involves an evaluation of the utility of the conduct engaged in and of the accident prevention efforts proposed.

Later on Judge Learned Hand captured the meaning of fault in a formula now famous among torts students: Negligence is measured by whether the probability of a loss occurring (P) times the likely amount of the loss if one occurs (L) outweighs the burden of preventing the loss (B). Is PL greater than B? In more modern language, this formula suggests that "unreasonableness" is determined by applying a cost-benefit analysis.

As juries are typically the deciders of whether conduct is negligent or not, tort law has largely turned over to the jury the task of applying the community standard of what due care demands. Since juries do not have to account for their decisions, some observers of tort law in practice have argued that juries often reject the reasonableness paradigm and, out of sympathy for the injured plaintiff and indifference to the presumably insured defendant, adopt strict liability in fact.

How then would victims of human experimentation broadly fare under this outline of negligence law? On the one hand,
individuals harmed through careless practices and those who receive inadequate warnings of the risks they face (and would have otherwise refused to participate) will be entitled to compensation for their injuries from the wrongdoing researcher. On the other hand, those adequately warned and those who receive careful treatment but who nonetheless suffer the misfortune of either recognized or totally unexpected side effects are supposed to bear their own losses.

Social Objectives of the Negligence System

During the years that negligence has dominated tort laws, scholars have elaborated upon the social objectives that the fault principle is supposed to serve. Just as Holmes' views drew on a philosophical perspective of the time concerned with individual action and responsibility, more recent writers have turned to psychology and economics. As a result, defenders of negligence now employ a variety of justifications in support of fault liability.

In capsule form, liability based upon fault is now variously claimed to serve the following functions:

1. Deterring socially undesirable conduct
2. Punishing wrongdoers
3. Satisfying the victim's desire for vengeance while at the same time preventing violent self-help
4. Allocating resources efficiently, by attributing social costs to the activities that "cause" them
5. Compensating deserving victims
6. Spreading widely the costs of accidents.

As applied to human experimentation victims, a negligence supporter might put it this way: this loss spreading regime will deter careless conduct by researchers, punish those who are not deterred if their carelessness causes harm, mollify the outrage felt by those human subjects who have been wronged, attribute to research those accident costs that should be avoided, and make whole those wronged victims who deserve compensation.

Of course, not everyone accepts all of the social goals that negligence is said to further; nor do people agree upon their relative importance. More important, however, many have charged that negligence law in action simply fails to advance these goals or that the administrative costs of running the fault system outweigh the social benefits achieved. Let us turn then to a critique of negligence.

Deterrence and Punishment. Emphasis on punishment rests primarily on a moral basis, while emphasis on deterrence looks more to efficiency. The first seeks to inflict pain in retribution for the wrong done to the victim; and since it is the victim, not the state, who calls for the punishment in torts cases, punishment and vengeance are closely related. In contrast, deter-
Compensating Accident Victims

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rence principally aims at the reduction of accidents by imposing a toll on unsafe conduct. Since unreasonable injury to person or property causes a reduction in society's wealth, any deterrent therefore serves the purpose of economic efficiency.

Although the twin purposes of punishment and deterrence have furnished the classical rationale of tort liability, their credibility has increasingly declined under the changing conditions of modern society. Perhaps the principal cause is that the admonitory effect of an adverse judgment is today largely diffused by liability insurance which protects the injurer from having to pay the accident cost and instead distributes it among a large pool of premium payers and thereby "socializes" the loss. Liability insurance is considered against public policy only in cases of intentional injury or other forms of truly heinous misconduct, for which punitive damages may also be awarded. In many countries the victim no longer even in form addresses his claim to the injurer but proceeds directly against the latter's insurance carrier or compensation fund, thereby even eliminating the symbolic tokens of individual blame.

Other realities of tort litigation may undermine the vengeance objective. Hence, although the victim's psychic satisfaction in making his adversary "pay" is claimed by some legal psychologists as a significant rationale of tort liability, the delays and aggravations of American tort law in action probably impose psychological hardship and anxiety on victims that more than make up for what little satisfaction some victims receive.

Nonetheless, some admonitory effect of a tort award is still retained. Insurance premiums are commonly adjusted in the light of the insured's accident record, and fear of substantial rises and possibly even policy cancellation arguably has some effect on individual conduct. The broad American consensus in favor of basing premiums for both liability and workmen's compensation insurance on the enterprise's accident record rests largely on this belief. Other countries, including Great Britain, however, are skeptical about the effectiveness and worthwhileness of such finesse.

The admonitory effect of liability probably varies with different classes of potential defendants. Some are particularly sensitive to the stigma of an adverse judgment wholly apart from any financial detriment. The most obvious example is the medical profession whose members dread liability for its adverse reflection on their professional competence or integrity. More immediate and quicker response to an adverse judgment is also likely to be forthcoming when the consure falls on a repetitive process in industry or business rather than on random failures in activities like driving automobiles. This for the reason that the former are susceptible to managerial correction and monitoring, while the latter are in practice merely amenable to such controls. By the same token, large, stable and well managed enterprises
are far more likely to recognize and act on the potential variability in insurance costs they face than are small firms fighting for economic survival; indeed, because of premium setting practices, small enterprises might not even face the opportunity to lower insurance costs through safer conduct.

In any event, one must be skeptical about the effectiveness of tort law in promoting accident prevention as compared with other legal or social mechanisms. The three most important of these are government regulation, criminal sanctions and ordinary economic pressures.

Regulations can play an educative role in prescribing clear procedures designed to avoid accidents. Negligence law by contrast condemns people, after it is too late, for what they have done. That is especially unsatisfactory since successive juries can and do give different answers to the same problem, thereby encouraging investment in litigation rather than safety. Also, while regulatory standards are established by experts, tort law leaves to inexpert juries the bewildering task of resolving disputes between partisan expert witnesses. While tort law has come to take advantage of statutory standards by treating their violation as fault without more (per se), it is unwilling to treat compliance with prescribed standards as conclusively exonerating. Thus even licensing of products after a rigorous official testing procedure, as in the case of drugs by the Food and Drug Administration, is not accepted as necessarily acquitting the manufacturer.

This attitude reflects the other side of the coin: regulation may be ineffective and out of date; and industry might "capture" the regulators with the result that regulatory standards may reflect a wholly inadequate concern for safety. Moreover, many human activities and enterprises altogether lack promulgated standards or regulations. Nor is it imaginable or desirable that a regulatory net would encompass the whole of human conduct. Perhaps, then, tort law does have at least an incremental role to play in promoting safety and punishing those who fail to respond.

Regulation is not the only alternative scheme of behavior control, however. What about criminal law? An important advantage of the criminal sanction is its concern with punishing the offender for engaging in prohibited conduct; it will fall on the culprit regardless of whether he happened to victimize anyone. By contrast misconduct, however reprehensible, remains outside the reach of civil process so long as it does not injure anybody. That is why motorists today fear criminal penalties more than civil sanctions.

Even if there were no public controls and no tort law, potential injurers would face substantial economic pressures favoring safety. Adverse publicity has repeatedly proved itself a potent sanction against accident-prone activities. For example, as already mentioned, physicians are peculiarly sensitive to publicity of adverse judgments in malpractice actions which are apt to cast
a stigma on their competence. Of greater effect yet is the impact of widely-publicized condemnations of particular products on their competitive appeal to the consumer public. In the same vein, drivers' concern for their own safety surely counts for more than the fear of having to pay damages.

Still, tort law may play a key signalling role in stimulating the market to work. An outstanding illustration is the Pinto litigation. Although the publicity must have cost Ford Motor Corp. far more in lost future sales than in the damages awarded in successive actions, the avenue of private (and later criminal) litigation may have done much to focus public attention on the car's dangers. Indeed, plaintiffs' personal injury lawyers often claim that their efforts bring to light dangerous business practices that would otherwise go unchecked. Whether a system of bounties paid to private whistleblowers would be as or more effective is as yet untried.

Internalization of Costs. Lawyer-economists have argued that all costs ought to be debited to the activity that causes them, so that they are reflected in the price of the resulting product or activity. The cost of accidents, in short, is properly a part of the overhead costs of a particular operation. In this way activities with higher accident rates will properly have lesser attraction in the market place and will thus be carried out to a more socially desired extent. By contrast, it is claimed, if activities do not bear their accident costs they are in effect subsidized and will thus be over-produced. This creates both an inefficient allocation of resources and excess accidents to boot.

There are many problems with this line of analysis, however. First, negligence law does not in fact attempt to assign all accident costs to activities that cause them. Rather, it only purports to assign the costs of accidents that reasonably should have been avoided. To some, this is an indictment of negligence. To others it reveals a fundamental ambiguity about the internalization argument. What is a cost of what?

In many situations policy makers have acted as if there were no problem in attributing particular types of accidents to a specific activity. For example, work injuries are, by general consensus, regarded as part of the cost of industrial operations; accordingly workmen's compensation is charged to the cost of the industrial product. Similar claims are made to justify products liability as well as automobile compensation plans. But on closer examination, the problem becomes very thorny indeed. Is an accident caused by failure of an industrial tool to be internalized to the maker or to the user of the tool? Is serum hepatitis a cost of blood, a cost of hospitalization, a cost of the ailment requiring the transfusion or what? If mother mink eat their young upon hearing sonic booms, is this a cost of national defense or mink farming?
Furthermore, given all the market imperfections otherwise existing in the American economy, even if the tort system did achieve acceptable cost-attrition there is no guarantee that this will have moved our economy closer to an efficient level of various accident-producing activities. For example, if a monopolist producer of a product otherwise underproduces a product (as economic theory suggests), then the failure to impose accident costs on that monopolist could be just the right subsidy needed to boost production to the socially desired level.

It must also be admitted that, in the real world, it is frequently impossible to internalize accident costs to the specific offending product or activity. For example, in the case of a dangerous drug, not only would the drug in all likelihood be totally withdrawn from the market after its risks have been discovered but the cost of compensation would in any event probably be spread among all or most other products of the particular manufacturer, with result that the consumers of the safe drugs would in effect be bearing the accident costs of the dangerous drug. In a theoretical free market, this “externalizing” of the cost might be blocked, but often—and prescription drugs is a good example—such a hypothesis is wholly unrealistic.

In another real world sense, internalization may also be bought at too high a price. Instead, it may be administratively far more sensible to “channel” liability exclusively to a defendant selected for his greater ability to absorb the cost. Thus an aircraft manufacturer may be a wiser target than the manufacturer of a defective component part, the manufacturer of radioactive isotopes rather than a negligent transporter of those isotopes.

Compensation of the Deserving. From a compensatory point of view, another serious flaw of the negligence system is that it discriminates between different accident victims not according to their own deserts but according to the culpability of the defendant; a plaintiff’s recovery is dependent on his ability to pin responsibility for his injury on an identifiable agent whose fault he can prove. Put differently, negligence deems as deserving only those who can trace their harm to someone’s wrongdoing. To critics, this causes unfair unequal treatment in several ways: between victims of the same kind of injury, one of whom can but another cannot point to a responsible cause, e.g. of a particular type of cancer; between one who does and one who does not succeed in proving fault in a defendant (a distinction exacerbated by the vagaries of jury trial long after the accident in question and the fine line that often divides minimally acceptable and culpable conduct; between those with especially effective lawyers and those without and between those who are personally attractive victims and those who are not—both of which are thought by critics to influence the jury unduly. Not least of all is the fortuitous exclusion of victims unable to collect from responsible defendants who turn out to be judgment-proof, i.e. lacking liability insurance or other financial resources to pay.
Even among those fortunate enough to obtain some damages, studies show a capricious relation between the total amount of compensation recovered from all sources and the gravity of the injury. While slight injuries tend to be overcompensated (because of medical insurance and other sources of compensation which do not set off each other or tort damages and because of the nuisance value of small claims), the graver the injury the smaller the share of compensation. Among the reasons for this parlous state of affairs are the low liability insurance coverages held by many motorists and the gaps in tort recovery. With some justification, the process has been called a "Forensic Lottery" in which a small minority obtain a pot of gold but the majority go empty-handed or obtain only tokens of solace.

**Calculus of Negligence.** At the level of principle, negligence is criticized on the ground that the reasonableness paradigm unfairly allows some injurers to pursue activities for their benefit and impose losses on others without paying for them. Therefore, if efficiency counselled against, say, increased quality control at the end of an assembly line, to some this would seem to argue for, rather than against, responsibility for consequential accidents as the calculated price for avoiding increased costs. In sum, social fairness rather than economic efficiency should be the criterion of legal liability.

On the other hand, if one accepts the reasonableness paradigm as proper, then a different sort of criticism can be made. To the extent that promoting the socially optimal amount of safety depends upon a careful balance of the risks and benefits in the negligence calculus, many claim that juries are often incapable and frequently unwilling to make the proper tradeoff, especially when confronted with difficult technological issues going to both fault and causation.

**Costs of Administration.** Perhaps the most serious criticism that can be levied against the tort system is its inordinate expense. Two recent studies of different areas of tort liability tell the story. One dealing with automobile accidents concluded that it cost $1.07 in total system expenses to deliver $1.00 in net benefits to victims, claimants' legal expenses being 23% and insurers' claims expenses (attorney's fees, etc.) 25% of total operating expenses. So also the Inter-Agency Task Force on Products Liability estimated 40% for underwriting expense and profit and an additional 20% for loss adjustment expenses, leaving 40¢ of the premium dollar for the victim's compensation. The combined legal expenses for plaintiff and defendant, as well as the underwriting expense and profit, each exceeded the claimant's compensation.

These very high transaction costs of the torts system compare very unfavorably with the costs of compensation plans, especially social security. In New Zealand, which abolished the tort system in 1974, compensation was introduced for all victims...
of personal injury from accident without any additional cost—far more from saving the transaction costs of the tort system than from curtailing compensation for non-pecuniary injury.

The high transaction costs of the tort system are inherent in the system itself. Primary is the adversary relationship between claimant and the compensation source. Liability to compensate is dependent on issues of causation and fault, which require investigation and are frequently contested. The assessment of damages, tailored to each case, invites additional controversy. In sum, the system is geared to individualized processing and does not favor economies of scale.

Moreover, these costs are incurred in the processing of all claims, not only those that are eventually successful. The reluctance of the drug companies and their insurers to participate in the 1976 swine flu program stemmed less from their fear of successful claims than from their concern over the cost of handling claims, spurious as well as meritorious. In the upshot, the government agreed that rather than indemnify the manufacturers (for successful claims) it would handle (defend) all claims directly with a mere right of reimbursement from the manufacturers for negligence.

The high legal costs are themselves reflections of the law's complexity and delay. Claimants do not usually fare well at the hands of insurance adjusters unless they are represented by lawyers who work for a contingent fee and therefore have a personal incentive to secure the highest possible settlement or award. (Whether the contingent fee system otherwise tends to increase the cost of the system is, however, open to debate.) Finally, the substantial cost of underwriting expenses is in the last resort the price exacted by a free insurance market in which competitive coverages, rates and services are offered to the consumer through the agency of independent brokers (in contrast to some other countries where at least the rates of mandatory insurance, like automobile liability, are regulated and agencies excluded).

Another source of cost inefficiency is that tort damages are awarded in lump sums rather than as periodic payments. Juries must therefore guess as to the future duration and extent of injuries and, in the result, either over or undercompensate the victim; periodic benefits (as under social security) last only for the actual duration of the need, determined by hindsight, not foresight.

Defenses to Negligence

This critique of negligence has implicitly assumed that negligent parties can be made to pay for the harms they cause. But this is not the full story. Even negligent insurers are freed from liability (or have reduced liability) in certain circumstances.

When the victim's own carelessness contributed to his injury, the common law rule was to bar his recovery entirely. For
example, if in a railroad crossing accident, the engineer negligently failed to sound the whistle and the victim negligently failed to look out for an oncoming train, and reasonable conduct by either would have avoided the collision, the railroad was completely relieved of liability. Some defended the result by saying, in effect, that courts ought not to help those who ought to have helped themselves. Indeed, some imagined that this rule encouraged caution by would-be victims. Others emphasized the common law's general practice of assigning losses entirely to one party or another and argued that when both were at fault it was not fair to assign all the loss to the injurer; as a result it had to lie with the victim. Still others claimed that the rule's purpose was to subsidize railroads.

By the middle of this century it was commonly claimed that juries in fact often disregarded the judge's instructions on the issue of contributory negligence, and by 1980 a substantial majority of the states, through legislation or judicial decision, had overturned the all-or-nothing rule in favor of sharing the loss between victim and injurer (comparative negligence). Not that this is the only plausible alternative. In Swedish tort law and in American workers' compensation schemes, for example, mere contributory negligence, as distinct from much more heinous fault by the victim, is simply disregarded.

Another common law defense is voluntary assumption of the risk by the plaintiff. It once played a big role in shielding negligent employers from liability to their own employees who became aware of some danger on the job and yet "chose" to continue to work; indeed this defense furnished the central argument for replacing the employer's tort liability with workers' compensation. Because of its odious past, the defense is today viewed with suspicion and distaste. In the stock situations where the plaintiff unreasonably "assumed" the risk, like accepting a ride from a drunk or incompetent driver, the defense is nowadays merged in that of comparative negligence and therefore merely reduces, rather than bars, recovery. But what to do about reasonable assumption of risks?

The variety of situations continuing to impose the entire loss on the victim is perhaps best explained, not on the ground of "assumption of risk," but rather because the defendant was not negligent. Often in these cases the injurer has offered to provide a benefit to the victim which can practically only come with a risk attached; and the well-warned victim has quite reasonably chosen to confront the risk. This applies to advanced skiers who reject the beginner slopes for more difficult runs, to sports fans who sit in the open bleachers exposed to the danger of a hard hit ball, and to patients who elect surgery despite the possibility of adverse side effects. While it is not always easy to sort out the cases, a crucial difference between these examples and that of choosing to ride with a drunk is that in the former, society endorses the parties' arrangement as reasonable, whereas in the
latter it does not. Thus, after the fact we allow the passenger vic-
tim to turn to his host and say that although he conceded took
the physical risk that the driver might negligently crash, he
should not be deemed to have agreed to hold the driver harmless.

The foregoing may help clarify why it is unnecessary to use
the doctrine “assumption of risk” to explain why well warned
research subjects whose misfortune it is to suffer from a carefully
run experiment will fail to recover damages in a suit based on
negligence. This analysis also makes clear that, by their conduct
alone, human subjects do not waive their rights to sue if the
experimenter is negligent.

In some circumstances, however, we can actually sign away
all right to complain of negligence by accepting a service or
benefit that is offered by another only on condition that we ex-
pressly assume the legal risk of loss. Some countries, including
England, nowadays subject such waivers to a test of reason-
ableness. Although courts in the United States have become mor-
ning to uphold these private arrangements, recent decisions
have been less hospitable to defendants, like public hospitals and
public housing landlords, where the public interest and unequal
bargaining power are involved.

Let us assume for the present that American courts would
uphold an agreement not to sue for negligence if properly exe-
cuted by human research subjects. An issue for the Commission
then becomes whether sponsored researchers should be permit-
ted, or even encouraged, to obtain such waivers.

From the viewpoint of consent, although volunteers are pre-
pared to face the physical risk, they may well entertain reserva-
tions about assuming also the legal risk in the sense of waiving all
recourse for negligence. Nor is it, in practice likely to be free
agents—sufficiently free, that is, to eliminate concern over
the fairness of the bargain. Certainly those undergoing ther-
apeutic experiments are apt to view them as their last chance of
regaining their health. As for volunteers of non-therapeutic ex-
periments, their pay, if any, is not reasonably viewable as “dan-
ger money,” like a monetary incentive for steeplejacks or bomb
disposers; rather it is compensation for their time and trouble.

If, on the other hand, research subjects were guaranteed
adequate compensation from non-tort sources in case of misfor-
tune, a waiver of tort liability would have more appeal. It would
be unwise, however, to assume that experimental participants
would all provide for that financial contingency by themselves.
There is an analogy to fire fighters here. If researchers, their
employers or financial sponsors guaranteed victim compensa-
tion, then human subjects might seem like professional firemen
injured in their work who are traditionally barred from suing
those who negligently created the emergency. The rationale here
is that firemen are hired specifically to cope with fire risks and
that a special compensation fund is set up by the public to take
care of their injuries. Without the alternative compensation guarantee, the position of research volunteers is more akin to that of volunteer fire fighters who, far from being disqualified like professionals, are treated with exceptional favor in order to encourage publicly beneficial conduct [e.g., ordinary contributory negligence does not count against them].

Sometimes the policy considerations favoring non-liability of injurers (immunity) are so strong as to justify victim assumption of risk as a matter of law. Immunities are recognized, for example, in order to protect the integrity of governmental policy making. This concern imposes an important qualification on the entitlement of an injured citizen to obtain redress against governmental decisions on a policy, as distinct from an "operational," level. For example, community mental health policy itself cannot be challenged in a tort suit: although the risk to public safety in releasing psychiatric patients is substantial, public officials are supposed to weigh without fear of liability the competing value of the personal freedom of most state inmates who are not dangerous. In the same vein, the high risk of recidivism by parolees may have to be assumed by the public in order not to impede the parole system. While this means that the policy choice to engage in experimentation on human subjects will be insulated from tort suits, it does not follow that individually negligent researchers should be. Therapists who know their patients are about to harm another do, after all, have a legal obligation to warn of the danger.

Liability Without Fault

The Principle of Strict Liability

Many tort scholars have rejected the "reasonableness" paradigm on which negligence rests. Rather, they believe it proper for tort law to adopt a broader basis for liability—usually termed strict liability. Advocates of strict liability differ both as to its true basis and conceivable advantages, but share the common view that—at least under certain circumstances—it is enough that the defendant's conduct is dangerous though not necessarily unreasonably dangerous.

Indeed, the early common law was to all appearances long content to base liability on a mere causal test—"did the defendant injure the plaintiff directly?"—without reference to any additional requirement of blameworthiness. And strict liability for some accidents (e.g., from dangerous animals; has retained a vitality to the present. One distinction that eventually emerged was between activities that were deemed safe enough when conducted with reasonable care and those ultrahazardous or abnormally dangerous activities (dynamite blasting is a good example) which reasonable care could not render safe. Many such activities, linked to advancing technology, are generally beneficial
and therefore should not be enjoined. Thus, tort liability here is designed neither to condemn nor to deter. Rather, these activities are to be tolerated on condition that they “pay their way” by providing compensation even for “unavoidable” injuries. Included among such enterprises are those that pose either a greater than average risk of accidents or a risk of catastrophic accidents. Examples of the former are conventional utilities (gas, electricity, water); an example of the latter would be a nuclear power plant. This rule was firmly established in tort law at the very same time that Victorian age scholars were intoxicated with the potential of the fault principle to provide an overarching explanation of the law of accidental injury.

Judicial opinions seem to justify strict liability in such circumstances primarily on the ground that subjecting the public to an extraordinary risk for one’s own benefit should entail a corresponding obligation to compensate those at whose cost in life and limb the enterprise was conducted. On this rationale, just why there is strict liability for dynamiters and not, say, railroads is not very clear. What is an “extraordinary” risk, and why should that matter anyway? For example, in many other countries auto transport is an activity to which strict liability has been attached since its infancy; and so it has to aviation.

In the last twenty years the dichotomy between fault and strict liability has increased in importance as manufacturers of defective products have joined those who carry out abnormally dangerous activities as candidates of strict liability. Simply put, makers of products that go awry in the manufacturing process are liable for the harms the products cause, no matter how careful the manufacturing process (e.g., training of employees, inspections, machine maintenance).

However, since that liability is imposed on manufacturers and distributors of all manner of defective products, not only those posing extraordinary danger like, say, explosives or poison, the rationale is obviously different from that for extrahazardous activities. Plainly, the key is the general concern for consumer protection which gained remarkable impetus in the later 1930’s and 1960’s. The consumer and user of modern merchandise has fallen under increasing handicap with advancing technology as regards his ability to assess risks, detect flaws or prove specific negligence in the process of production or design. On the other hand, manufacturers are not only strategically placed to assure safety through quality control but exercise a dominant role in promoting consumer confidence through advertising and other forms of public relations. The onesidedness of the relationship alone is widely regarded as justification enough for strict liability.

Yet whatever its justification, the greatest challenge today is to provide a rationale that will contain the rule. If car makers are strictly liable, why not car drivers? If table saw manufacturers, why not their repairers? Yet, despite a few spillovers at the blurry
edges between, say, products and services (which is a blood transfusion?), the fault principle has so far fended off the challenge. In sum, in 1980 tort liability itself is an uneasy mixture of liability for objectively defined fault and liability without fault.

The way the tort system treats human experimentation victims nicely illustrates this point. We earlier explained the intended application of negligence to such accidents: and the fault principle would indeed apply to experimental medical procedures—e.g., new types of surgery, surgery rather than radiation, etc. If, however, the experiment involves new drugs, then the rules of strict liability take over. Later we will comment on the uncertainty with which the law is now treating new drugs with unexpected side effects. For now it is enough to say that it would make a great deal of difference for tort purposes if the human subject dies from a batch of a drug that happens to be contaminated as opposed to dying from being unable to tolerate some new surgical procedure.

Some respond to this inconsistency by proposing that tort law generally shift to strict liability. This has been justified not only with principled claims about justice, but also on the ground that strict liability has these instrumentalist advantages over negligence. First, its net of compensation is cast more broadly: more victims are compensated and their losses widely distributed. Second, strict liability, far from condoning indifference to risks (arguingo, because it does not offer a reward for observing care) in reality provides a stronger incentive to invest in desirable safety measures in order to avoid accidents than to invest in settlement and adversarial strategies afterwards. Third, strict liability is seen as better promoting cost internalization by including as a charge against activities the costs of those injuries that are both reasonably and unreasonably caused. Finally, strict liability is supposed to streamline the litigation process.

Yet our experience with strict liability in the products and extrahazardous activities field has also generated criticism and doubt about its vaunted advantages.

Strict Liability Criticized

With regard to promoting safety, it has been argued once more that in reality managerial decisions relating to safety are more likely to be influenced by criminal and competitive pressures, by the effect of accidents on workers’ morale, and by dislocation and public relations concerns than by calculations about compensation costs.

Nor has the switch from negligence to strict liability resulted in a reduction of transaction costs or an otherwise demonstrably more efficient allocation of resources. Under strict liability the price of a product in effect includes an insurance policy to cover any injury to the purchaser and other users resulting from a product defect. But as already pointed out, the cost of this form
of compulsory insurance is exceedingly high, with less than half the premium dollar reaching the victim. One major reason for this is that compensation is payable only on proof that the product was defective, an issue that becomes controvertible: the more one moves from manufacturing to design defects or requirements of warning. Those who initially commended the move from negligence to strict liability because it would substantially reduce litigation were to be sadly disappointed; for precisely the opposite occurred as the result of the growing claims-consciousness of the public, stirred by sensational media publicity, combined with a corresponding resistance to claims by defendants concerned alike over costs and adverse publicity.

Again disappointing many of its early advocates, strict liability developed into a "sorcerer's apprentice" as it came to be extended to design defects. Manufacturing or production defects (like failures of the assembly line) pose a problem merely of quality control: they are therefore mostly avoidable (though sometimes perhaps only at excessive cost in terms of efficient resource allocation) and raise no serious difficulty in deciding whether a product is "defective" since it actually deviates from the manufacturer's own standard. Design defects, on the other hand, lie in a different dimension. For here we typically lack any easily available standard of minimum safety by which to measure the accused product, and in any event conscious design choices are often made on the basis of relative cost so as to accommodate consumer preferences or even the public interest (e.g., light automobiles offer less collision protection but are cheaper and save gas). To commit such issues to the litigation process probably overtaxes the capacity of judge and jury. While most courts have more or less reintroduced the negligence standard for judging design defects, others are striking out more boldly in favor of victims; indeed current litigation involving drugs like DES may even make manufacturers answerable for so-called "development risks" that were unknowable at the time of marketing.*

Views are bound to differ on the desirability of expanding tort liability. The affirmative case rests not only on the need to compensate victims but also on the incentive provided for victims to blow the whistle and caution manufacturers against subordinating safety to costs and profits. The negative side makes two arguments. First, the potential burden on industry receives inadequate weight by judicial decision makers. In some industries it turns out that insurance is practically unavailable against design defects, and very costly (especially for smaller producers) even for production defects, contrary to the facile belief by many courts that risks can be pooled and the cost easily absorbed.

*One of the authors of this paper, John G. Fleming, is of counsel to Eli Lilly in the DES litigation.
Besides, the enormity of the risk when one can be held for initially unknowable side effects of drugs is apt to discourage the marketing of new products, especially by the pharmaceutical industry, with the resulting possibility of more long-range detrimental effects on the potential consumer than on the industry itself.

Secondly, opponents of expanded liability argue that the excesses of products-liability zealots limit the individual's legitimate and desirable consumer choice. Risk takers might prefer to take their chance with lower quality products obtainable for a lesser price or make their own arrangements against contingent injury. Under the torts system, as already pointed out, victims are often over-protected (e.g., by virtue of the collateral source rule): why, one might ask, should I have to pay for the cost of strict liability when I am already entitled to Medicare and social security? Or why should I be charged for the extra cost of absolute liability for accidents on international flights under the Warsaw Convention when I already carry accident insurance of my own? On domestic flights, by contrast, the traveller still enjoys an open choice between buying flight insurance and assuming the risk of a non-negligent accident. Such freedom of choice, however, may exact too high a price. Flight insurance purchased over the counter is exceedingly expensive because of the high marketing costs compared with group insurance procurable by the airline. More important, the consumer rarely has access to information for assessing the true cost (including the risks) between competing alternatives. Given these sorts of disputes, it is not easy to predict for the next decade what direction product liability doctrine will take.

Tailored Compensation Plans
Whereas advocates of strict liability have sought to secure greater protection for accident victims by expanding the individual responsibility of defendants within the tort system, other negligence critics have turned to the alternative paradigm of "compensation plans." Workers' compensation was the first such major inroad into tort liability—and remains so today. For workers injured on the job misfortune rather than individual responsibility became the organizing principle for finance recovery, by the state in effect taking up Holmes' challenge of creating a state insurance scheme. Thus for nearly seventy years now in the United States and longer elsewhere, tort law has not only been two-tracked (negligence and strict liability) but has had to share the field with an important external competitor.

Tailored compensations can be rather broad—covering, say, all work injuries—or rather narrow—covering, say, only sonic

*In the 1970's auto no-fault promised (or it: wept) to become the second but now its progress seems stalled.
boom injuries. Their common characteristic, however, is a focus on a subset of accidents generally. Moreover, nearly always tailored plans envision the costs of compensation being paid by those carrying out the activity in question (plans for victims of violent crimes, for obvious reasons, are an exception).

Advantages of Compensation Plans

For some plan advocates, compensation schemes are little more than a legislatively enacted analogue to strict liability in tort. And the same justifications for such plans are advanced as in support of strict liability—a wide net of compensation, internalization of costs, safety promotion and the like. Indeed, some like England's Pearson Commission seem unclear, if not indifferent, to the choice between strict liability and a compensation plan.

Yet for most plan advocates there are important differences that do matter. Perhaps most significant, plans covering personal injury contain or contemplate compensation awards that are markedly lower than American tort law is now willing to provide; not only is pain and suffering usually ignored, but there are also typically limits on earnings replacement. Moreover, many plans only supplement, rather than duplicate, collateral sources available to the victims. To some critics each of these limits represents a breach in the initial "internalization" justification for a tailored plan. In the face of this criticism some defenders of compensation schemes have converted the internalization argument from an efficiency one into a moral one; financing arrangements are defended on the basis that the "injurer should pay." Yet for compensation plans just as in the tort system, the "what ought to be a cost of what" issue is frequently perplexing. For example, is a traffic accident by an employee on the way to work or during working hours properly attributable to the cost of motoring or of the employer's business? Is a pedestrian's injury in a collision with a non-negligent motorist a cost of walking or of driving? Notwithstanding provocative challenges such as these, tailored plan promoters usually have little patience for them; in the auto no-fault debate this issue is simply resolved by the practical expediency of charging motorists and the difficulty of attributing pedestrian injuries.

This practical bent pervades the approach of compensation planners. Benefits are usually to be paid periodically rather than in a lump sum as in tort. The need for costly lawyers is to be done away with whenever possible. (This aim does not always succeed as the experience with workers' compensation has shown.) If

*The Pearson Commission recommended strict liability for human research experimenters (Report 1 §§ 1340-41) and for vaccine damage (ch. 25) but a compensation plan for auto victims—without explaining the reason for these choices.*
private settlements are not reached, the claimant is often directed
to take his case to a specialized (and, it is hoped, cheaper) admin-
istrative body rather than to court.

The firm rejection of individual responsibility as a relevant
principle is illustrated in at least two important ways. First, victim
fault (short of intentional self-injury) is usually of no con-
sequence in compensation plans, whereas courts are now coming
around to the view that in torts cases plaintiff's negligence calls
for reduced recovery in strict liability as in negligence. Second,
strict liability, as we have seen, is often justified on the ground
that the injurer is morally responsible for the victim's loss; by
contrast, when it is convenient, compensation schemes such as
auto no-fault are quite content to impose the loss on the compul-
sory insured victim. In short, the choice between first-party and
third-party insurance is seen largely as a matter of expediency.

We next wish to explore from a slightly different angle our
general submission that compensation plans are typically
justified by one or more complaints about why the tort law pecu-
liarily fails to handle well the class of accidents in question. We
do this at the risk of repeating some of our negligence critique in
order to show that the problem of victims of human experiments
is in important ways different from many of the problems that
have led to proposed compensation schemes.

The literature is rich with the writings of law reformers who
studied a particular type of accident and became convinced that
a compensation scheme was needed because of the shortcomings
of tort law. Auto accidents, nuclear accidents, adverse con-
sequences of drugs, injuries from toxic chemicals or violent
crimes, sonic booms, railway and street care accidents, injuries
incurred during medical treatment, and workplace accidents are
examples.

However, the complaints about tort law vary from one plan
to another. One claim is that the tort treatment is peculiarly
unjust. For example, workers' compensation arose in response to
the harsh application of assumption of risk and other defenses.

A second claim is that the tort system's way of dealing with
the problem is not only administratively too costly but also beset
with fraud. Such has been emphasized in the debate over auto
no-fault.

A third claim is that the tort system requires unusually
difficult determinations of causation (as in toxic chemical and
nuclear accidents) or of negligence (sometimes alleged for both
auto and drug accidents).

A fourth and related claim is that tort law in action takes on
a lottery aspect as exactly situated victims are treated unequally
by juries—a claim often made about auto and medical accident
victims.
A fifth justification rests on the claim that the compensation plan will better deter socially undesirable conduct and a sixth related claim is that the compensation plan will better promote the efficient allocation of resources. With the rise in popularity of law-and-economics, these justifications are heard with increasing frequency.

A seventh argument focuses on the insolvent wrongdoer, for example, in plans for victims of violent crimes. An eighth justification is the desirability of compensation itself. Sometimes it is linked with the claim that tort damages over-compensate—e.g., in auto nuisance claims and, for some, in all awards for pain and suffering. Usually, however, the driving concern is the failure of tort law to compensate victims adequately—in particular, its failure to compensate some victims at all. This justification—but only this one—is nearly universally invoked by compensation supporters.

In considering the desirability of a compensation scheme for a new area, it may advance analysis to consider which of these justifications is applicable. In the problem area under consideration by the Commission, for example, it seems that only the last is apt. Tort law does not treat victims of human experimentation abnormally harshly. To the contrary, the main feature of such accidents, it appears, is that they almost always occur through no one's fault, with the result there are at present virtually no lawsuits filed. Because of this, tort law is not now wasting transaction costs on this problem nor treating victims in this class unequally, nor imposing liability on judgment-proof defendants, nor struggling with imponderable cause or fault issues. On the contrary, the introduction of a compensation plan for such victims would create difficult cause and other boundary problems such as have plagued proposed medical accident compensation schemes.

Nor finally does there appear to be any real consensus that a compensation plan would either promote safer conduct by researchers in carrying out the experiments or engineer a more desirable allocation of resources. The argument has been made that researchers are the best "cost avoiders" and therefore in order to create desirable economic incentives they, rather than the government, should support a compensation plan for victims.* Because of the way research is funded and the way research institutions are likely to distribute compensation costs, we are doubtful whether this targeting will work as intended. Moreover, we think there is much to be said for the view that regulatory review, peer pressure, moral and professional feelings, and even perhaps the tort law, together already achieve an appropriate level of caution in carrying out human experiments.

*Havighurst, following Calabresi's theories, so recommended to the HEW task force in 1977. It may be that the Pearson Commission's choice of the same solution was similarly motivated.
Compensating Accident Victims

In sum, of the justifications here canvassed, the case for human experimentation victims rests primarily on compensation per se. In this respect accidents occurring in the course of human experimentation are perhaps analogous to home accidents or routine recreational accidents in that at present most such victims simply have little prospect of tort recovery. A compensation plan for such harms would largely be just that—an assured source of compensation. This alone, of course, does not make it a bad idea; and a scheme that would, say, provide medical and income protection along with ski lift tickets, campground permits and the like is readily imaginable. On the other hand, it is not irrelevant that many who have considered these sorts of injuries have concluded that if a compensation plan is to cover them at all, it should be a broad accident scheme such as that now in place in New Zealand and to be discussed below in our section on general compensation plans.

Horizontal Equity

In America tailored compensation plans have been adopted or seriously considered for only some classes of accidents. One hypothesis, explored above, is that special shortcomings of tort law are a precondition of reform. A different hypothesis is that tailored compensation plans are prompted by a sense that the victims in question are peculiarly deserving of compensation. Inasmuch as desert is a highly elusive concept, it is tempting to test it by analogy to victims who already benefit from tailored plans.

The problem the Commission is considering nicely illustrates the point. Aren't accidental victims of human experimentation doing a job for the government? If so, aren't they entitled to compensation provided for other workers who are injured on the job? Alternatively, aren't they patriots volunteering their bodies for the public good? If so, shouldn't we provide them with benefits like those awarded to injured members of the armed services? These arguments evidently appealed to the Pearson Commission in England (1978).

However, the problem with this horizontal equity approach is that there are also analogies pointing the other way. For exam-
Compensating for Research Injuries: Appendix F

...not all victims of programs carried out under government sponsorship for the benefit of the general public fare so well. As already noted, the Federal Tort Claims Act specifically exempts the government from liability for high level discretionary activities and also from any strict liability that would have applied to private parties. Why then are human experimentation victims any more entitled to compensation than are victims of military jet sonic booms or exploding weapons transported through inhabited areas?

The postures adopted by Congress with respect to the swine flu program and the risk of nuclear accidents are also instructive. In the former, the Congressional objective was to take responsibility for obtaining "informed consent" from those who took the shots and then fending off what were assumed v*uld be baseless lawsuits. In short, assuming the government revealed all the risks it knew and reasonably should have known about, unexpected consequences were to be shouldered by the victims. Thus Congress never meant to embrace full financial responsibility for all unfortunate victims of the vaccine despite the broad public health reasons claimed for the program. But if these victims are not assured compensation why should human experimentation victims be? Surely, at least therapeutic experiment participants are seeking personal benefit in the same way flu shot takers are.

Even stronger, conceivably, is the analogy to potential victims of a large nuclear accident. The Price-Anderson Act not only set a dollar limit on the total liability for an accident, but left the applicable standard of liability (negligence or strict) to the varying perceptions of individual states. If Congress thinks that innocent, involuntary victims of this grand experiment in harnessing the atom need not necessarily be assured compensation in case of a disaster, why should it offer better treatment to volunteers in other experiments?

These various analogies suggest an uncertainty about the impact of the public benefit of an activity. On the one hand we are heir to a cultural predisposition that commonweal activities justify sacrifices (war casualties) and subventions (immunity of governmental activities) by individuals. On the other hand, there is now increasing acceptance of the idea that losses caused by publicly beneficial activities should be borne by the public. This perhaps explains the erosion of governmental immunity and widespread support of no-fault compensation for victims of public immunization programs, not only for the sake of encouraging participation but also because of the incremental health benefit for the rest of the community.*

*The Pearson Report recommended strict liability (ch. 25). Our own case law, and the Swine Flu epid. estra... toward the same conclusion.
Public conduct analogies are not the only relevant ones, however. In the ordinary context of medical treatment, doctors who properly warn patients of potential side effects are not responsible for those effects assuming the treatment was not negligently administered. In case of untoward consequences, such victims and their families must rely upon whatever private health insurance and income protection they have previously obtained or else turn to general public sources such as Social Security and Medicare or Supplemental Security Income and Medicaid. Why, it may be asked, are victims of medical experiments either any more deserving or needy?

Victims of drug side effects are, formally at least, in the same boat. Despite the adoption by most courts of strict liability in drug injury cases, victims must still show that the drug was “defective.” And the general rule is that absent a manufacturing failure (e.g., this batch is sub-standard), adverse consequences alone do not demonstrate a defect. Rather, in the usual case we are really thrown back to negligence; did the manufacturer test sufficiently and did he effectively warn of dangers he should have known about? Put simply, those who unluckily suffer the bad consequence of rabies vaccine cannot complain to its maker. The argument by analogy, then, is quite clear. So long as experimental participants know well that they face a clear or potential risk, why is their situation more compelling than that of ordinary drug victims? Indeed, in the unexpected side effect drug cases are not the victims, at least in retrospect, unwilling participants in an experiment since often, it appears, only by mass application to humans do the side effects become detectable?

Analogies, in short, do not readily point the way to any one solution. To the contrary, they suggest a potentially serious problem of injustice. If the current treatment of a given class of victims is altered so that it better conforms to that afforded some other similarly situated victims, the change will at the same time place the altered class out of harmony with yet another class of similar victims.

One way out of this dilemma is to argue that the change proposed is a politically ripe part of an evolving pattern that over the long haul is headed toward consistency. In short, when public and official attention is focused on a specific class of injuries, the opportunity should be grasped for reform even if it is only part of the package eventually desired. This argument apparently assumes that the ultimate objective is a series of tailored compensation schemes (perhaps somehow linked together) that together cover most or all accident victims.* Alternatively, the in-

*For example, in Sweden some measure of horizontal equity was achieved by procuring insurance for human subjects of non-therapeutic research in the same way as for beneficiaries of medical and general
incremental accumulation of tailored plans might be seen as a halfway station on the way to a single comprehensive plan.*

Whether an incremental reform strategy of either sort is politically sensible is not for us to judge. We will say, however, that some have objected to national auto no-fault proposals on the very ground that putting in place this enormous new system and its accompanying bureaucracy would diminish the chance for any truly sweeping reform proposal covering accidents generally.

Politics aside for the moment, we think that a base a series of tailored compensation plans and a general compensation strategy stem from differing philosophies. Moreover, it is important to understand that even general plans could have rather differing scopes. We take up these points in the next section.

**General Compensation Plans**

**Social Security**

Many see the accident compensation problem as essentially concerned with providing people with income and paying for their medical bills. From this broadest of vantage points not only do accident victims present the same social concern as do the disabled generally but also their need is much the same as that felt by the retired, the unemployed and perhaps even the poor. In other words, an adequate and comprehensive social security program might take care of the needs of accident victims incidentally to providing income security and health insurance generally. For this set of critics, therefore, the basic reform strategy in America lies in changing the Social Security Act.

At present the act provides, among other things, for wage-related income payments for retired workers and their dependents, totally disabled workers and their dependents and dependent survivors of deceased workers. Today nearly all American workers with substantial employment histories are covered by “social security”—with the exception of most Federal and many state and local government employees who typically have comparable or even more generous plans of their own. Thus, if a human research subject with a substantial work history is killed or totally disabled as a result of the experiment, he or his family can typically count on a public pension in the same way as if he had died or become disabled from other causes. Indeed,

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*As was the declared strategy of the Pearson Commission in England: see esp. Report I, ch. 11 (1978). But its failure to properly confront the issue of horizontal equity has been sharply criticized.
some critically ill subjects of therapeutic experimentation might well be receiving social security disability [or retirement] benefits even before the experiment. Even if the experimental victim is not covered by "social security" [e.g., a student not yet in the labor force], a fully disabling accident would generate an entitlement to a Federal needs-tested cash payment.

Does this mean that we already have an adequate scheme of public income support benefits? Many think not, and could point to what is implied or unsaid by the preceding paragraph. First, there is a question of adequacy. Social security will replace about 55% of the earnings of a low earner, with the percentage dropping to about 35% of covered wages for someone who was earning as much or more than the maximum of covered wages (about $23,000 in 1980). Workers' compensation by contrast tends to replace about 2/3 of the worker's prior wage—at least, in the more progressive states; and auto no-fault plans tend to replace about 85% of wages, mostly subject however to rather low ceilings. From this it may be argued that social security is rather less generous toward the disabled than are tailored compensation plans aimed specifically at accident victims. There are two counters here, however: one goes to the accuracy of the argument; the other to the fairness of the pattern, assuming the argument is correct. On the facts it must be remembered that, because of payments to dependents, social security often replaces 85% or more of the worker's wages; that social security has a cost-of-living escalator which is better than that provided, if at all, by other compensation plans; that over the long haul many tailored plans actually fail to deliver benefits of anything like 2/3 of indexed past wages; and that social security benefits for dependents of deceased workers are frequently rather better than those offered by tailored plans. In short, as compared with real world alternatives, social security does not seem to us to fare badly on adequacy grounds. Even if it did, and now we turn to the fairness aspect, we are by no means convinced that accident victims ought to be better treated than, say, those disabled by illness or from degenerative or congenital conditions.

More serious is the failure of social security to cover either temporary disability (expected to last less than a year) or partial permanent disability. Even so, in a handful of states, including both California and New York, a state temporary disability scheme provides wage-related income protection for about six months. Moreover, a large fraction of workers is covered by formal or informal sick leave plans which are the private counterparts to the New York and California statutes. Even more important is the failure of social security, in contrast to workers' compensation, to cover partial permanent disabilities. Like the preceding, this again contrasts strongly with other nations—the Netherlands has an especially liberal plan, out Congress' recent tightening up on social security disability benefits offers little prospect of any reform of this sort in the short term future.
In sum, whether or not the existing American social security system adequately provides for the income loss of victims of any particular class of accidents probably depends upon the sorts of injuries that predominantly occur. Turning to the Commission’s problem again: if, for example, victims of human experiments typically suffer either trivial injuries (requiring no lost work) or else fatal injuries, then our social security scheme is probably far more satisfactory than if many such victims miss a few months of work and are left with some partial and permanent harm.

Besides income losses, medical expenses are probably the most serious. Here a comprehensive national health insurance scheme would go a long way toward defusing the need for either tort law or tailored compensation plans—as it has in many countries, including Canada. Yet in the U.S. a national health scheme is hardly imminent. All the same, between private health insurance, Medicare (for the elderly and the totally disabled) and Medicaid (for the poor) most American do have health insurance already. The problem, of course, is that there are some serious gaps (for example, the unemployed often are without coverage) and many private policies are wholly inadequate in amount or duration of benefits. Of course, the targets of the Commission’s investigation might well have special characteristics: for example, if most were already either over 65, or in public hospitals and on Medicaid, or students with college-provided health care, the medical expense gap might not be very serious. Indeed, it may turn out that research institutions by and large already provide free medical care for accidentally injured human subjects.

General Accident Plans

Pessimism about the political prospects for making our existing social security system more complete has caused some reformers to narrow their focus. A first line of retreat would be to limit compensation to the disabled, to the exclusion of the unemployed, retired, etc. but including victims of accident and disease, as recommended in 1974 by the Woodhouse Commission for Australia. More practical, however, is to retreat one more step and focus on accidents alone. Thus in New Zealand, following the celebrated Woodhouse Report (1968), tort liability for personal injury or death by accident has since 1974 been entirely replaced by a compensation scheme, administered by a national agency, which provides periodical benefits for income loss, reimbursement for medical expenses other than those covered by the free hospital scheme, and modest awards in serious cases for pain and suffering. The scheme is funded by contributions from employers (replacing workers’ compensation) and motorists (replacing liability insurance) and while providing 24-hour coverage for the whole population, costs no more than the system it replaced.

The principal attractions of the latter approach include: (1) a sense by its supporters that accident victims (or perhaps the dis-
Tailored and General Accident Compensation Plans Compared

What then are the comparative merits of broad and narrow compensation schemes? General plans like New Zealand's offer the advantage of horizontal equity among accident victims; tailored plans by contrast invite the complaint "why these victims?" General plans promise relatively few what we call "boundary" issues; either you are an accident victim or you are not, and the conceptual and technical difficulties of attaching your injury to a particular accidental cause are avoided. For example, is someone who slips and falls into a parked car covered by an auto injury scheme? Narrow compensation plans require such decisions which general plans avoid. This saves administrative costs as well as frustrations and felt injustice if the network of tailored plans has gaps in coverage. On the other hand, even in general accident plans there sometimes arises the difficult issue of whether a person is suffering from illness or accident. A classic example, from the workers' compensation field, is a worker who suffers a heart attack on the job. Was this an "accident in the course of employment" (e.g., from over-exertion) or the culmination of a continuing disease? As the New Zealand experience confirms, this sort of problem is particularly acute in the area of medical treatment and therefore in the area being considered by the Commission. Is the victim's condition the result of his original illness or the treatment given? Would the victim have been any better off had traditional rather than experimental treatment been tried? To many, both questions would have to be resolved favorably toward the victim before accident compensation would be properly payable. Yet these can be difficult determinations to make. Nor can they be avoided by a tailored plan for human subjects. Not only are these issues still alive, but also on occasion one will probably have to decide further whether the harm is from the experiment as opposed to other injurious causes to which the victim was simultaneously exposed. Only a plan covering all disabilities escapes these conundrums. Yet, of course, new boundary problems then arise; is the victim unable to work because there are no job openings?

Another administrative issue is the efficient size of the plan's bureaucracy. Plans that are too narrow run the risk of having a corps of administration spread over too few benefits. On the other hand, plans that are truly modest just might get away with
very simple management that could plausibly piggyback on another related scheme. The Commission's subject just might have this advantage. General plans, in short, have the potential of both economies and diseconomies of scale.

Both tailored and general compensation plans are presented with the problem of potential double recovery by victims. Because of public and private insurance and other arrangements any new scheme is apt to duplicate existing benefits. There are really three separate issues. The first is whether double recovery is desired; and while we think it fair to assume that the general answer is no, this is probably not meant to apply to all collateral sources. For example few would think that accident compensation benefits on the death of a victim should be reduced by his life insurance. Even if life insurance policies (as well as savings, private pension benefits and the like) are to be disregarded, the same does not necessarily go for, say, social security benefits and even private health insurance benefits. This brings us to the second issue: in principle, which benefits should be primary? That is, in order to avoid double recovery which source ought eventually to bear the loss? We say "eventually" because it is quite imaginable that the victim might be free to collect from either of two sources which, in turn, would settle up later. Alternatively, the victim might collect from both, with one having a right of reimbursement; or finally the plans could be dovetailed so that their payment terms resolved the double recovery issue at the outset. These options lead naturally to the third issue: to what extent, if any, do practical administrative concerns point to a solution at variance from that which might be desirable in principle. We will not seriously address this third issue here; we do, however, wish to return to the second one—which source ought to be primary.

It is here that tailored plan advocates often claim the superiority of their approach. The argument, put simply, is that tailored plans—assuming they are primary—concentrate the cost of accidents on the sources that ought to bear them. This cost internalization is then said to promote social values we have already canvassed: stimulating safety; achieving the optimum amount of the accident-causing activity; serving justice by making those pay who benefit from the activity.

As in our discussion of the tort system, it is not clear that tailored plans actually effectively further these goals. Without replying the same ground too much, we register again our skepticism about the marginal impact of both safety and general allocative efficiency of any compensation plan in a world such as ours where various regulatory regimes, market pressures and market imperfections already exist. Moreover, as to the fairness of cost allocations, we continue to wonder just what is fair about assigning bicyclist injuries to motorists. These puzzles are largely responsible for common law judges falling back on the concept
of defect—a complication we assume plan advocates would hope to avoid.

Another way into this issue is to ask just what is the problem of which this accident is a part. Again illustrating from human subject injuries, is the problem really a problem of human experimentation, or is it rather simply an aspect of the problem of drug injuries or of medical accidents, etc.? But these are not questions that can be resolved in neutral ways. Even if you thought you knew the answers to these questions, it is not clear that private behavior would not defeat the cost assignment strategy of the drafters. For example, a scheme intending to impose accident costs on cars that prove to be especially dangerous may turn out to be borne in part not just by other cars of the same auto makers, but also by their other vehicles and even other products. This all depends on the mechanisms available to them to distribute the costs. If, for example, the compensation scheme involves private insurance, the way risk classifications and prices are set can be crucial. Even if targeted governmental taxes are employed (say on vehicle maximum speed), the true incidence of those taxes then matter.

Moreover, to the extent that tailored plans do promote fairness and efficiency goals after all, the financing mechanisms of general accident compensation plans could be used to further the same objectives. Some plans envision that charges be levied on accident causing activities, and over time the agency in charge presumably could refine its targeting in both sensible and fair ways.* Such a general plan would then begin to look very much like a fully integrated and complete series of separate plans, in genuine contrast to one that simply locked to payroll tax for its financing. The lesson here is that financing arrangements are a vital aspect of this debate.

In the end, it is hard to deny that the political reality of capturing public and governmental attention to a problem counts importantly in determining just what social changes are made. Witness the government’s riot insurance, flood insurance, bank deposit insurance, mortgage insurance, and pension insurance programs. In short policy analysis can carry us only so far.

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*New Zealand’s legislation contemplates adjustments of just this sort, although so far the government has made little use of this power.
My mission is to provide an overview of the vast patchwork by which society provides compensation for personal injury. This great quilt includes much technical doctrine, primarily under the heading of "tort law," but it also features, in quantitatively important dimensions, various legislative compensation schemes.

LEGAL DOCTRINE

My primary focus, in accordance with my assignment, is on tort law. This body of legal doctrine has often been said to embrace "non-contractual civil wrongs." The definition is at once too broad and too narrow. However, I will not expose you to the full range of doctrinal reasons that this is so. Rather, I shall present a practical view of tort law as a social response to the problem of personal injury caused deliberately or by accident. My perspective is, in the main, a general one, although the essay is biased when possible to the selection and discussion of topics that are relevant to the Commission's inquiry.

Culpability Generally

My reference to "intentionally" and "by accident" brings us to a conceptual problem in tort law, which is defining the theory of liability. Tort doctrine is associated with notions of culpability which range from conduct defined as "intentional" to the activities of persons who cause injury even when it cannot be said in terms of a moral principle, or some other objectively determinable standard, that they were in any way "at fault." There is much talk in the cases, some of it rather confusing, about the

*Frederick P. Vose Professor, Northwestern University School of Law, Evanston, Illinois. February 1981

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nature of culpability. In one opinion in a workers’ compensation case, a Michigan chief justice, although noting that the statute absolved employers from “general liability for negligence,” said that it was “a mistake to say that employers were absolved from fault. Liability is the basis of legal remedy, fault is the basis of moral responsibility.” With the generality of “culpability” definitions in mind, we may proceed to a tour of tort theories of liability.

The Spectrum of Liability Theories

The analysis here straightforwardly views tort doctrine along a spectrum which ranges from liability for “intentional” conduct, defined as a term of art, to liability which is “strict” — a set of tort rules under which courts require one party to compensate another despite the fact that the defendant’s conduct was neither intentional nor negligent.

Intentional Tort

The Basic Case: Illustration of Torts

Assault and battery. The first tort I want to talk about is the action for battery. A battery, simply stated, is the infliction by one party on another of an intentional, unprivileged and unconsented contact. An assault is defined simply as an act that is intended to place the plaintiff in apprehension of a battery. I concentrate here on the tort of battery since it is not only one of the most basic tort actions, but specifically a theory that is likely to be fundamental in many cases involving biomedical research. For example, when the physicians in the notorious Hyman case injected the elderly residents of the Jewish Chronic Disease Hospital with live cancer cells, they committed a battery if the contact created by the needle was unconsented and unprivileged.

I should point out, as a matter of technical doctrine, that the definition of “intent” for purposes of the “intentional torts” which include battery is rather a more technical and limited one than the common connotations of the word might suggest. Besides signifying motive or purpose to cause the harmful or offensive physical contact which is a battery, “intent” has been defined to mean that the actor, the defendant, “believes that the consequences are substantially certain to result from it.” Thus, along the spectrum of tort culpability, intention means at least “substantial certainty” as contrasted with “recklessness” or “negligence.” The importance of this definition is evident in a famous case often used for pedagogical purposes, in which the elderly plaintiff alleged that a five-year-old boy had pulled a lawn chair out from under her, causing her to fall and break her hip. Appealing from an adverse judgment based on instructions that required her to show that the defendant had a “purpose, intent, or design to perform a prank or to effect an assault and battery,” the
plaintiff convinced the appellate court that all she need show in such a case would be a "substantial certainty" in order to make out the requisite "intent" for the battery tort.

False imprisonment. The analysis which I have lined out for assault and battery applies also to the tort of "false imprisonment," a theory which requires that the defendant act "intending to confine" the plaintiff "within boundaries fixed by the actor." It is implicit that the confinement must be unconsented and unprivileged. There is currently controversy over the question of whether the plaintiff must be conscious of the confinement, or must suffer actual physical harm. The Second Restatement of Torts states these requirements—consciousness or actual harm—as alternatives. There has been argument recently that the existence of both of these requirements does not serve the cause of justice, and the focus of this argument is partly on cases which have relevance to your present inquiry. One instance given is that of the case in which police imprison a diabetic who is having an insulin reaction, because they think he is drunk. The argument is that the plaintiff, although oblivious that he is confined because he is in shock, should be able to recover even though he is not able to show actual physical harm resulting from the confinement. This view takes into consideration the difficulties that might sometimes be attendant on showing physical harm in such a case, or even the psychological damage that would naturally be associated with the affront to personal dignity in such a confinement. In any event, a clinician who holds an experimental subject against his or her will is vulnerable to the charge of false imprisonment—and it should be noted that this would include not only confinement by physical force, or physical barriers, but by "threats of physical force" and "by other duress."

Invasion of privacy. I should mention one other tort action that may have particular relevance to your task. This is the tort called "invasion of privacy." The name comes from perhaps the most famous piece of legal scholarship in this field, an article written by Louis Brandeis and his law partner in the late nineteenth century called "The Right to Privacy." A judicial decision has characterized the thesis of Brandeis and Warren as one centered on "the right to protect oneself from having one's private affairs known to others and to keep secret or intimate facts about oneself from the prying eyes or ears of others." The doctrinal label has evolved to embrace a variety of claims by parties who believe their privacy has been tortiously invaded. It has come to include the sort of physical intrusions symbolized by wiretapping. Quite separately, it also embraces a concept of personality being appropriated, a notion which has a strong commercial bias. Thus, a "human cannonball" may sue a television station for showing his entire act on a news show. Moreover, actions for "invasion of privacy" have included the publication of materials in a way that intrudes in extremely unreasonable fashion on an
area which people could reasonably expect to hold confidential. In a very few cases, the action has included the publication of true facts about individuals; in others, it has embraced only statements that tend to place true facts in a "false light," akin to the untruth required for defamation. The upshot of this multifaceted "privacy" tort is that one person may be liable to another for acquiring or revealing confidential information in situations in which the actor's conduct can be shown to be intrusive or outrageously violative of prevailing mores.

Consent as a Defense

An important category of tort doctrine from the standpoint of your inquiry, both directly and analogically, involves consent as a defense to intentional tort actions. Naturally, consent may be a subjective state of mind. However, courts may infer consent from objectively manifested action. In a famous old case with medical implications, an immigrant was going through a vaccination line and held up her arm to be vaccinated, an action which the court found manifested her consent despite her subjective desire not to undergo the procedure. There are some other complexities of tort law, with which I shall not burden you, that are tied in with the notion that one consents to the kinds of touching that are associated with everyday life: Illustratively, one case extends this rule to taps on the shoulder to get one's attention. Yet consent does not extend to intimacies to which there is no express manifestation of unwillingness, or concerning which the circumstances are not unambiguous: While a text writer from an earlier generation has said that a man who kisses a non-protesting woman in the moonlight is privileged though she has private mental reservations, there is recent case law which suggests that a woman who goes to a man's apartment in the wee hours does not surrender her right to deny him a kiss.

With specific reference to the medical area, one must keep in mind the basic definition of a battery as being an intended, unprivileged and unconsented contact. Syllogistically, it would appear that any time a physician probes more widely in a patient's body than the patient would have desired, a prima facie case of battery has occurred. Because of the delicacy of the judgment that may be involved, and the pressure of time, the courts have begun to establish principles to guide physicians through this legal minefield. An important rule in this area declares that a surgeon may be guided by the standard of sound surgical procedure in the area of the original incision. Thus, a surgeon who punctures ovarian cysts while performing what was originally billed only as an appendectomy is safe from liability, if he or she acts carefully. On the other hand, it should be noted that the physician who does act carefully but goes beyond the scope of his or her consent may be liable for a battery.

The courts are now developing a special doctrine, familiar at least in terminology to any newspaper reader, as a response to
medical cases in which the patient complains that he or she has not been properly put on notice of the implications of a medical procedure. This is the doctrine of “informed consent.” Which applies to both batteries and negligence actions: I mention it here for the purposes of completeness, and will defer a fuller treatment to my discussions of medical malpractice and human experimentation.

Reckless Conduct

There are several linguistic categories of conduct that courts use as a kind of bridge along the spectrum of liability between “intentional torts,” with their requirement that the defendant be substantially certain that he will cause the harmful contact, and negligence, which requires a showing that the defendant’s conduct was unreasonable. In this bridge category fall definitions like “wanton, willful and reckless conduct,” sometimes simply “recklessness,” and, finally, “gross negligence.” These categories may be functionally important: a claimant who is able to show that the defendant has acted in a “wanton, willful and reckless” way may be able to impose punitive damages on the defendants. On another functional axis, automobile drivers in some jurisdictions may be liable to their “guests” only for “gross negligence.” Under such specific legal circumstances, terminology which might otherwise simply be thought of as epithetical takes on practical consequences.

Negligence

The Concept of Fault and the Standard of Care

The central doctrinal concept of personal injury law as it is practiced is that of negligence. The definition is a deceptively simple one. The Second Restatement says that “[N]egligence is conduct which falls below the standard established by law for the protection of others against unreasonable risk of harm.” One of the most famous judicial articulations of the negligence standard was one offered by a British judge in the nineteenth century. He said:

Whenever one person is by circumstances placed in such a position with regard to another . . . that every one of ordinary sense who did think would at once recognize that if he did not use ordinary care and skill in his own conduct with regard to those circumstances he would cause danger or injury to the person or property of the other, a duty arises to use ordinary care and skill to avoid such danger.

This definition embraces two major concepts of negligence: The duty and the standard of care. The question of duty is a very complicated one and has been the subject of much scholarly argument. For the purposes of this discussion, I need not involve you in some of the metaphysical controversies that spin around
the concept of “duty.” For our present purposes, I wish to empha-
size the use of negligence law as defining a standard of care. The
definitions I have given you are general ones. They become par-
ticularized with the factual situations of the various sorts of activ-
ities in which personal injuries occur. In many cases, where the
injuring episode is one that involves nontechnical matters and is
one to which laymen can easily relate, the court will allow the
jury to determine on the basis of lay testimony, or even circum-
stantial evidence, whether the defendant has measured up to the
standard of care of a reasonable person in those conditions. An
illustrative, homely case involves the question of whether a hotel
staging a banquet in its ballroom should have placed its tables
and chairs further apart, so that a departing guest would not have
stumbled over a chair as she left the festivities. The court held
that the jury could hold the hotel keeper negligent without either
expert testimony or evidence of governmental regulations to
prove the standard of care.

The standard of care also becomes particularized with re-
spect to the activities of landowners on whose premises large
numbers of people come, sometimes engaging in injurious inter-
actions with one another. Thus, a possessor of land who opens it
to public entry for business purposes may be liable if “the place
or character of his business, or his past experience, is such that he
should reasonably anticipate careless or criminal conduct on the
part of third persons.” An area of current controversy involves
the ancient classification of the standard of care of landowners
with reference to distinctions in the status of visitors. Thus, ac-
cording to the traditional common law categories, landowners
owe the highest standard of care to a so-called business invitee;
they owe a lesser standard to a “licensee,” a category that has
been defined to include social guests; finally, they incur the least
obligation to trespassers—in some states defined as no more than
duty to refrain from injuring trespassers in an intentional or
wanton way. At the same time, the common law developed a
rather high level of protection for child trespassers, when the
landowner was on notice of their presence and in situations in
which he knew of the high degree of risk to them.

With such a broad general definition, even as qualified as it
applies to particular activities, the concept of negligence is obvi-
ously an elastic one. The question of what reasonable persons
would do in particular circumstances turns on numerous consid-
erations. One strand of thought in the judicial decision-making
and scholarship of negligence has focused quite intensively on a
utilitarian analysis. The famous “Learned Hand test,” in its most-
cited statement formulated by that judge in a case involving a
barge that broke away from its moorings and hit other vessels,
defines the duty of the defendant to provide against injury as a
function of three variables:

(1) The probability that she will break away; (2) the gravity
of the resulting injury; if she does; and (3) the burden of
adequate precautions. Possibly it serves to bring this notion into relief to state it in algebraic terms: if the probability be called \( P \); the injury, \( L \); and the burden, \( B \); liability depends upon whether \( B \) is less than \( L \) multiplied by \( P \); i.e., whether \( B < PL \).

A broader—and in this writer’s view, more realistic—view of the negligence standard of care would import considerations of justice and equity into the decision of what constitutes the conduct of a reasonable prudent person. In any event, judicial definition of the standard of care is a very practical process, in some cases employing various kinds of safety codes—either statutory standards or regulations promulgated by police or safety agencies. In particular, when a workplace safety statute is used to prove the standard of care, the court may well be adopting a rule that embodies a social, rather than utilitarian, judgment as to what is appropriate conduct.

Proof

Technical causation. The proof of a personal injury action involves some science, a lot of guesswork and a certain amount of intuitive philosophy.

Logically, one may begin with the question of whether the plaintiff has crossed the threshold of physical causation, demonstrating that the defendant contributed to his injury in a significant way. Often an important issue is whether expert testimony is necessary to make the case of physical causation. Generally, the more complex the physical or chemical relationships involved, the more likely that courts will require that the plaintiff present expert evidence on physical causation. A case that indicates the frontier of judicial acceptance of lay testimony is one in which the plaintiffs complained that pollutants emanating from the defendant’s mill had caused physical harm to persons as well as injury to property, for example corrosion on aluminum windows. The court found that there was sufficient evidence for the jury on the question of physical causation in the testimony of six lay witnesses that they could see pollutants coming from the defendant’s stacks and that they observed them travelling through the air and landing on the plaintiff’s property.

This may seem an unobjectionable decision when the pollutants are visible and one of the complainants says that when they float over and drop on his house, his throat burns, his nose bleeds, and his chest becomes congested. The more difficult problems occur when courts find it necessary to make judgments about what is going on at the molecular level, and must rely on probabilities.

The area of workers’ compensation provides an interesting angle on the problem of technical causation, with special reference to carcinogenicity. An instructive case involved the question of whether firefighting had caused lung cancer in a fireman who was a smoker. The court refers favorably to expert testimony on
the claimant's behalf that it was "probable" that the smoke inhaled by the claimant contained carcinogens and that it was "reasonable" that his occupational exposure over a long period would lead to lung cancer. The court notes that a previously held that testimony of "reasonable" or "probable" causal connections was enough, as distinguished from evidence of the "merely possible." It said that it could not "demand that experts be more certain, particularly when industrial causation itself could not be certain, but only "reasonably probable." One may compare with this holding the statement of another court that "the mere coincidence of employment in a plant with a heavy dust environment and claimant's developing illness, the 'speculative conclusion' by claimant's physician that there is possible causation, and the equivocal fact that other employees developed similar symptoms although not similarly diagnosed, are insufficient bases for the Board's conclusion that claimant's illness was causally related to his employment."

From this and similar decisions, one may conclude, in general, that the more difficult issues of technical causation usually will require expert testimony and that an expert's opinion of "probabilities" will generally suffice to uphold a judgment that technical causation exists, whereas a statement of "possibilities" will not. A hazard of this sort of rule is that it tends to force scientists into precast legal molds. One may rationalize, however, that the legal judgments are no more uncertain than the state of scientific knowledge. The question of "technical causation" is itself, at bottom, one of policy. Indicative of the way that such issues spill into the arena of policy are decisions in both negligence and workers' compensation settings which declare that the test for causation is one of whether the defendant's conduct, or the conditions of the employment, were a "substantial factor in producing the injury" or "a causative factor" in a workplace injury. Holding thus, courts have said that jury instructions which referred to "the" cause, rather than "a" cause, or "a substantial factor," were erroneous.

"Res ipsa loquitur" and circumstantial proof generally. Everyone who has ever heard a television show or read a novel involving a trial will be familiar with the notion of "circumstantial evidence." Any time an event occurs for which the injured party cannot produce eyewitness testimony, the trier of the fact must draw conclusions from the circumstances. One court announces a typically worded general standard in a case in which a woman was found face down in a creek, with her survivors alleging that the defendant city had negligently left an opening in a bannister on the spanning bridge. The court says that the evidence must be considered in the light most favorable to the plaintiff, who must be given the benefit of all favorable inferences that "reasonably may be drawn from such evidence," but it also emphasizes that "liability cannot rest upon guesswork."
conjecture or speculation beyond inferences reasonably to be drawn from the evidence. "There are many cases which use language echoing the terminology of "speculation" and "mere conjecture," as another court puts it. In brief summary, one can say that circumstantial questions are usually for the jury if the court finds an analogical basis in precedent which indicates that reasonable persons could have drawn the conclusion urged by the plaintiff.

There is a special form of circumstantial evidence which is a staple of personal injury litigation: The doctrine known as "res ipsa loquitur." There are currently several versions of "res ipsa." We may consider, as a point of departure, the formulation that is adopted by the Second Restatement of Torts. This test allows a jury to infer that a plaintiff's harm was caused by the defendant's negligence when, inter alia, "the event is of a kind which ordinarily does not occur in the absence of negligence," and "other responsible causes, including the conduct of the plaintiff and third persons, are sufficiently eliminated by the evidence." Other elements which courts have blended into the "res ipsa" formula have included the requirements that the offending agency or instrumentality be within the exclusive control of defendant and that the accident must not have been due to any voluntary action or contribution on the plaintiff's part.

Employing the res ipsa doctrine, courts have held that juries could find that negligence has occurred when an airplane falls at sea, despite the defendant airline's offer of evidence concerning its care in the maintenance of the craft and in the training of its crew. Courts have also decided that one who hears a "loud siren noise" through his telephone receiver has not proved, without more evidence, that the telephone company was negligent. And they have divided sharply on the issue of whether the breaking of a grinding wheel is sufficient evidence that it was defective, in a suit by the employee-user of the wheel against its manufacturer.

In the medical malpractice area, the res ipsa formula has been used to justify a decision for an appendectomy patient who awoke from his operation with a continuing pain between the neck and the shoulder, given his testimony that he had been placed on the operating table against two hard objects on top of his shoulders just below his neck. It has been used, in conjunction with other evidence, to support a case against members of a surgical team because an anesthetic wore off prematurely. On the other hand, a court has refused to apply res ipsa in a case where a patient suffered facial paralysis, after an operation which severed a nerve for the purpose of producing numbness on a side of the face where the plaintiff suffered intense pain.

In the medical malpractice area, an important reason for judicial application of the doctrine relates to the superiority of information of the medical defendant. Courts have been con-
cerned with the fact that the defendants have control of the procedure, and some decisions have tended to presume that evidence of the cause of the injury is accessible to the defendants—or at least more accessible to them than it is to the plaintiff. On the other hand, there has been strong argument against use of the doctrine on the grounds that "a showing that such an accident rarely occurs does not justify an inference of negligence without a further showing that when the rare event happens, it is more likely than not caused by negligence." The writer of these words, a distinguished former chief justice of California, has expressed his concern that many medical applications of res ipsa may compel physicians to consider "not simply the best interests of the patient but the procedure that will be most readily justified to a lay jury." The Secretary's Commission on Medical Malpractice concluded that the doctrine performed "a useful purpose in common law," but emphasized that it "should not be applied differently in medical malpractice cases than in other types of court litigation."

I should add that the doctrine of res ipsa sometimes seems to focus on what I have called technical causation and at other times on the question of whether the particular defendant was negligent. In whatever sphere of proof it is used, it must be said that if the doctrine did not exist for the solution of personal injury cases, it, or something like it, probably would have to be invented.

Defenses based on the injured person's conduct: contributory negligence and assumption of risk. With regard to negligence actions, there is one—or perhaps there are two—principal defenses which involve the conduct of the injured person. The simplest way to go about discussing this technically confusing subject is to begin with the concept of "assumption of risk." It is clear that one may articulately assume certain risks. This can happen any time a commercial party agrees to a conspicuous statement in a contract which explicitly places the burdens of certain hazards of commerce on that party. In the context of complicated commercial arrangements, courts implicitly assume that such enunciated allocations of risk have been bargained for by the parties.

The courts are less sympathetic to efforts to impose the risk of personal injury on ordinary people. Illustrative is a series of cases involving the limits imposed by an international convention on damages recoverable for death and personal injury in air crashes. One court, dealing with the textual requirement that a ticket be "delivered" to an airline passenger in order for the rules of the convention to apply, went so far as to equate "delivery" with notice of the provisions of the convention. In other contexts, courts have referred to "public policy" considerations in refusing to allow institutional defendants to exculpate themselves in documents that they present to the consumers with
whom they deal. An example of such a decision is a judicial refusal to allow a public housing authority to disclaim responsibility for injuries to infant tenants caused by negligently maintained premises. This is not to say that documentary assumption of risk will never be enforced against consumers. A poignant example which may stir medically oriented people appears in a case in which a young geneticist, moving from the completion of the Ph.D. to his first teaching job on a medical faculty, shipped by air freight some test tubes of frozen chemicals, mouse blood and enzymes. Despite his claims that the ruined goods were worth $30,000, the court held that the air freight company could enforce its limitation of $30, to which reference was made on the air bill.

A more difficult set of problems appears when there are no documents embodying a determination by the injured party to "assume the risk," but the defendant's case is rather dependent on the victim's conduct. The most general category applicable to this sort of legal situation is that of "contributory negligence," which has been broadly defined as "conduct on the part of the plaintiff which falls below the standard to which he should conform for his own protection." The question of whether a plaintiff has been contributorily negligent, like the question of negligence, will vary with the innumerable fact situations which constitute the grist of personal injury law. It may involve an issue of whether an elderly school teacher took "due care" when she climbed through tightly packed chairs set up at banquet tables to leave a ballroom function. The concept of contributory negligence will also be applied to determine whether a fifteen-year-old boy acted with due regard for his own safety when he was engaged in the "rapidly moving process" of bringing back a calf that broke away during a round-up. In addition, the doctrine will often be invoked in cases involving the conduct of workers in industrial plants.

The industrial setting also raises questions discussed under the heading of "implied assumption of risk." The employee who continues to work with worn-out tools, the worker who opens valves on an oil well, the machine operator who sticks his or her fingers into a punch press—all of these may face the argument that they have "assumed the risk." The notion that a worker has "assumed the risk," although he or she has not explicitly done so in a document, overlaps the concept latinized as volenti non fit injuria. The idea that ties these categories together, at least at a general level, is that the plaintiff has voluntarily confronted a known danger.

Illustrative of the difficulties that arise under this doctrine is a case in which an employee had been working for several months around acid-filled vats which were not covered or railed, and had only narrow walkways between them. Concentrating on work that he was doing, he stumbled and fell into one of these
vats and died from the mixture of hot water and lethal chemicals that it contained. Two Texas courts differed on the question of whether he had taken a known risk by his misstep. An intermediate appellate court took the position that he had not "voluntarily" backed into the vat and had not made an "intelligent choice." The Texas Supreme Court rather summarily dismissed the action, referring to previous case law which barred workers who had "actual knowledge and appreciation" of dangers. At one level of abstraction, this argument was persuasive, for the deceased worker had had sufficient knowledge of the danger that he himself had warned fellow employees to be careful around the vat. The case simply provides an example of the kinds of factual issues that arise in connection with the question of whether one has impliedly assumed a risk.

I am omitting certain technical wrinkles from this discussion, but I think it is fair to bring out one particular issue of some refinement. This is the question of whether there really is a separate doctrine of "implied assumption of risk." Tort scholars have divided rather sharply on this issue. My own view inclines to the idea that there is more intellectual efficiency in deciding practically all "assumption of risk" cases on the question of whether the plaintiff has taken due care for his or her own safety. In this perspective, the question of contributory negligence essentially swallows the question of assumption of risk. The issue is generally not only whether the plaintiff has voluntarily confronted a risk about which he knew or of which he can be charged in law with appreciation; the central question is simply one of whether his confrontation with risk was reasonable or not.

Strict Liability

Two very distinct forms of "strict liability" flesh out the spectrum of tort liability theories. One of these theories relates primarily to dangerous activities conducted on land; the other applies to injuries caused by defective products.

Ultrahazardous Activities

The first modern "strict liability" doctrine originated with a nineteenth century English case in which water escaped from a reservoir constructed by a mill owner and passed down through the workings of a mine owned by the plaintiffs, causing damage. A much quoted opinion of a lower court judge, adopted by the House of Lords, set out this rule: "[T]he person who, for his own purposes, brings on his land and collects and keeps there anything likely to do mischief if it escapes, must keep it in at his peril; and if he does not so do is prima facie answerable for all the damage which is the natural consequence of its escape." In practice, as the doctrine has come into the twentieth century, it has been applied by American courts to activities considered "ultrahazardous"—a definition offered in the First Restatement of Torts—and "abnormally dangerous"—the definition provided by the Second Restatement of Torts. The Second Restatement's
definition of "abnormally dangerous activity" has identified as factors for consideration the high degree of risk of an activity and its great gravity of harm, as well as the questions of whether the risk cannot be eliminated by the exercise of reasonable care and whether the activity is not a matter of common usage or is appropriate to the place where it is carried on. These factors, together with the element of the activity's value to the community, are to guide courts in determining whether such activities as blasting, dam keeping, or the emission of pollutants are grounds for imposing strict liability under this doctrine. Courts have principally used the theory in cases involving activities conducted on the land of the defendant, but at least one decision has imposed this sort of "strict liability" in a case involving the transportation of gasoline in a tank trailer on the public highways.

Products Liability
The other judicial creation of a doctrine of "strict liability" has had a very different history. This theory, articulated invented after the middle of the twentieth century, applies to defective products, at least in cases of personal injury and property damage. Some courts have extended it to cover situations in which the defendant sustained only "economic loss." The doctrine is discussed more fully below in the section on "functional applications" of tort law.

Rationales of Tort Law
There is considerable discussion in the scholarly literature—and, some discussion in the case law, if not nearly so much or in as much depth—about the rationales of tort law.

Recent writing on the subject tends to center on two main lines of reasoning. The first emphasizes judicial decision as a vehicle for optimizing the cost of risky activity, an idea borrowed from microeconomic theory. The model is one of consumers of goods and services in a free market making judgments on what risks they wish to assume at what prices. In this view, the courts become an agency of cost-benefit analysis, with the primary goal one of achieving a level of accident-caused injury which accords with the true desires of consumers.

Another tradition concerning the rationalizing principles of tort law emphasizes considerations of justice and fairness. Some commentary suggests that the key to various forms of tort liability, especially strict liability for abnormally dangerous activity, lies in the non-reciprocal nature of the risk that the defendant has imposed upon the plaintiff.

There are many other rationales which come into play in tort cases, at varying levels of explicitness. They include references to "deterrence" which apparently go beyond the standard of conduct that would simply result in optimizing the cost of accidents. Courts also refer from time to time to considerations of
“risk spreading” and “loss spreading.” Additionally, many products liability cases have emphasized the protection of consumer expectations as a goal which may be vindicated by the rule of strict liability in tort.

The writer is currently engaged in a close analysis of the judicial statements of these rationales. It may suffice for present purposes to say that in my view, tort law is a pluralistic response to a variegated set of social problems, and that the richness of its stated rationales is simply a manifestation of the complexity of the universe to which it responds.

Practicalities of Personal Injury Litigation

Personal injury law is a legal specialty, and the skilled practitioner has developed many intuitions concerning the way to approach litigation, as well as holding firm opinions on the value of tort law as a vehicle for the adjustment of competing interests in society. I wish to make particular reference here to only a couple of practical aspects of the practice of tort law: First I should note that most tort cases are litigated on the basis of a “contingency fee.” Under this sort of arrangement, the plaintiff’s lawyer often spends considerable sums of money in the investigation and trial of a case. He or she gets no payment if the case is lost, but receives a substantial percentage of the recovery—sometimes ranging up to half of it—if the plaintiff is successful.

A second practical point, which has a basis in substantive law, concerns the quantification in tort judgments of many intangibles, in addition to such conventionally documentable items as wage loss and hospital bills. These intangible damage accounts include the controversial element known as “pain and suffering,” as well as judicial sanction of dollar valuations on personal relationships. Thus, personal injury awards may include a dollar figure representing the nurture that a parent gives his or her children, as well as the element of “consortium” in spousal relations, which has been defined as including “sex, society and services.” The world of personal injury law, like most branches of the law, thus deals at many levels with money. A considerable practical literature has grown up on settlement practices in tort cases. Illustratively, it instructs plaintiffs’ attorneys in the use of a device known as “the brochure.” This is a collection of evidence, including pictures, that is designed to communicate to defense lawyers and insurance companies the gravity of plaintiffs’ injuries and the saleability of those injuries to sympathetic jurors.
SOME FUNCTIONAL APPLICATIONS OF TORT LAW

This section examines tort law in a group of functional settings, the first two of which have produced much litigation in the last decade or so, the others involving oncoming societal problems to which tort law is episodically responsive.

Medical Malpractice
Because of its relation with the delivery of health care services, and the rising costs in that area generally, the tort province of medical malpractice has generated considerable concern. That concern grows out of rising insurance premiums, with the attendant allegation that physicians practice "defensive medicine," using tests that are not cost-effective under good medical practice. It stems also, however, from a widespread sense that there are, in fact, numerous occasions on which doctors render medical care in a substandard way.

Culpability Requirements
The law of medical malpractice partakes principally of the tort doctrines of battery and negligence. A patient's complaint that literally hands-on treatment by a physician has resulted in injury may naturally fall under the heading of "battery," if the allegation is included that the patient did not assent to the touching, in light of its consequences. I shall discuss consent in this context immediately below. Another theory with an "intentional tort" cast to it is "fraud." Principally used in commercial contexts, this doctrine is based on the idea that the defendant has misrepresented a material fact to the detriment of the plaintiff, and has made this misrepresentation at least recklessly of whether it was true or false.

The principal doctrinal area of litigation in the malpractice arena is that of negligence. The threshold question in medical negligence cases is whether a defendant's conduct fell below the standard of care of a reasonable prudent practitioner. In some cases where carelessness is palpable, and the court believes that the common knowledge of jurors is sufficient to permit a lay decision that a physician's conduct was substandard, it may only be necessary to present proof of the defendant's conduct through the plaintiff's testimony. Illustrative is a Pennsylvania case, in which an elderly man took a fall and upon examination was found to have severe pain, an outward turning of his leg, and a "crunching" noise in his hip. The court found that the failure of
his doctor to use X-rays presented a prima facie case of negligence, despite the fact that there was no expert testimony on the point.

Often, however, it is necessary for malpractice claimants to use experts to prove the standard of care. The testimony of a single expert as to the relevant standard may be enough to bring a case to the jury. However, the question of whether the standard of care is one defined by specialty or by geographical area remains a live issue. There has been a judicial trend to hold that specialists must practice at the level of specialists across the nation, but there is still some support for the rule that physicians are bound only to the standard of care of their "locality." Obviously each time a decision is made on issues of whether expert testimony should be required in malpractice cases, or of whether the standard of care is defined nationally by specialty or by local practices, the court is at least interstitially influencing the allocation of medical resources.

The Consent Issue

Much of the recent discussion in judicial decisions and scholarly literature on medical malpractice, and the most controversy, has surrounded the doctrine of "informed consent." This verbal label spans both the battery tort and the negligence action, implicating both the definition of the standard of care and notions of "assumption of risk." It is worth reiterating that from a technical point of view, whenever a physician touches a patient in a way to which the patient does not expressly or impliedly consent, in theory one may argue that the physician has committed a battery. This idea is sometimes explicit and otherwise usually implicit in the case law of medical malpractice. However, judicial references to "informed consent" are at least as often focused on doctrines of negligence. The theory often appears to be that the physician has a duty to inform a patient of the possible consequences of a procedure and that the physician falls below the standard of care if he or she does not provide that information in the way that a reasonably prudent doctor would provide it in the circumstances.

The notion of "informed consent" has now acquired a fairly technical meaning. A case decided by the United States Court of Appeals for the District of Columbia has been often cited for its statement of practical premises about the philosophical bases of consent. Quoting a precedent, the court said that "[e]very human being of adult years and sound mind has a right to determine what should be done with his own body." The court then proceeds on the premise that "true consent to what happens to one's self is the informed exercise of a choice, and that entails an opportunity to evaluate knowledgeably the options available and the risks attendant upon each." Tempering this very broad statement, the court says that it is "prohibitive and unrealistic to expect physicians to discuss with their patients every risk of
proposed treatment—no matter how small or remote—and generally unnecessary from the patient's viewpoint as well.” In this context, the court defines the duty to disclose the risks of medical and surgical treatment in terms of what it calls the “patient's right of self-decision.” It says that the question of whether there has been proper disclosure should depend on “the reasonableness of the physician's divulgence in terms of what he knows or should know to be the patient's informational needs.” With this reference to the traditional negligence standard of “knew or should have known,” the court enjoins doctors to disclose “material” risks, quoting a definition of materiality. In terms of whether “a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy.” Mindful of the exigencies of practice, the court declares some exceptions to this standard that are governed by considerations of necessity and medical judgment. An exception which would seem to pose some of the most difficult issues is the case in which disclosure is medically contraindicated—particularly when to disclose a risk would upset the patient so much that it would “foreclose a rational decision.” The court also excludes from the disclosure requirement the case of patients who are “unconscious or otherwise incapable of consenting.” It focuses in this regard on episodes of “genuine emergency,” saying that consent should not be required when “harm from a failure to treat is imminent and outweighs any harm threatened by the proposed treatment.”

This set of standards has been the subject of fierce discussion as to its reality and its practical applicability. Involved in the argument is the question of how much choice any patients, even the most sophisticated, truly have in a world of medical uncertainty. An anesthesiologist has captured the practical problem by describing in several paragraphs what a truly informed consent would require with respect to the risks from various drugs and anesthetics. He then concludes, “I have not told her about the risk of each drug, the danger of air embolism from the needle stick, the possibility of death from vomiting and aspiration, the danger from explosion from the anesthesia that I am using.” He then wryly remarks, “So I have not really informed her, literally I could go on for hours without [explaining] all the possible complications she may have.” Despite such criticisms, however, there is a practical core to the standard of “informed consent,” one that depends on a model of rational persons exercising reasonable choice within the boundaries to choose that are practically available in given situations.

**Causation in Medical Cases**

The problem of physical causation often presents a crucial issue in medical malpractice cases. The uncertainties inherent in
many such situations put a considerable burden on the language used by expert witnesses. The closeness of the linguistic tolerances is evident in a case in which the plaintiff claimed that the defendant doctor was negligent in failing to take the necessary steps to detect and treat peritonitis. The question was whether the failure to render “reasonable medical care” was a “substantial factor” in the patient’s death. The plaintiff’s expert said, “I feel that there is good reason to believe that if this shock had been promptly treated and that she had come out of shock and had been successfully operated upon,” the patient would have lived. On cross examination, asked whether he could say with “any certainty” that the patient would have survived the night, the physician answered, “I feel that she would have, but I cannot state that with any degree of certainty.” The defendant argued that the expressions “there is good reason to believe” and “I feel that she would have” were tantamount to saying that death “might have resulted or possibly” or “probably” would have resulted from defendant’s conduct and that this language was insufficient to sustain a plaintiff’s judgment under state law.

The court found, however, that “[I]t is the use of ‘I believe’ amounts to an assertion of an expert’s professional opinion,” and was adequate for the jury to form an opinion on causation. This appears to stretch judicial patience with expert testimony on probabilities as far as it will go. An illustration of where the line is drawn appears in a decision in which the court confronted testimony by an intelligent and competent appearing physician that “precipitant labor” was “a possible cause” of the rupture of a child’s spinal cord. Deciding that the witness “intended to say just that, and not that he regarded ‘precipitant labor’ as necessnarily being the most likely one among the possibilities in the situation,” the court found that this testimony “could not be viewed as having sufficiently, on context or ingredinci, crossed the line between the possible and probable medical cause.”

I conclude this cameo picture of malpractice doctrine with a portrait of a case which combines two difficult problems, presenting an interesting twist on the problem of causation in conjunction with the issue of informed consent: A federal district court has recently declared that while a physician may breach his duty of informing a patient of an undesired outcome, if a properly informed patient would likely have gone ahead and undergone the procedure, it must be held that the patient “has failed to establish the causal link between the failure to inform and his injury.”

Products Liability
The area of products liability encompasses a wide range of injuries to which all consumers are vulnerable, and involves numerous problems of consumer expectations, comparative risks and benefits, and social policy.
Theories of Liability and Defenses

Courts dealing with products liability cases have recourse to numerous theories of liability. Some of these theories require that the plaintiff allege some sort of explicit representation. There are some theories of culpable misrepresentation, including fraud or deceit—which is an intentional tort—and a doctrine of negligent misrepresentation. There are also some non-fault theories which apply when the defendant has made a misstatement of fact, without intending to make a false statement and without negligence in doing so. Besides the tort theories that cover this kind of situation, there exists a commercial law doctrine, that of "express warranty," which has been defined as "any affirmation of fact or promise made by the seller to the buyer which relates to the goods and becomes part of the basis of the bargain."

In addition to these theories based on explicit representations, there are several other doctrines, drawn from both tort and commercial law, which have been used as grounds for imposing liability on various sellers of products, even in the absence of a breach of "express warranty" or misrepresentation. The bedrock tort doctrine remains that of negligence. However, there are two theories, one drawn from commercial law and one from tort, that do not require findings of fault. The commercial law theories are those of implied warranty—the implied warranty of merchantability and the implied warranty of fitness. Scholars have discerned a tort character in these "warranties," especially the merchantability warranty. Whatever the broad doctrinal category, the notion of the merchantability warranty is that product sellers must be taken to have warranted that their products are of fair average quality; the idea of the fitness warranty is that products conform to particular preferences concerning which the buyer relies on the seller's skill or judgment to select suitable goods. Unsatisfied that these doctrines constituted the last word in solving the product liability problem, American courts, with some help from scholarly commentary, invented a theory called "strict liability in tort" for product injuries. The idea, according to one of the classic formulations of this doctrine, is that one who "sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property" is subject to liability even though he has not fallen below the standard of due care in the preparation and sale of the product. A very important facet of this doctrine of strict products liability is that it applies despite the claimant's inability to show that he had a direct contractual relation with the seller he is suing.

I should note that there exist defenses to actions brought under several of the theories specially associated with products liability which are counterparts of the defenses in negligence actions. Basically, these defenses take the labels of "contributory negligence" and "assumption of risk," with an allied doctrine of product "misuse." There are some courts that hold that conventional contributory negligence is a defense to products liabil-
ity cases. Others require the defendant in such a case to show that the plaintiff engaged in conduct that merits the characterization of “assumption of risk”—a voluntary confrontation with a known danger. One battleground in this area has been the question of whether plaintiffs should be barred from recovery because the danger which they confronted was “patent.” There appears to be a trend of decisions hostile to the idea that the “patency” of a danger should destroy an otherwise meritorious case. In an interesting recent decision involving an industrial machine, the court finds the “patent danger” defense a “harsh” one. It quotes favorably a precedent which declares that “the manufacturer of the obviously defective product ought not to escape because the product was obviously a bad one. The law, we think, ought to discourage misdesign rather than encouraging it in its obvious form.”

The Problem of “Defect”

Perhaps the core problem of products liability today lies in the question of how to define a “defect.” Courts and scholars have engaged in numerous efforts to resolve this problem and their labors have yielded a variety of characterizations. The definition of “defect” which most American courts accept is one which requires that the product be in a condition “unreasonably dangerous to the user.” This definition has often stimulated courts to line up lists of factors or elements which might be associated with the concept of “unreasonably dangerous.” In a design defect case, one thoughtful federal trial judge has set out these factors in a jury charge as including the likelihood that the product as designed would result in injury to a user, the seriousness of potential injury, the ability of the manufacturer to eliminate unsafe characteristics in the product, and the expectations of the ordinary consumer. In another very controversial decision, the California Supreme Court has refused to accept the terminology of “unreasonable dangerousness,” and has defined a design defect in two modes. First, one is to determine whether the product failed to perform as an ordinary consumer might expect, when it was used in an intended or reasonably foreseeable manner. Second, one may find a defect on the basis that the benefits of the challenged design do not outweigh its inherent risk of danger. Of particular controversy in this decision is the California court’s holding that the manufacturer must shoulder the burden of showing that, on balance, the benefits of the design outweigh its risks. A considerable tension exists in this area between the notion that courts should not be in the business of designing products, and the idea that juries are surrogates of the community for the purpose of defining its expectations, and should have a substantial voice in the determination of whether a product is “defective.”
Causation

The problems I have identified in my general discussion of causation in tort law carry over into the products liability area. With particular reference to prescription drugs—a frequent subject of human experimentation—or e may identify what appear to be three different tiers of causation issues. The medical problem of oral contraceptives and thromboembolic disorders provides an instructive legal example. In a case in which a woman claims that the ingestion of "the Pill" caused a blood-clotting disease, the court must determine: (1) Whether oral contraceptives generally cause strokes, (2) whether they caused one in the particular individual, and (3) whether the manufacturer's failure to warn contributed to that causation in the sense that a proper warning would have impelled the physician to withdraw the medication. In one illustrative case, which involved the first two issues, the court accepted the plaintiff's argument that case reports and clinical studies showed conclusively a "causal relationship between Enovid and thromboembolic disorders." However, it reversed a plaintiff's judgment on the grounds that the claimants' decedent may have died as a result of "predisposing causes"—including prior pregnancies, prolonged bedrest and an overweight condition—rather than as a result of taking the Pill.

Cases Involving Human Experimentation

Medical malpractice law and the rise of products liability jurisprudence have in common a feature of experimentation, broadly defined. Our mental associations with the term "experiment" connote a certain scientific elegance. Yet much experimentation in this society is what I have called, in my book A Nation of Guinea Pigs, "market experimentation." By this I mean "the ongoing inquiry into hazardous effects, using members of the general public as subjects, that is a necessary part of the conduct of new activities and the marketing of new products." This insight, I believe, provides an interesting framework for the Committee's deliberations on avowed experimentation. The discussion below deals with cases in which experimentation in the conventional sense is more or less at issue.

The appellate decisions concerning experimental procedures are not numerous. I will refer briefly to three cases which discuss different facets of the problem, all turning on questions of consent. One case, in which the procedure arguably had passed the experimental stage, involved the use of chemotherapy aimed at destroying cancer cells. After noting some rather definite shadings of risk conveyed to the patient by different members of the surgical team, the court rejected the plaintiff's argument that disagreement among members of the team after surgery had
begun should have been disclosed to him or to his wife in order to secure a further consent. The court said that it would not require surgeons to terminate an operation in progress in order to seek an extended consent when "the best interest of the patient may require . . . an on the spot decision."

Another decision involved a procedure which could fairly be called experimental. The defendant was a physician who had devised a spinal operation which employed the detachment of the aorta and the vena cava from the spine and the use of a metal bar and a turnbuckle to straighten the spine of a teenage patient with scoliosis. The only surgeon in the country to perform the operation, the defendant had used it thirty-five times, with results including one death, one case of paralysis and four other cases of serious complications. Faced with a consent form which gave permission to the defendant "to do whatever operation in his judgment may be necessary on my son," the court held that the jury could reasonably find that the surgeon had never explained to the patient's mother "the hazards of the operation, the available alternatives, or the fact that the procedure was not employed by anyone else in this country." This, on the facts, is a fairly standard application of rather conventional tort doctrine.

A most dramatic case, and one involving quintessential experimentation, arose from the difficult situation surrounding the first implantation of a totally mechanical heart in a human being. This litigation included the side drama of a conflict between two prominent physicians involved in research on the frontiers of coronary care. The case involved a rather detailed consent form, which explained the risk of the surgery which would initially be attempted—a resection of the heart. The document then mentioned the possibility that if this surgery appeared to be infeasible, the operating team might use a mechanical heart as a stopgap to finding a transplantable heart from a human donor. The court found that the debilitated patient had bound himself by a legally valid consent, given the backdrop of two conversations between him and the surgeon; it also decided that under state law the consent of the patient's wife was not necessarily required. The plaintiff also claimed that her husband had not been told about the nature of the animal testing which has been done on the device, or about the possibility of permanent injury to his body by its use. However, the court rejected this contention, emphasizing that "each step of the three-stage operation" was set out in the consent form, which among other things had recited that the patient realized that the device had not been used on human beings. The court's view of the case embraced claims based on several different legal doctrines—lack of informed consent, fraud, and a separate issue which it characterized as "experimentation." On the "experimentation" issue, the court emphasized that the patient had expressly consented "to all three stages of the operation actually performed." An interesting sidelight to the case, involving the collateral drama between the
physicians, appeared in the trial court's refusal to admit the testimony of the surgeon Dr. Cooley's great medical rival, Dr. DeBakey, concerning the alleged deaths of experimental animals from renal failure. The court noted that Dr. DeBakey had refused to say that the mechanical heart used in those experiments was "the reasonable medical probable cause of the renal failure," and that he would not give an opinion specifically on the particular pump used on the plaintiff's decedent.

This trio of cases represents several aspects of the application of tort law to human experimentation: The variety of available theories of liability, the application of the doctrine of "informed consent" under dramatic and rending circumstances, and the problem of using expert testimony to prove causation.

Other, Functionally Defined Personal Injury Problems Arising from a Technological Society

I make brief reference here to some problems which, at least in degree and often in kind, would have been unknown one hundred years ago. They are outgrowths of an advancing technology which constantly threaten to leap beyond effective legal control.

The first of these problems is that of pollution—particularly airborne emissions of various kinds from manufacturing plants. The doctrinal basis for the law in this area is well established. It includes the theory of "trespass"—a doctrine that historically came into operation when a person made a physical entry on land, or pushed or hurled an object onto another's property. Liability for trespass is traditionally absolute. Other theories mentioned in this essay which may be applied to pollution cases are those of negligence and of strict liability for "abnormally dangerous activities." There also exists a theory known as "nuisance," under which the traditional key phrase is "invasion of another's interest in the private use and enjoyment of land." The term "nuisance" is a kind of legal chameleon, which at various times has itself included subclassifications of intentional conduct and negligence, as well as "strict liability."

The same battery of theories might well be employed in cases involving radiation emissions from nuclear plants, and the discharge of toxic chemicals into waterways. The difficulties would often be in the proof, particularly when there may be more than one alleged corporate culprit in the discharge of chemicals. Insuperable legal problems are likely to appear in the inability of claimants to pin a particular disease or injury on the release into the environment of one form of energy or of a single combination of chemical elements. This sort of problem is complicated by the fact that diseases typically alleged to result from these sorts of emissions and discharges often fall under the general heading of
cancer, and have long latency periods. In such circumstances, to bring a tort claim frequently will be like trying to catch a will-o'-the-wisp. Not only is the victim often unlikely to pinpoint the source of his or her disease; a statute of limitations may bar the action, unless there are judicial decisions which postpone the operation of the statute until the claimant might reasonably have discovered the onset of the illness.

RELEVANT STATUTORY
BACKGROUND OF TORT LAW

I examine here several statutory schemes which lie in the background of tort law. I select the area of prescription drugs as an example of a regulatory framework which embraces products and processes ranging from the emission of pollutants to problems of occupational health and safety, and including the regulation of food additives, automobiles and flammable fabrics. I then turn to a somewhat more detailed examination of statutory compensation plans, including some existing laws and others that have been proposed to deal with the problem of compensating victims of personal injury.

Regulation: The Statutory Framework of New Drug Regulation

Defining "New Drugs"

The process of drug regulation is an exceedingly complex one. Relevant sections of the Food, Drug and Cosmetic Act, after providing a definition of "drug," define "new drug" in a very technical way to mean drugs that are not generally recognized as safe and effective for use under their prescribed conditions. If a product is a "new drug" under this definition, it must pass through a complex procedure of investigation, during which it may be used only for experimental purposes, and only after animal tests have established that it is reasonable to experiment with the product on human beings. The law requires that the reviewing agency be satisfied that there is evidence of safety and effectiveness before it approves a "new drug application," enabling the product to be generally marketed. The requirement of drug safety has been in the law for several decades, but it was not until the 1962 drug amendments that Congress required manufacturers to present "substantial evidence" of effectiveness—with "substantial evidence" being defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience" to evaluate effectiveness. The FDA has been involved in numerous litigations over its processes for clearing new drugs for the market. It won a major challenge to its "summary judgment" procedure for passing on drug effectiveness, although it
has not always been successful in its specific attempts to apply that procedure to particular products. In a particularly dramatic factual setting, the agency recently turned back a challenge from terminally ill cancer patients who demanded that they be allowed to obtain laetrile. In this case, the Supreme Court went through the statutory drill that I have described, utilizing the technical definition of "new drugs" and holding that the law's requirements of safety and effectiveness are not suspended when the patient is terminally ill.

The Prescription List

The law declaring that certain drugs should be available only by prescription is now a part of our social landscape, although Congress only acted to enact this requirement in 1951. The law says that a drug shall be dispensed only on prescription if it is not safe for use except under the supervision of a practitioner because of its "toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use." Although the provision has been seldom litigated, I include this reference to it because it is part of the practical structure of drug regulation which confronts all consumers. I mention it particularly because of its implication for personal choice, and the social compromise it implicitly represents. It is clear from the legislative history that Congress did not intend aspirin, for example, to be a prescription drug. Yet were aspirin coming on the market for the first time today, the risk it presents of shock and gastrointestinal bleeding might well lead the FDA to conclude that it should be placed on prescription. Its continued status as an over-the-counter product provides a practical symbol of social attitudes, associated with economic practicalities as well as philosophical predispositions, which favor self-medication. The case of aspirin, in particular, also exemplifies the fact that once a product is on the market, it carries with it a practical presumption of acceptable risk.

This brief rehearsal of the structure of the laws surrounding drug marketing is simply illustrative of the complex background of regulation against which common law tort cases are played out.

Compensation Plans

Schemes Particularized by Activity

A Well-established Plan: Workers' Compensation

The most well-established general compensation scheme for personal injuries is workers' compensation. Every state has its own workers' compensation statute, generally providing compensation to injured employees on a no-fault basis with no defenses allowed to the employer based on employee contributory negligence or assumption of risk. The typical verbal formula
requires a claimant to show an injury that arose "in and out of the course of employment." The practical basis of workers' compensation, as a national commission explained it in a 1972 report, was that "the costs of work-related injuries were to be allocated to the employer, not because of any presumption that he was to be blamed for every individual tragedy, but because of the inherent hazards of industrial employment." Since this report was issued, numerous bills have been introduced in the Congress to set federal standards for the state systems. These efforts at lawmaking, which have not yet resulted in legislation, respond to the conclusions of the commission that workers' compensation coverage is "inadequate," and that "wide variations among the states in the proportions of the labor force covered" are "inequitable." The commission further criticized the lack of coverage for non-union, low-wage workers and the fact that several states did not provide full coverage for work-related diseases; it also condemned statutes of limitations which effectively barred recovery for diseases whose symptoms appeared long after exposure. From the standpoint of those interested in introducing other legislatively based compensation schemes, a particularly sobering conclusion is the commission's judgment that "in general, workmen's compensation programs do not provide adequate income maintenance."

A Recent Compromise Solution: Modified No-Fault Legislation for Auto Accidents

Since the evolution of workers' compensation laws, principally in the second decade of this century, the automobile has become a central part of American life, its extraordinary utility accompanied by a costly burden of personal injury and death. A Cincinnati judge proposed a no-fault insurance plan to compensate the victims of automobile accidents as early as 1925. A 1932 report by the Columbia University Council for Research in Social Science represents the first comprehensive investigation of compensation for automobile accidents. The subject came into sharper focus in the 1960's with the publication of several notable studies and proposals; in 1970 Massachusetts adopted the first state statute to replace part of the tort action for personal injury with compulsory accident insurance. A recent study by the Department of Transportation on experience under state automobile plans has defined no-fault insurance as being characterized by three elements: "First, regardless of fault, victims of auto accidents receive economic loss benefits to the extent of no-fault coverage provided. Second, no-fault benefits supplant tort liability insurance. Third, there is some restriction on the right of the victim to sue for intangible damages, such as pain and suffering." A majority of the states have now adopted a no-fault plan with at least some of these elements. Typically, the change to no-fault involves a change to insurance that is first-party rather than third-party. The focus shifts from indemnity for liability—with one insuring himself against having to pay damages to others whom he may harm—to accident insurance, which provides pay-
ments for harms to the insured party himself. Most state no-fault plans have involved rather low dollar “thresholds”—the figure below which no-fault benefits operate and above which the tort system is retained.

The DOT study of no-fault experience from 1971 to 1977 finds much to praise in the new laws. It concludes that no-fault plans “in varying degrees provide more adequate and equitable benefits than the tort liability system.” Specifically, it notes that there has been a “major increase in the percentage of paid claimants, such as those injured in single vehicle accidents, who would not have been compensated under the tort system.” It also refers to “unprecedented levels of compensation” being paid to grievously injured accident victims. It finds that no-fault regimes result in prompter payments of economic loss and significantly more efficiency in administrative costs, and that they reduce the burdens on the court system. The study does however, refer to the “paucity of data with which to measure the administrative cost efficiency” of plans and says that this makes it difficult to render “firm conclusions.” It also notes that the thresholds in the no-fault statutes remove the less serious tort cases from the court system, “cases which presumably use less of the system’s resources ... than the more serious accident cases.” It says, therefore, that the actual decline in the use of court resources will “probably be some fraction of the decline of the motor vehicle torts.”

It seems intuitively obvious that no-fault plans will produce quicker compensation and greater numbers of payments to auto accident victims. It has been argued, however, that some states have experienced net increases in average cost. The writer has heard anecdotally that in at least one jurisdiction, no-fault payments have been used as financing vehicles for personal injury claims above the threshold.

Beyond questions of cost, there is duality about automobile no-fault plans from a philosophical point of view. In one of their notable essays on the subject, Professors Blum and Kalven question the justice of no-fault schemes from at least two points of view. They raise first the issue of whether it is just to do away with the fault system, with its equation of compensation with culpability. At the same time they ask why automobile accidents should be separated from other “human misfortune calling for a welfare remedy”: “The welfare universe is not limited to victims of auto accidents but includes victims of all other kinds of human misfortune. We can think of no ground for singling out the misfortune of auto accident victims for special welfare treatment.”

Many of the arguments concerning the costs of auto no-fault plans may have little relevance to the problem facing the Commission. I include this discussion, in part, because of the continuing controversy about a kind of compensation scheme which represents a recent effort by the states to attack a discrete person-
Injury problem, on which some data has now been collected. I also describe these developments because they may provide some useful analogies on the issues of compensatory justice associated with the problem of research injuries.

Proposals in Other Areas

Public discussion of American law in the last several years has identified two areas of tort practice as having generated "crises." They are products liability and medical malpractice.

Products liability. An interagency task force on products liability reported in 1977 that certain industries had experienced substantial boosts in their products liability insurance premiums and that the rate of increase of products claims appeared to have been rising in excess of the rate of increase in actual injuries. The task force did not unambiguously substantiate the cries that a "crisis" was at hand, since it also concluded that the cost of products liability insurance premiums had accounted for less than one per cent as a percentage of sales. Moreover, it indicated that the expansion of products liability law had driven industries and insurers to spend more time and effort at prevention techniques. Whatever the judgment on the existence of a "crisis," however, it was clear that the problem of products liability was "being viewed as a serious one. In response to that perception, a number of states have engaged in piecemeal reform of products liability law. New state laws have created statutes of repose, setting absolute cut-off dates on the amount of time during which personal injury actions may be brought. Such laws have prohibited the imposition of liability on manufacturers for products that have been altered or modified. They have declared that it is an affirmative defense to prove that product defects were not discoverable under research techniques prevailing at the time when the defendant sold the product. They have also established a concept of the "ordinary useful life" of products, beyond which actions cannot be brought.

A "Model Uniform Product Liability Act," issuing from the Department of Commerce following on the interagency task force report, undertakes to outline a comprehensive reform of the common law of product liability. Besides provisions along the lines of some of those in the state statutes summarized above, this model act offers a definition of defect which "places the burden of proof on the claimant to show that in light of a balance of practical, objective factors, the product seller should bear the full cost of the injury and should have responsibility for attempting to distribute that cost through the price of its product." The act refuses to allow tort recovery for purely economic losses. It prevents plaintiffs from introducing post-manufacturing changes in design or the warnings accompanying a product to show that it was defective at the time of manufacture. It also provides that a product's compliance with a legislative or administrative regulatory standard will compel the conclusion that the product is not
defective unless the claimant proves by a preponderance of the evidence that “a reasonably prudent product seller could and would have taken additional precautions.”

**Medical malpractice.** The other litigation area of perceived “crisis” has been that of medical malpractice. Many states have passed legislation aimed at reforming medical malpractice law. Many of these statutes have created insurance plans designed to provide doctors with liability coverage when it is unavailable or unsatisfactory, sometimes typing into these plans a dollar limitation on the amount of liability to which physicians are subject.

There is a wide range of other proposals for modification of the law of malpractice, and many of these changes have been adopted in different jurisdictions. These proposals have included the elimination of the “collateral source rule,” which permits plaintiffs to keep insurance payments in addition to tort judgments which presumably represent the full amount of their compensation. Some states have moved to eliminate the “ad damnum clause,” utilized in complaints by plaintiffs’ attorneys to state a particular amount as the total damage award. Some laws have shortened statutes of limitations for medical malpractice cases, and still others have placed various limits on the charging of contingency fees in this kind of litigation. At least a couple of states have modified the doctrine of res ipsa loquitur in medical cases.

An important procedural feature of many recent statutes has been a required pre-trial screening of medical malpractice cases, combined sometimes with the use of arbitration panels. State courts have split in their review of such provisions, with some upholding laws that provide for such procedures and others declaring them unconstitutional. There appears to be substantial conflict in the evidence as to the effectiveness of these panels. On one hand, early experience with the New York panel system yielded a report that “some administrators are pleased with the panel system and feel that it has saved the court’s time, money and space.” On the other hand, while striking down an arbitration panel provision, one court referred to ”unconscionable” delays in the resolution of cases which it said ripped “the fabric of public confidence in the efficiency and effectiveness of the judicial system.”

A radically different approach to the medical malpractice problem has been the proposal for a system of “medical adversity insurance.” Although one of the chief architects of no-fault insurance in the automobile area expressed considerable doubt about the possibility of effectively defining the class of compensable cases, the authors of the “medical adversity insurance” proposal suggested that the administration of such a scheme could evolve a list of “compensable events” over time, developing experientially a list of case categories which deserve compensation. These authors declared that they were “not reluctant
to classify some events as compensable even though they may be literally unavoidable under good medical practice," saying that the "possibility of overbreadth is incidental to any classification effort in an impure world."

**Broad Social Insurance for Accidents**

Thus far, I have dealt with plans that are activity related—the driving of automobiles, the manufacture of products, the rendering of medical services and the operations of the industrial workplace. I now turn to the question of whether compensation for personal injuries, whatever the activity, would better be achieved in a broader legislative framework.

**The New Zealand Law**

The most discussed comprehensive plan of accident compensation in the English speaking world is that administered through the New Zealand Accident Compensation Commission. This law began with a basic scheme under which self-employed persons paid into an earners' fund, with employers contributing to the fund for their employees. It includes a separate plan, financed by annual taxes on vehicles, which compensates all persons suffering "personal injury by motor vehicle accident." An amending act extended compensation to all non-earners injured in non-vehicle accidents, with their benefits being financed by general taxation.

This law appears to have been working well in New Zealand. Professor Palmer, now a member of the New Zealand legislature, said that the "signal achievement" of the statute's first two years was the fact that it was "running fairly smoothly," with "few signs of public dissatisfaction." Palmer reports that the "overwhelming impression" of a review of decisions of the accident compensation commission was "how simple it all is." With the panoply of trials stripped away, there is "no mystique and precious little drama." He adds that "a lot of people who receive nothing under the old system are being compensated and compensated quickly."

Accompanying these positive results, however, is a problem of public understanding of the scheme which originates "in the proximity of the legislation." This vice was due in significant measure to the fact that massive amendments were instituted when "the act should have been scrapped and re-drafted from scratch." A possibly daunting facet of the history of the legislation in New Zealand, with reference to possible adoption of such a plan in the United States, inheres in Palmer's comment that "the dominant feature of the scheme after two years seems to be an air of pragmatic experimentation" with "the scheme remain[ing] in a constant state of evolution." Given the complexity of American society and of the legal background of our personal injury law, one would be well-advised to ponder the legislative and legal
tangles that would attend the fashioning and administration of such a statute.

A Domestic Proposal

A particularly interesting proposal for comprehensive solution of the accident compensation problem in America has come from Professor Franklin. He has suggested a fund, based on a social welfare model, which would benefit all victims of accidents, with a substantial part of the financing coming from the general revenues. The plan, as Franklin conceives it, would require “selective reimbursement” to the fund from firms engaged in business enterprise. This reimbursement liability would be strict, which Franklin suggests would have “salutary deterrent aspects.” A separate account, covering motoring accidents, would be based on license fees and money derived from traffic fines.

These brief summaries of the complicated existing law of New Zealand, and a comprehensive proposal for America, supply some perspective for the Commission on the option of a general scheme of accident compensation, under which payments for those injured in medical research could be one very specific coverage. This discussion begins, at least, to provide a philosophical roof for the notion that as a practical matter one ought not legislatively to distinguish among types of misfortunes.

A General Social Security Welfare Approach

It is useful, finally, to mention briefly some even broader-based alternatives for social compensation of injuries caused by research procedures. The most general proposition would be to remit the problem to coverage already provided under social security and welfare legislation. Many people injured in the course of medical research would be eligible under various social security programs, including the law which provides for payments to those who become disabled after having achieved the requisite number of “covered quarters” in employment. The social security system which provides for these disability payments is theoretically an insurance system, at least basically funded by payments from both employees and employers. The Social Security Administration also administers the federal Supplemental Security Income Program, which provides, among other categories, aid for needy disabled persons. Financing for this program comes from general federal revenues with the states contributing supplementary payments. The federal government is, of course, involved in direct payment for medical care. It makes substantial transfers to recipients of “Medicare,” a Social Security-based program, and it provides money grants to needy recipients under the “Medicaid” legislation, in the administration of which the states have a share. In addition to all of these schemes which make money payments to or for those who are disabled or require financial assistance for medical problems, there exist residual
“general assistance” welfare programs. These are administered entirely by states and localities for persons who have serious economic needs but cannot fit themselves into particular statutory categories.

Each of these classifications will include a certain number of persons injured in the course of medical research, but none are fully inclusive of that group of persons. If the Commission concludes that research victims lack just compensation or are undercompensated, it must then face the question of whether to recommend that these persons be compensated on some social welfare basis. This question would, in turn, necessarily involve a number of issues about which standard of payment should be used as a matter of fairness and equity. Specifically, the Commission would have to decide whether the level of compensation should be that of similarly afflicted persons who receive federal money under Social Security disability, under Medicare, under Medicaid, under the Supplemental Security Income program, or under state general welfare assistance. Alternatively, it might refer to state workers compensation payment levels, which would immediately entail the problem of lack of uniformity among the states. Finally, it might choose to recommend another, original standard of payment—concerning which its choice of premises for compensation would be important.

Screening Panels and Other Substitutes for Adversary Litigation

It is appropriate at this point to emphasize a procedural reform to which reference has already been made in my discussion of state statutory modifications of the common law of medical malpractice. This is the use of screening panels. I simply wish to note several possible structural elements of such panels, each of which raises questions about the most effective way of devising plans to weed out personal injury claims that would otherwise occupy court time. A threshold problem regards the composition of the panel itself: Should it be comprised only of physicians? Should it include attorneys? members of the community? Should parties have the right to question panel members, as at least one state law provides? Another important issue is whether use of the panel should be compulsory. Still another is whether the panel’s deliberations should be limited to written evidence or whether they may include oral testimony. Finally, a crucial issue from the standpoint of the judicial process itself is whether panel findings should be admissible in a subsequent jury trial.

One should also make brief mention of the alternative of arbitration, which may be generally defined as a process in which findings of fact, at least, are binding on the parties. In theory, arbitration provides a method of grievance solving that is speedy and inexpensive. It is, however, vulnerable to various
constitutional difficulties, particularly including obstacles posed by state constitutional provisions guaranteeing the right to jury trial.

TENSIONS BETWEEN TORT LAW AND STATUTORY COMPENSATION AND INSURANCE SOLUTIONS

The body of this essay implies the tensions and complexities of a system that leans in part on tort law as a solution for personal injuries, which relies partly on statutory compensation systems, and which also utilizes private insurance, with various federal and state social security and welfare programs standing in the background. Consider the compensation problems posed by the case of a person who claims that he or she has become psychotic because of the administration of an experimental drug. Private insurance might provide payments to aid this person in his or her disability; the legal model here is one of “contract.” By contrast, tort law generally would require a showing of fault—either “an intentional tort” or “negligence.” The rationales of tort liability would be fragmented, referring among other policies to notions of utilitarianism and to considerations of ethics and morality. Congress might pass a statute that provided aid specifically for victims of personal injury inflicted by biomedical and behavioral research. It might do this on a social welfare model: it yet might require reimbursement from culpable parties, in order to achieve resource allocation effects, and also, perhaps, to insure that feelings of justice be assuaged.

Continuing the spectrum of possible social responses to this hypothetical case, the problem of compensation for research victims might be solved in a broader context as part of the enactment of a general accident compensation statute. Alternatively, one might decide that the existing systems of social security and various welfare-type payments from general revenues sweep in as many of the victims of biomedical research as is practically possible in a way that provides adequate income maintenance and medical payments. Or one might conclude that the Social Security Act or the Supplemental Security Income program should be amended to explicitly include persons injured in this way—which would seem to have the same effect as an activity-directed statute focusing on this class of victims.

Compensation for personal injury in America has proceeded piecemeal into a grand blanket of common law and statutory provisions. This Commission obviously faces the limitations of practical politics in deciding how to solve the problem which it addresses, and this professor is practical enough to know that any solutions that may emerge in legislation will have rationales that are likely to be rather fuzzy. Yet it seems to me that at least at the proposal stage one must endeavor to define rationales for action
as clearly as possible. It may advance this process to conclude Socratically, with a series of questions: Are we concerned with culpability, and is that concern one which is primarily fixed on a utilitarian cost-benefit model, or does it embrace ethical values as well? Should our focus emphasize a model of private contract between research subjects and experimenters, with bargains of personal safety for money being freely allowed? Should compensation be based on broad considerations of social welfare, in the sense of assuring to all injured persons a minimum floor of income maintenance and other elements of succor? Finally, how should the Commission respond to the issues of fairness that arise when research subjects—as often seems to be the case—stand in an inferior power relationship with the experimenters? Each of these questions implies a different standard by which to judge issues of compensation for persons injured in research activities. The Commission's selection of one rationale or another or a combination of them will give important fiber to recommendations it makes.
Existing Compensation Programs
A Report on Adverse Effects Insurance for Human Subjects

Diana J. McCann*
John R. Pettit, J.D.†

Introduction

The University is a major research institution with all of its graduate and professional programs located on one campus. For eight years it has provided adverse effects insurance for human subjects, both of unfunded activities and activities funded through grants and contracts conducted under University auspices. The insurance program has had two distinct phases since its inception on July 1, 1972. During the first phase, which continued through June 30, 1979, commercial insurance was procured; during the second phase, which began July 1, 1979, and has continued until the present time, the University has provided compensation for adverse effects through a self-insured program. It is expected that this second phase will continue in the future. The procured insurance program had as its model the State Workmen's Compensation Act, and coverage was provided during year 1 by Argonaut Insurance Companies and during years 2 through 7 by the Aetna Casualty and Surety Company; the self-insured compensation program is a modification of the Workmen's Compensation model.

Concern for the risks which individuals assume as human subjects, including economic risks, has had a long history at the University. Committee review of research involving humans began as early as 1946. Procurement of insurance against economic risks became possible, however, after 1970 when the review of and records on the use of human subjects became centralized within the University.

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Prior to the procurement of insurance, the institutional review boards had required that all relevant consent forms include information with respect to costs for adverse effects. The typical statement added to consent forms read: In the event of an adverse effect, the University cannot automatically provide reimbursement for the costs involved.

In December 1971 a survey was distributed to investigators to determine the number and types of adverse effects that had been experienced during a one-year period and the cost of such adverse effects.

Data were requested for studies scheduled to begin between January 1 and June 30, 1971. Of the 138 survey forms sent out, 110, or 80%, were returned. Respondents reported 14,942 subjects, and as the number of studies included in these data represented approximately 42% of the total number to be undertaken in 1971, the total number of subjects for all studies for one year was projected to be 35,000. Investigators estimated the length of time subjects were exposed to risk, and the average duration of this exposure for all studies was 1½ hours for each subject.

The survey respondents indicated that adverse effects attributable to research occurred in only five studies, involving four different fields and ten individuals. None of the ten individuals suffered partial or total permanent disability, and there were no fatalities.

The survey results led to the acquisition of insurance through a special endorsement to the University’s comprehensive general liability insurance policy. The initial premium was 50c per subject or $17,500; in subsequent years the cost was a fixed charge of $35,000 without regard to the number of subjects covered.

For the second year of coverage, investigators were again surveyed. There was one significant difference in the data: the average risk time per subject was about 10½ hours. This difference in risk time between years 1 and 2 was probably attributable to three causes: 1) the elimination of “no risk” studies from the analysis in year 2; 2) the lengthy risk periods reported for three studies during year 2; and 3) the natural variations in risk duration from year to year which are dependent upon the types of studies approved. No further surveys were conducted after year 2.

The Adverse Effects Insurance program has relieved concerns within the University for the economic protection of human subjects. There have been no complications in the insurance program.

The material set in italics in the remainder of this paper restates the request for information included in the Work Scope provided by the President’s Commission.
Insurance for Research Subjects

Incidence of Injuries
The number of research protocols covered since the beginning of the compensation program.

Since July 1, 1972, 5,376 research protocols have been covered by the compensation program out of a total of 8,739 protocols reviewed (University-wide figures). Yearly figures are given in Table 1, below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Protocols reviewed</th>
<th>Protocols insured</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>475</td>
<td>475</td>
</tr>
<tr>
<td>2</td>
<td>557</td>
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<td>3</td>
<td>710</td>
<td>481</td>
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<td>4</td>
<td>942</td>
<td>587</td>
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<tr>
<td>6</td>
<td>1,086</td>
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<td>9</td>
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</tr>
<tr>
<td>Totals</td>
<td>8,739</td>
<td>5,376</td>
</tr>
</tbody>
</table>

*These are University-wide totals.
*Year 1 includes the interval July 1, 1972-June 30, 1973, and so forth.
*These include biomedical and behavioral studies.
*These include biomedical studies only after year 1.

During year 1 of the compensation program (July 1, 1972-June 30, 1973), all protocols were covered by the insurance without regard to type of risk, i.e., physical, psychological, social, or legal. In years 2 through 7 coverage was provided almost exclusively for protocols which included physical risks. This change aligned the coverage with the State Workmen's Compensation Insurance Program after which the University's coverage was modeled. It will be noted from the data above that the number of applications reviewed during the eight years nearly tripled whereas the number of protocols insured increased only 70%. This reflects the significant increase in behavioral and social sciences protocols now being reviewed, for which insurance is not provided (see section II.A.1., below). During year 8 the Workmen's Compensation model continued with adjustments introduced to bring about greater equity in the coverage.

The number of research subjects who have participated in these protocols and the duration of their participation (e.g., number of hours or days, as appropriate). If possible, include information on demographic characteristics of subject population.

Since July 1, 1972, an estimated 356,000 research subjects have been covered by the compensation program. Yearly figures are given in Table 2, below.
TABLE 2. Subjects insured*, July 1, 1972-June 30, 1981

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of subjects insured</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>32,000</td>
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<tr>
<td>9</td>
<td>50,000</td>
</tr>
<tr>
<td>Total</td>
<td>356,000</td>
</tr>
</tbody>
</table>

*These are University-wide totals.
*Year 1 includes the interval July 1, 1972-June 30, 1973, and so forth.
*Estimates based on the average of the first four years.

No data are available on numbers of subjects who were not covered by the compensation program; however, experience in the review of behavioral and social sciences protocols suggests that the numbers are roughly equivalent to biomedical studies.

With regard to the data given in Table 2, during year 1 all subjects were covered by the insurance without regard to type of risk. In years 2 through 7 the coverage was aligned with the State Workmen’s Compensation Insurance Program. During year 8 adjustments were made (see section II.A.1., below).

The 1971 survey of investigators asked for the average duration of risk per subject; the resulting over-all average was 1½ hours per subject. This figure did not distinguish between biomedical and behavioral research. Further analysis of the 1971 data discloses that the average risk time per subject remained the same even when psychological, social, and legal risks were excluded. When a comparison was made between the average risk time for patient-subjects and for normal subjects, it was found to be over three times greater for patients. There were approximately three times the number of normal subjects as patient-subjects. Data from year 2 show a 10½-hour average risk per subject, but with patient-subjects having an average risk time 20 times greater than that for normals. Normals continued to outnumber patient-subjects by about 3 to 1. Data were gathered on risk time only, and none are available on “no-risk” time for any subjects. Also, no additional data were gathered after year 2.

Descriptive information on the number and nature of adverse effects.

The University has two means of reporting adverse effects internally: an Adverse Effect Report, in use since 1972, and an annual Status Report, in use since 1978. The former is completed when there is a likelihood of a claim against the University; the latter is appropriate for all other adverse effects. Whether “adverse effect” means “unanticipated” or both “anticipated and
unanticipated” has not been resolved; therefore, investigators determine which adverse effects to report. Altogether this procedure works, and a resolution of the issue will not likely be forthcoming, as the prevailing concern is the protection of human subjects against economic risk. This matter, of necessity, involves subjective opinions from investigators, as well as subjects, and sometimes outside sources, such as the institutional review board, an ad hoc committee, or a claims agent. Subsection 2, below, might be considered a report on anticipated adverse effects; and subsection 3, is a report on unanticipated adverse effects. It should also be noted that investigators report adverse effects, as appropriate, to funding and regulatory agencies.

Because of the two reporting mechanisms, the response to each of the subsections under section C. will be divided into two parts: the first on Adverse Effect Reports will cover eight years; and the second on Status Reports will cover three years. The information from the Adverse Effect Reports will be reported in greater detail, reflecting the differences in the availability of data and in the decisions which have been made on what represents a potential claim. Further, only professional fields will be identified in order to protect the confidentiality of individuals. The incidents reported are intended to assist the President’s Commission in its consideration of a compensation program for injuries to human subjects. The report is not intended to suggest any misconduct on the part of any investigator or department. The record herein reported does, in fact, suggest the opposite. The small number of adverse effects is surprising in the light of the high volume and substantial risks associated with the University’s research program with humans.

- Effects considered unrelated to participation in the research protocol and reasons so considered

Adverse Effect Reports

Cardiology (1972) Report 1. The purposes of the study were:
1) evaluation of exercise response, ventricular function, and coronary anatomy of survivors of sudden cardiac death;
2) comparison of survivors who had myocardial infarctions to those without; and
3) evaluation of possible therapeutic intervention. One 42-year-old patient-subject developed decreased pulses and signs of femoral thrombosis several hours after cardiac catheterization to diagnose the etiology of ventricular fibrillation from which that person had been resuscitated. A Fogarty thromboembolectomy was performed to restore distal circulation. Four months later there was an absence of pedal pulses; then symptoms of ischemia in the right leg. These symptoms eventually led to below the knee amputation of the leg. The adverse effect was the result of a standard diagnostic procedure which was indicated even if the patient had not been on the study. An insurance claim resulted (see section II.D., below).
Compensating self-administered study.

Cardiology (1973) Report 2. The purposes of the study were: 1) to determine the natural history of patients resuscitated from ventricular fibrillation outside the hospital; 2) to determine the need for an appropriate form of antidysrhythmic therapy in such patients; and 3) to assess coronary anatomy and ventricular function in such patients. One 21-year-old patient-subject, who had previously been resuscitated from ventricular fibrillation, experienced another episode which was a probable complication of cardiac catheterization performed on the same day. The subject received cardiopulmonary resuscitation and electrical defibrillation, and was transferred to the coronary care unit. The adverse effect was the result of a standard diagnostic procedure which was indicated even if the patient had not been on the study. No claim resulted.

Rehabilitation Medicine (1978) Report 3. The purpose of the study was to examine the activity of several muscles in normal individuals, including those muscles used for postural adjustments while the subject moved his or her arm in different directions and at different speeds, in order to design motor tasks to be used to investigate motor control in individuals with neurologic diseases. One 34-year-old normal subject fainted, scraping and bruising the back against equipment. The subject was seen by the resident in the department. It was subsequently learned that the person had not eaten lunch and had a history of fainting when hypoglycemic. Fasting was not a requirement of the study. There was no claim filed.

Laboratory Medicine (1980) Report 4. The purpose of the study was to compare a drug authorized for testing by the Food and Drug Administration with a placebo in the treatment of genital herpes. One adult patient-subject claimed that the result of participation was an increase in both the frequency and the severity of herpes recurrences. The individual had been treated with the placebo salve, and data indicate no effect of this substance on the natural history of genital herpes. Although all treatment of genital herpes is experimental, the investigator offered to place the subject in another treatment program. No claim resulted.

Status Reports

Infectious Diseases. Study 1: one patient-subject of 104 patient-subjects on a drug study for the treatment of venereal disease developed a pruritic rash which turned out to be due to scabies. Study 2: one patient-subject of 65 patient-subjects on a drug study for the treatment of venereal disease developed redness and pruritis over the entire body, which turned out to be an allergic reaction likely to a self-administered drug obtained elsewhere.

- Physical effects possibly related to participation in research but not requiring termination of the subject's participation in
the experiment, additional hospitalization, or loss of time (one full day or more) from work or normal activities

Adverse Effect Reports
No Adverse Effect Reports were filed for such studies in which participants were or would have been continued in the study after the effect occurred.

Status Reports
Allergy Study 1: two patient-subjects of 13 patient-subjects on a drug study for allergy developed self-limited nausea and vomiting—the drug dosage for all subjects was reduced.

Arthritis Study 1: several patient-subjects of 20 patient-subjects on a drug study for arthritis developed diarrhea—the drug dosage was reduced.

Cardiology Study 1: six patient-subjects of 2,936 patient-subjects on a symptom-limited maximal exercise study developed post-exertional cardiac arrest—defibrillation was successful, and there were no evolving myocardial infarctions or brain damage in these high risk coronary patients. Study 2: one patient-subject of 11 patient-subjects on a drug study for the treatment of angina developed headaches—these were treated with aspirin.

Dermatology Study 1: one adult normal subject of 42 normal and patient subjects on a topical medication study developed perioral dermatitis—local compresses and topical corticosteroids cleared it up.

Endocrinology Study 1: two adult normal subjects of 10 normal subjects on a drug study on blood glucose levels developed nausea—the nausea disappeared on cessation of the drug. Study 2: one patient-subject of 5 patient-subjects on a drug study for cancer developed renal tubular acidosis—it was transient, and spontaneous regression occurred. Study 3: one patient-subject of 16 normal and patient subjects on a study involving a medical device in the treatment of hormonal abnormalities of diabetes developed near syncope from insulin infusion—after rest in a recumbent position, recovery was complete in 15 minutes. Study 4: some of the 6 adult normal and patient subjects on a drug study of the hepatic hormone developed nausea—it resolved quickly.

Gastroenterology Study 1: one patient-subject of 19 patient-subjects on a graft-versus-host-disease study involving a rectal biopsy developed bleeding from the biopsy—surgical oversew of the biopsy site was required. Study 2: one patient-subject of 8 patient-subjects on an esophageal reflux study involving biopsies developed bleeding—hospitalization and observation occurred; no transfusion or other therapeutic maneuver was necessary. Study 3: one subject of 7 normal and patient subjects on a study to understand how the small intestine absorbs fatty acids de-
Compensating headache—no corrective measures were necessary.

Gerontology Study 1: some subjects of 50 normal subjects on a drug study of the autonomic nervous system developed transient hypotension—observations occurred until symptoms resolved.

Hematology Study 1: one patient-subject of 2 patient-subjects on a drug study involving a medical device for the treatment of sickle cell anemia developed a skin rash believed to have been caused by contaminated fluid coming from part of the machine—the skin rash disappeared without specific treatment: the machine part was replaced. Study 2: some patient-subjects of 10 patient-subjects on a drug study for the treatment of chronic bone marrow failure developed sterile abscesses at the injection site—temporarily stopping the injections and draining the abscesses corrected the problem.

Infectious Diseases Study 1: three patient-subjects of 11 patient-subjects on a drug study for venereal disease developed nausea or lower abdominal pruritis—these complaints resolved spontaneously. Study 2: some patient-subjects of 45 patient-subjects on a drug study for the treatment of nongonococcal urethritis developed nausea, diarrhea, or rash—none were serious enough to discontinue therapy. Study 3: three patient-subjects of 12 patient-subjects on a drug study for the treatment of venereal disease developed nausea or diarrhea—no treatment was prescribed. Study 4: two patient-subjects of 65 patient-subjects on a drug study for the treatment of venereal disease developed mild contact dermatitis—treatment was adjusted.

Kinesiology Study 1: the 17 adult normal subjects of a dehydration study for oarswomen developed nausea—each left the study site until it subsided.

Laboratory Medicine Study 1: one patient-subject of 5 patient-subjects of a drug study for the determination of acetylator phenotype developed a headache—no treatment was indicated.

Medicine Study 1: four adult subjects of 100 normal and patient subjects on a bone formation study for the determination of the pathogenesis of bone disease developed a hematoma and infection—these problems resolved spontaneously.

Metabolism Study 1: nine adult subjects of 95 normal and patient subjects on a study of the pathogenesis of genetic forms of hyperlipidemia developed minimal pain caused by an adipose tissue biopsy—no treatment was necessary. Study 2: three adult normal subjects of 100 normal subjects of a study of plasma cholesterol metabolism developed hematomas from venipuncture—each was kept under observation until the symptoms were gone. Study 3: two patient-subjects of 49 patient-subjects on a study of serum high density lipoprotein concentrations and
microangiopathy in juvenile-onset diabetes mellitus developed a skin rash after the injection of fluorescein dye—the rash subsided without treatment.

Nephrology Study 1: six adult patient-subjects of 13 patient-subjects on a study for the determination of adequate dialysis showed statistical changes in nerve conduction velocity—one patient's data stabilized in the normal range; the remaining five had their dialysis times changed or more efficient dialyzers prescribed. Study 2: ten adult patient-subjects of 20 patient-subjects on a study to evaluate hemodialysis supplies and equipment developed hypotension—blood volumes were repleted with intravenous fluids. Study 3: of twenty adult patient-subjects on a study to evaluate a fistula catheter for hemodialysis, there were 2 cases of thrombosis of the vein; 3 cases of infection; 4 cases of extrusion of the dacron cuff through the skin; 1 case of suture reaction; 3 cases of stenosis of the vein around the catheter; 10 cases of inadequate flow through the catheter; and 2 cases of accidental removal—all cases were treated, as appropriate. Study 4: some adult patient-subjects of 39 patient-subjects on a study of the recirculation of dialysate developed nausea—this was reversed with standard dialysis treatment. Study 5: some adult patient-subjects on a study of dialysis fluids developed headache, muscle cramping, post-treatment disequilibrium, and hypotension—all were treated symptomatically, as indicated.

Neurological Surgery Study 1: one patient-subject of 8 subjects on a drug study for the control of epileptic seizures developed mild dizziness and a headache—the problem cleared up spontaneously. Study 2: four patient-subjects of 16 subjects on a drug study for the treatment of intractable seizures developed dizziness and signs of drug excess—reduction of the study drug or concurrent medications corrected the problems.

Oncology Study 1: some patient-subjects of 28 patient-subjects on drug therapy with marrow infusions for the treatment of cancer developed varying degrees of skin pigmentation, desquamation at pressure points, and tingling at extremities—all were reversible with time. Study 2: some of the 125 patient-subjects (cancer) on a serum study for the treatment of graft-versus-host disease developed fever and/or chills—all received some form of treatment. Study 3: four patient-subjects of 111 patient-subjects on a bone marrow transplant study for the treatment of aplastic anemia developed chronic graft-versus-host disease—each was treated with various immunosuppressive agents. Study 4: twenty-eight patient-subjects of 105 patient-subjects on a bone marrow transplant study for the treatment of severe aplastic anemia rejected the marrow—supportive measures and/or second transplants were given. Study 5: most patient-subjects of the 14 patient-subjects (cancer) and 14 normal donors on a bone marrow transplant study with identical twins developed nausea and diarrhea from medication; all developed
temporary alopecia—appropriate therapies were applied.
Study 6: some normal subjects of 119 normal and patient subjects (cancer) on a bone marrow transplant study developed anemia—transfusions and/or iron were given, as appropriate. Study 7: thirty-one patient-subjects of 62 patient-subjects (cancer) on a laminar air flow room study developed intolerance to antibiotics or did not comply with recommended dosages—appropriate remedial actions were taken. Study 8: the 10 patient-subjects (cancer) of a drug study in the treatment of aggressive non-Hodgkin's lymphomas developed depression of the marrow with decrease in the white cell counts—drug dosages were modified. Study 9: the one patient-subject on a drug and radiation study for the treatment of cancer developed fever, chills, nausea, and vomiting—the symptoms were appropriately treated. Study 10: seven patient-subjects of 9 patient-subjects on a surgical study for the treatment of cancer developed various problems: postoperative leg pain, slight edema, depression, leg and groin swelling, and wound infection—all were treated appropriately.

Ophthalmology Study 1: four patient-subjects of 33 patient-subjects on an intraocular lens implantation study developed dislocation and endothelial touch; wound leak; displacement of superior loop; or corneal decomposition—all but one were resolved without removal of the lens.

Pathology Study 1: three adult normal subjects of 15 normal subjects on a study of the mechanisms of decreased glucose tolerance in the aged developed vomiting on a hot day, constipation, or diarrhea—the vomiting did not recur; the other effects were treated.

Pediatrics Study 1: seven patient-subjects of 15 patient-subjects of a serum study for the treatment of antibody deficiency developed headaches, muscle aches, back pain, and/or fever—these side effects were diminished by decreasing the rate of infusion and by treating the rate of infusion and by treating the patients with oral aspirin.

Pharmacology Study 1: two adult patient-subjects of 19 patient-subjects on a drug study for the treatment of hypertension developed thrombophlebitis with pulmonary embolism or a skin reaction—neither was on the study drug as yet; each was treated for the symptoms.

Pharmacy Practice Study 1: eleven dry sockets occurred to patient-subjects who had a total of 42 clinically-indicated extractions in a study of the effect of corticosteroids on the incidence of dry socket after third molar extraction—all were dressed and given treatment for pain. Study 2: of 7 adult normal subjects on a pharmacokinetics study, 3 experienced gastrointestinal upset: 1. nausea; 2. diarrhea; 2. tiredness; 3. nasal congestion; and 2. hot sensations—each was treated appropriately.

Physiology Study 1: five patient-subjects of 10 patient-subjects for a study on the relative efficacy and toxicity of anti-
epileptic drugs developed nausea or drowsiness—both effects subsided with a decrease in drug dosage. Study 2: each of the 4 adult normal subjects on a study of eye movement systems developed slight irritation of the eye—the irritation disappeared in one hour.

**Psychiatry Study 1:** one adult normal subject of 16 normal subjects on a drug study for the treatment of acute psychosis developed transient dystonia—this was treated with anti-Parkinsonian medication. Study 2: three patient-subjects of 30 patient-subjects on a drug study for the management of psychogeriatric patients experienced sedation or drowsiness—the dosage of the study drug was adjusted accordingly.

**Pulmonary Disease Study 1:** two adult normal subjects of 6 normal subjects of a drug study on the enhancement of ventilatory drives developed increased breathlessness during usual levels of exercise—the symptoms abated when the medication was stopped.

**Radiation Oncology Study 1:** some patient-subjects of 200 patient-subjects (cancer) on a study involving fast neutron beam radiotherapy had a slight increase in normal tissue reactions—these were closely observed and conservatively managed.

**Radiology Study 1:** some of the patient-subjects of 40 patient-subjects on a drug study for the treatment of postmenopausal osteoporosis developed minor skin irritation and/or tenderness at the site of the bone biopsy—these were observed, but did not require modification of the protocol. Study 2: some of the patient-subjects of 40 patient-subjects of a drug study for the treatment of postmenopausal osteoporosis developed transient deviations from normal liver function or acneiform lesions over the face—each was treated by a reduction in the drug dosage. Study 3: one patient-subject of 8 patient-subjects on a drug study for the treatment of postmenopausal osteoporosis developed psychosomatic symptoms which were questionably related to the study—the drug dosage was reduced.

**Rehabilitation Medicine Study 1:** two adult normal subjects of 8 normal subjects on a study of the effects of exercise on maximal isometric strength developed shin splints or severe quadriceps muscle pain—the complaints resolved with the cessation of exercise.

**Respiratory Diseases Study 1:** two patient-subjects of 20 patient-subjects on an immunologic study requiring lung biopsy developed self-limited episodes of hemorrhage—no treatment was necessary. Study 2: a few of the 18 normal and patient subjects on a drug study for the treatment of respiratory disease complained of rapid heart rate and dizziness—subjects were closely observed; these symptoms ceased in 5–10 minutes.

**Surgery Study 1:** twenty-two patient-subjects of 80 patient-subjects on a study comparing oxygenators for open-heart
surgery had to have adjustments on the oxygenators—there were no sequelae. Study 2: one patient-subject of 15 patient-subjects on a burn dressing study developed staph infection—it was treated with antibiotics. Study 3: one patient-subject of 604 patient-subjects on a study of diabetic vascular disease developed a callus while on the treadmill—it was cleaned, dressed, and followed up in one week. Study 4: four patient-subjects of 18 patient-subjects on a drug study for the treatment of stress ulcer in hospitalized patients experienced diarrhea (3) or vomiting (1)—each was shifted to a different drug.

- More significant physical effects possibly related to participation in research requiring or resulting in:
  (a) termination of the subject's participation in experiment;
  (b) short- or long-term medical care, including but not limited to hospitalization;
  (c) loss of time from work or other normal activities;
  (d) death; and
  (e) termination of research activity.

Adverse Effect Reports

Hematology (1973) Report 5. The purposes of this study were to characterize the pathophysiology of the platelet in clinical disorders of hemostasis thrombosis and to define the therapeutic role of inhibiting platelet function with pharmacologic agents. Four adult patient-subjects received infusion of their own autologous platelets which had been inadvertently contaminated with bacteria. They developed fever and chills. (a) The subjects' participation in the study was terminated. (b) All four subjects were hospitalized and received appropriate treatment. (c) It is assumed that the subjects, although patients, had lost work time. (d) All subjects recovered. (e) The research activity continued, but the laboratory procedures were immediately modified to prevent future occurrences. A claim resulted (see section II.D.2., below).

Cardiology (1974) Report 6. The purposes of the study were:
(1) to define in cardiac patients the electrocardiographic and hemodynamic status before, during, and after exercise on a treadmill; (2) to evaluate coronary arterial disease by selective angiography; and (3) to evaluate lung and vascular dynamics by angiocardiography. One 52-year-old patient-subject developed a small hematoma from percutaneous puncture of the left brachial artery after removal of the arterial catheter. There was subsequent temporary nerve damage with hypesthesias, as well as phlebitis of superficial forearm veins distal to the site of catheterization for several weeks. (a) The subject was terminated from the study. (b) The subject was hospitalized and received medical treatment. (c) The subject lost two weeks of work, but apparently it was covered by accrued sick leave or the patient was already on medical leave. (d) The subject recovered fully.
from the episode. (e) The research activity continued. No claim was filed.

*Environmental Health (1974) Report 7.* The purpose of the study was to determine the usability of a set of medical procedures designed for diagnosing occupational disease by relating health findings of a sample of workers in a given area to results of studies of their work environment. One normal subject developed a hematoma with inflammation and secondary lymphangitis at the venipuncture site. (a) The subject's participation in the study had already concluded. (b) The subject was treated by his private physician with parenteral penicillin and was advised to apply warm compresses to the inflamed area of the arm. (c) The subject lost no work time. (d) The problem was resolved without sequelae. (e) The research activity continued. No claim was filed.

*Nephrology (1974) Report 8.* The purpose of the research was to study renal function and structure using biopsy materials for diagnosis and clinical evaluation. One 49-year-old patient-subject developed complications after the biopsy: acute gastric dilation, and urinary retention and infection. (a) The subject's participation in the study had already been completed. (b) Antibiotics were given and a catheter used to relieve urinary stress. (c) No work time was lost. (d) The subject recovered. (e) The research activity continued. No claim was filed.

*Anesthesiology (1975) Report 9.* The purposes of the study were to determine the cardiovascular and respiratory effects of anesthesia and to correct alterations of functions by appropriate means in order to lessen the hazards of anesthesia to the parturient, fetus, and newborn. One 31-year-old experienced weakness and numbness of the upper right extremity many weeks after the study. The procedure of the study was the drawing of arterial blood gases. (a) The subject's participation had already concluded. (b) Although it was not likely the study procedure was the cause of the adverse effect, the subject was given a complete examination. (c) No work time was lost. (d) The subject recovered from the episode. (e) The research activity continued. No claim was filed.

*Cardiology (1975) Report 10.* The purposes of the study were: (1) to develop an understanding of the clinical features, pathophysiologic mechanisms, and predictive characteristics associated with sudden cardiac death and ultimately to develop rational intervention for prevention of sudden cardiac death; (2) to define the natural history of patients resuscitated from prehospital ventricular fibrillation and to assess the prognostic significance of specific findings and observations, i.e., patient profile, post-resuscitation clinical evaluation, prevalence and types of dysrhythmias, responses to standard exercise testing, coronary anatomy, ventricular function, and therapy; and (3) to initiate a controlled pharmacologic study of prevention of sudden
cardiac death in patients at very high risk for recurrent ventricular fibrillation. One 56-year-old patient-subject had a cardiac arrest following an episode of ventricular fibrillation about two minutes into the recovery period after a treadmill exercise test. (a) The subject's participation in the study was discontinued. (b) Resuscitative efforts were initiated immediately, including intubation, subclavian intravenous line, counter-shock, and pharmacologic intervention. After approximately one hour, stable sinus rhythm was restored and the subject was admitted to the critical care unit. (c) No work time was lost as the subject was retired, but the subject was removed from other normal activities by the brief hospitalization. (d) The subject recovered from the episode. (e) The research activity continued. An insurance claim resulted (see II.D.2., below).

Anesthesiology (1976) Report 11. The purpose of the study was to determine if tricyclic anti-depressants have an analgesic effect in normal man; and, if effects are there, to determine if they reflect sensory change and/or response bias. One 40-year-old normal subject experienced exaggerated sedation and some clouding of mentation for two days. (a) The subject's participation in the study was terminated. (b) The subject was told to discontinue the medication and received a follow-up examination. (c) No work time was lost as the subject was unemployed. (d) The subject recovered fully. (e) The research activity continued. No claim was filed.

Psychology (1976) Report 12. The purpose of the study was to develop methods for evaluating the effects of anticonvulsant drugs upon cognitive functioning in epileptic patients. Seven to ten days after completing the study, one 33-year-old normal subject experienced depression. (a) The subject's participation in the study had already been concluded. (b) The medical investigator on the study met with the subject. The subject, a university student, was uncertain whether the depression was related to the study or to "end of the quarter blahs." (c) The subject had found it difficult to attend to homework during the eleven days on the study and for a period following. The anticipated effects had been disclosed in the consent form which the subject had signed. (d) The subject recovered fully. (e) The research activity continued. No claim was filed.

Anesthesiology (1976) Report 13. The purpose of the study was to more precisely define the potency of nitrogen by the acquisition of response (depression) data for various nitrogen partial pressures above one atmosphere. One 26-year-old normal subject developed weakness, coolness, and paresthesias of both hands two days following the second (of two) hyperbaric exposures. (a) The subject's participation in the study had already concluded. (b) The subject was sent to the emergency room of a local hospital having a hyperbaric chamber, was examined by a neurologist, and then treated with recompression. (c) The subject
did not lose work time. (d) The subject recovered fully. (e) The research activity continued. An insurance claim resulted (see II.D.2., below).

**Obstetrics and Gynecology (1977) Report 14.** The purpose of the study was to test the effectiveness of an investigational new drug in Phase III of testing in bringing about a cessation of lactation, a resumption in menses, and possibly pregnancy. Seven patient-subjects, age 27 to 35, were on the study when the drug was withdrawn by the Food and Drug Administration because laboratory rats on a concurrent study had developed ovarian tumors. (a) All seven subjects were terminated from the study. (b) Subjects were contacted and asked to immediately discontinue the drug. Each receives an annual examination. (c) No work time has been lost. (d) There have been no deaths. (e) The research activity was terminated. No insurance claims have been filed.

**Hematology and Oncology (1977) Report 15.** The purpose of the study was to determine the optimum concentration of dimethyl sulfoxide and the proper rate of freezing and thawing to obtain the most viable, functional platelets. The information was to improve the management of patients on high-dose chemotherapy protocols. Multiple unit platelepheresis to obtain platelets for cryopreservation before marrow suppressive therapy would allow readministration of the platelets if thrombocytopenia developed following treatment. Two normal subjects, ages 28 and 35, received infusions of their own autologous frozen platelets which during their preparation had been inadvertently contaminated with bacteria. One subject developed fever, slight chills, and myelagia approximately one hour after the injection; the other developed a mild fever and nausea. (a) The subject's participation in the study was terminated. (b) Both subjects were hospitalized for four days on the Clinical Research Center and received intravenous antibiotics and, subsequently, oral antibiotics. (c) Both subjects lost several days of work which were covered by accrued sick leave. (d) Both subjects recovered fully. (e) The research activity continued, but the laboratory procedures were immediately modified to prevent future occurrences; ultimately the laboratory was relocated. Insurance claims resulted (see II.D.2., below).

**Endocrinology (1977) Report 16.** The purposes of the study were to determine plasma lipoprotein concentrations in uncontrolled diabetic patients prior to the commencement of therapy and to test whether insulin therapy influences plasma lipoprotein levels. Following the withdrawal of 20 milliliters of blood, one 57-year-old patient-subject developed venous thrombosis probably attributable to the use of estrogen in the management of hyperlipidemia, and venous stasis resulting from being confined to bed during a lipoprotein turnover study. (a) The subject's participation in the study had concluded. (b) The subject was hospitalized following assessment of the problem by the investigators.
Compensating Chair Front Fall Stones Other Inal

Although ulcer testing fair for patient-subject find subject clinically checked after the incident. (c) The research activity continued. A claim resulted (see II.D.2., below).

Psychiatry (1976) Report 17. The purpose of the study was to relate results of pre- and post-treatment urinary laboratory tests for depressed outpatients and to correlate these with the clinical response to two commonly used antidepressant medications. One 24-year-old patient-subject experienced hypoventilation associated with sharp, localized (costochondral junction) pain which elevated with cough and deep breathing and dropped without breath. Peptic ulcer disease and colitis were other symptoms the subject reported. (a) The subject's participation in the study was terminated. (b) The immediate action taken was to have the subject breathe with a bag. There was no hospitalization. (c) The subject did not lose work time. (d) The subject recovered from the incident. (e) The research activity continued. A claim resulted (see II.D.2., below).

Laboratory Medicine (1978) Report 18. The purposes of the study were to determine variability of clinical values in blood, urine, or stool for University clinical laboratories and to provide blood, urine, or stool specimens for use in quality control of clinical laboratory measurements. One 20-year-old normal subject broke a front tooth in a fall from a chair following venipuncture performed after a 12-hour fast. (a) The subject's participation in the study had concluded. (b) The subject was taken to the emergency room where vital signs were checked and a glucose-level test ordered; then the subject was advised to see a dentist for repair of the fractured left maxillary central incisor. (c) It was thought the subject had lost 9 hours of work time, but as no claim for lost wages was submitted, apparently this was not so or accrued sick leave covered. (d) The subject recovered fully. (e) The research activity continued, but subsequent donors were seated on a low chair at a desk and were provided fruit juice immediately after blood withdrawal. A claim resulted (see II.D.2., below).

Arthritis (1978) Report 19. The purpose of the study was to find out whether an investigational new drug in Phase II of testing would decrease morning stiffness, pain joint symptoms, or other manifestations of rheumatoid arthritis. One 78-year-old patient-subject died after complications which may or may not have been associated with the study drug. The first symptom was sudden severe abdominal pain, diagnosed as a ruptured viscus, for which the patient underwent a laparotomy. A perforated ulcer of the duodenum was found and surgically treated; gallstones which had inflamed the gallbladder were removed. Although apparently recovering, after the second day the abdominal pain returned. Respiratory arrest followed aspiration of a fair amount of blood, from which the patient was successfully
resuscitated. Subsequent blood transfusions and life support measures failed to prevent a rising hemogram and falling blood pressure and eventual expiration. (a) The subject's participation was terminated. (b) The subject was hospitalized and received excellent care. (c) The subject's normal activities had previously been curtailed by the illness. (d) The subject died. (e) The research activity continued. No insurance claim was filed. Further, the subject had no direct family.

Nephrology (1979) Report 20. The purposes of the study were: (1) to determine the effect of decreased renal function on serum concentrations and urine excretion of an experimental new drug in Phase II of testing, used to decrease heart-rate, control some forms of irregular heartbeat, and reduce blood pressure in hypertensive patients; (2) to propose, from single dose kinetics, a multiple dosage schedule for patients with decreased renal function; and (3) to determine the safety and efficacy of the study drug in patients with impaired renal function. One 57-year-old patient-subject experienced a sudden onset of generalized seizure and ventricular tachyarrhythmia, as well as brief sinus pause. The patient received cardio-pulmonary resuscitation, neurological consultation, an electroencephalogram, and was admitted to the Clinical Research Center. It was later discovered that the patient had hypokalemia. (a) The subject's participation in the study was terminated. (b) The subject received short-term hospitalization and follow-up examinations until returned to the pre-treatment status. (c) No work time was lost as the subject was not employed. Also, normal activities had already been curtailed due to the disease. (d) The subject recovered from the incident. (e) The research activity continued. No insurance claim was filed.

Ophthalmology (1980) Report 21. The purposes of the study were to answer three questions: (1) when in the course of the diabetic retinopathy process should photocoagulation be initiated; (2) what is the effect of photocoagulation on diabetic macular edema; and (3) what is the effect of aspirin on the diabetic retinopathy process? Following a fluorescein injection, one 29-year-old patient-subject complained of a flushed sensation and burning in the throat, which progressed to symptoms of difficulty in breathing. (a) The subject's participation in the study was terminated. (b) The subject was treated in the hospital emergency room. The antidote given further aggravated the problem: a further examination showed a hoarse voice and mild bronchospasm. (c) The subject did not lose work time and apparently continued with normal activities. (d) The subject recovered from the incident. (e) The research activity continued. A claim resulted (see II.D.2., below).

Status Reports
Arthritis Study 1: one patient-subject of 7 patient-subjects on a drug study for the treatment of rheumatoid arthritis suffered a stroke and died—the stroke was thought to be unrelated to the
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study drug. Study 2: one patient-subject of 2 patient-subjects on a drug study for the treatment of rheumatoid arthritis developed an ulcer—the drug was discontinued and another substituted. Study 3: eleven patient-subjects of 47 patient-subjects developed various effects: gastrointestinal discomfort (1), rash (1), ulcer (2), nervousness (5), constipation (1), and anorexia (1)—discontinuing the drug alleviated all symptoms. Study 4: one adult normal subject of 10 normal subjects on a drug study for rheumatoid arthritis developed gastrointestinal distress—the drug was discontinued. Study 5: some patient-subjects of 20 patient-subjects on a drug study for the treatment of osteoarthritis of the knee developed rashes—subjects were withdrawn from the study and treated. Study 6: one patient-subject of 4 patient-subjects on a drug study for the treatment of rheumatoid arthritis developed gastrointestinal distress—discontinuing the drug alleviated the symptoms. Study 7: three patient-subjects of 12 patient-subjects on a drug study for the treatment of osteoarthritis of the hip and knee developed mouth sores or gastrointestinal distress—discontinuing the drug alleviated the symptoms. Study 8: four patient-subjects of 22 patient-subjects on a drug study for the treatment of rheumatoid arthritis developed proteinuria (2), rash (1), or gastrointestinal distress (1)—discontinuing the drug alleviated the symptoms.

Cardiology Study 1: one patient-subject of 45 patient-subjects on a drug study for the prevention of recurrent ventricular fibrillation developed worsening symptoms of heart failure—the subject recovered after the drug was discontinued.

Endocrinology Study 1: one patient-subject of 16 normal and patient-subjects on a study involving a medical device for the treatment of hormonal abnormalities of diabetes experienced syncope—the subject was withdrawn from the study and recovered. Study 2: one adult normal subject of 17 normal subjects on a male contraceptive study developed acne on the back and chest—the subject was taken off the study and recovered.

Gerontology Study 1: one patient-subject of 3 patient-subjects on a drug study for the metabolic control of high density lipoprotein experienced a myocardial infarction not clearly related to the study—the subject was hospitalized on the coronary care unit, and the drug discontinued.

Hematology Study 1: one patient-subject of 13 patient-subjects on a study of iron chelation developed a skin rash—discontinuing the subject from the study alleviated the problem. Study 2: one patient-subject of 8 normal and patient subjects on a prophylactic transfusion study developed severe febrile transfusion reactions—transfusions were discontinued in the subject. Study 3: one patient-subject of 18 normal and patient subjects on a study concerning the storage of platelet concentrates developed chills and fever—these were successfully managed by a drug after the subject was terminated from the study.
Infectious Diseases Study 1: twelve patient-subjects of 87 patient-subjects on a drug study for nonspecific vaginitis had post-treatment vaginitis (10) or severe nausea (2)—appropriate medications were given and the subjects were terminated from the study. Study 2: three patient-subjects of 21 patient-subjects on a drug study for the treatment of nonspecific vaginitis had post-treatment yeast vaginitis—another medication was given.

Medicine Study 1: one adult normal subject of 33 normal subjects of a drug study for depressed patients developed postural hypotension—the subject was terminated from the study and recovered.

Metabolism Study 1: four adult subjects of 25 normal and patient subjects on a study of the relationship of thermogenesis to obesity experienced an infiltration of intravenous lines—these were discontinued, pressure applied, and treatment given.

Nephrology Study 1: one patient-subject of 15 normal and patient subjects of a drug study for the treatment of patients with renal failure developed a transient skin rash—the subject was terminated from the study and recovered.

Nursing Study 1: one of 14 mothers whose normal babies were on a study of light and sleep behavior of the neonate felt the light irritated the baby—the baby was terminated from the study.

Oncology Study 1: one patient-subject of 5 patient-subjects (cancer) on a drug study for treatment following bone marrow transplantation developed hives—the study drug was discontinued. Study 2: one patient-subject of 22 normal and patient subjects on a taste study for leukemic children experienced nausea—the subject was discontinued from the study.

Pediatrics Study 1: one patient-subject of 20 patient-subjects on a drug study for the treatment of malignant disease developed severe transaminasemia—the subject recovered after termination from the study. Study 2: one patient-subject of 3 patient-subjects on a drug study for the treatment of diseases associated with altered immune function developed transient granulocytopenia—the subject was terminated from the study.

Pharmacology Study 1: one patient-subject of 19 patient-subjects on a drug study for the treatment of hypertension developed asthmatic-type breathing—the subject was terminated from the study and the symptoms abated.

Pharmacy Practice Study 1: one normal subject of 7 normal subjects on a pharmacokinetics study had a febrile reaction—the subject was terminated from the study and recovered.

Psychiatry Study 1: one patient-subject of 30 patient-subjects on a drug study for the management of psycho-geriatric patients experienced orthostatic hypotension—the symptoms abated when the subject was terminated from the study. Study 2: two patient-subjects of 20 patient-subjects on a drug study for the
treatment of cognitive dysfunction developed headaches—the subjects were terminated from the study and recovered.

Rehabilitation Medicine Study 1: one patient-subject of 14 patient-subjects on a drug study for the management of patients undergoing intermittent catheterization was uncomfortable with the procedure—the subject was terminated from the study.

Respiratory Diseases Study 1: some of the 19 patient-subjects on a drug study for the treatment of respiratory disease were unable to tolerate the side effects (palpitations, tachycardia, flushing, and tremulousness) of the drug—these subjects were discontinued from the study. Study 2: one patient-subject of 18 normal and patient subjects on a drug study for the treatment of respiratory disease developed increased bronchospasm—the subject was terminated from the study and recovered.

Surgery Study 1: two patient-subjects of 35 patient-subjects on a drug study for the treatment of intermittent claudication developed severe nausea or intractable diarrhea—the subjects were discontinued from the study and recovered. Study 2: one patient-subject of 45 patient-subjects on a drug study for the treatment of intra-abdominal sepsis developed a skin rash—the subject recovered after termination from the study.

- Psychological or social injuries possibly related to participation in research (e.g., disclosure of private information without subject's consent, inability to work or to perform normal activities)

Anthropology Study 1: one legislator of 15 contacted for a study on legislators' perceptions of their role as delegates or trustees objected to the investigation because the investigator was a lobbyist at the time—the study was discontinued.

Cardiology Study 1: one patient-subject of 11 patient-subjects on a drug study for the treatment of angina experienced depression—the subject was terminated from the study and improved.

Education Study 1: one patient-subject of 20 patient-subjects on a study to examine the relationship between structure in a counseling interview and client characteristics worried about the tape recording of interviews—the subject was terminated from the study in order to avoid interference with the progress of the counseling.

Endocrinology Study 1: one adult normal subject of 35 normal subjects of a drug study on gonadal function in normal men developed a fluctuating libido, not proven to be drug-related—the subject was terminated from the study and followed during the recovery period.

Oncology Study 1: some patient-subjects of 62 patient-subjects (cancer) on a laminar air flow room study complained of
the isolation from direct family contact and about the sterile food diet—psychological support and reinforcement were given.

Psychiatry Study 1: one adult normal subject of 16 normal subjects on a drug study for the treatment of acute psychosis-developed a brief syncopal episode—the subject was seen by medical personnel and reassured. Study 2: two of the husbands of patient-subjects on a study to assess psychosocial aspects of parenteral nutrition at home resented psychiatric examination of their wives, perceiving this as a threat to marital equilibrium—distress was relieved by adoption of a neutral, nonintrusive stance by the investigator.

Psychology Study 1: some adult normal subjects of 150 normal subjects of a study on aging and inhibition were upset by not doing well on a test which they perceived as a type of intelligence quotient test—the test was dropped from the study. Study 2: one adult normal subject of 3 normal subjects on a study of life-style intervention on smoking, eating, and drinking behaviors underwent major life stresses during the study—supportive counseling was given; the subject was terminated from the study.

Women Studies Study 1: one adult normal subject of 14 normal subjects on a study of sociocultural roles of women in a specific industry developed stress from discussions of uncomfortable topics and the taping thereof—uncomfortable topics were dropped from this subject's interview or the tape recorder turned off.

- Latent effects not evident at termination of subject's participation in research protocol but discovered subsequently.

To the present time there has been no report of latent effects from any investigation.

Compensation Program
A description of the compensation program

- Definition of research qualifying for coverage (and identification of any categorical exclusions from coverage—e.g., oncology patients or research identified as posing special risks)

During the two phases of the insurance program (described in the Introduction), biomedical research has been covered and behavioral research has been excluded (after year 1) with two unwritten exceptions: use of psychiatric patients and of infants. If a psychiatric patient were to have therapy prolonged by behavioral research, it is expected that the adverse effects insurance would cover the additional costs. If infants were to experience accidental injury while being handled in the course of a behavioral study, it is expected that the costs of treatment would be covered by the insurance. The exclusion of behavioral research from coverage developed because the Workmen's Compensation Insurance used as a model did not provide coverage for psychological, social, or legal risks. This exclusion was considered
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liable in view of the right of individuals to sue the institution, in which case the University's liability insurance would be applicable. Also excluded during both phases has been research conducted by University investigators in foreign countries.

Procedures covered during both phases of insurance have been those conducted primarily for the purposes of biomedical research. Unwritten exclusions have been: 1) adverse effects experienced to standard medical procedures performed as part of patient management; 2) effects from the natural course of a disease, or condition; and 3) non-compliance with study procedures (also see II.A.4., below). REPORTS 1., 2., and 4. described above all fall under these exclusions (also see II.D.2., below, REPORT 1). Presently under consideration is the desirability of exclusion of biomedical research funded through organizations other than the University, but involving University investigators.

- Events for which compensation is provided (nature of the injuries covered, e.g., physical, psychological, social)

During the first phase of the University's compensation program, the insurance policy provided that there was coverage "if a volunteer participating in an authorized research program . . . shall sustain injury, including death, resulting therefrom, while participating in such program . . . ." In the second phase of the program, coverage exists for "adverse effects" resulting from approved projects. Specific definitions of the terms "injury" and "adverse effects" have not been included in the coverage documents in either phase of the program; however, as suggested in the immediately preceding section, the use of Workmen's Compensation as a model has resulted in an unwritten definition of those terms which—in most respects—conforms to the definition of "injury" in the Washington State Workmen's Compensation Law (See RCW 51.08.100, a copy of which is attached as Exhibit A).

- Any time limitations on filing of claims

By reference to the Washington State Workmen's Compensation law, the insurance coverage in effect during the first phase of the program implicitly placed a one-year limitation on the filing of a claim (see RCW 51.28.050 and 51.28.055, copies of which are attached as Exhibit A). In the second phase of the program, this one year limitation has been made explicit; however, it is expected that there may continue to be some situations in which imposition of an absolute time limit would be inappropriate. REPORT 14 describes an example of such a situation.

- Other restrictions or limitations on recovery (e.g., incomplete or inaccurate disclosure of medical history by subject; failure by subject to follow directives of researcher regarding use of drugs, alcohol, etc.)
Insurance for Research Subjects

An explicit restriction has not been placed on the adequacy of medical history disclosures. Several factors suggest that this would not be in the interest of the University: (a) subjects may forget important medical facts; (b) investigators may not ask for all the pertinent facts; and (c) subjects may not recognize the importance of a specific fact and decide to omit it. The issue of inducements to research subjects is relevant to (c); this is discussed under II.F., below.

While non-compliance with study procedures will in general be considered justification for disapproving a claim for an alleged adverse effect, certain factors suggest flexibility in resolving such matters: (1) consent forms are often long and complex (the University of Michigan report entitled “A Survey of Institutional Review Boards and Research involving Human Subjects,” 1977, commented on this matter); (2) the subject's copy of the consent form may be mislaid; (3) the oral explanation given by an investigator may be forgotten; or (4) the subject may not recognize the importance of compliance.

During year 1 of the program, the upper limit on compensation was $100,000 per person and $100,000 per accident or “aggregate” disease. In years 2 through 7, the stated policy limits were $1,000,000 per subject or per incident; however, given the fact that compensation payable under the policy was tied to Workmen's Compensation benefit levels, the maximum amount which actually could have been paid to a subject was probably in the range of $100,000-$150,000.

In the second phase of the program, all medical expenses immediately and directly associated with the adverse effect are automatically covered, up to $10,000. In addition, a subject is eligible for “such additional expenses or compensation as may be agreed to by the parties.” This language was incorporated to allow for greater flexibility and equity in payments to various classes of subjects than was possible under the Workmen's Compensation Model, while retaining University control over the level of benefits to be provided. The figure of $10,000 as a standard maximum figure for medical expenses was felt to be ample, based on past claim experience.

- The method of computing the amount to be paid for specific injuries or for specified classes of patients (e.g., patients seriously ill at the outset of the research; children; students; the elderly; other non-wage earners)

During the first phase of the University's compensation program, employed adults could expect to receive the types and levels of benefits provided under the Washington State Workmen's Compensation law:

[a] Full costs of treatment associated with injuries, including such items as hospitalization, medical care, and nursing services.
(b) Where time was lost from work, time loss (or wage loss) payments up to a certain percentage (normally, 60-70%) of the person's regular salary or wages.

(c) Where a permanent disability or death was involved, pension or death benefits based on actuarial tables.

As there were no claims for benefits under either (b) or (c), these portions of the insurance program were untested. Children (including students under 18 years of age) and unemployed adults (including many students over 18 and most elderly) could expect to receive immediate medical care during the first phase of the insurance program, but subsequent compensation would have been negotiated. This portion of the program was also untested. Finally, the costs of psychiatric care incurred by psychiatric patients as a direct result of participation in research would have been covered.

During the second phase of the program, the greater flexibility provided by self-insurance makes it possible to remove inequities which previously existed in coverage for children and the unemployed, and to align the benefits with those provided to employed adults. Again, however, much of the program remains untested, as there has been only one claim under this phase of the program, and it did not involve such a subject. As a result, the details of benefits to be provided beyond medical and other treatment costs have not as yet been fully developed.

A description of legal and insurance aspects of the plan, including the relation of the program to state workers' compensation programs, to the overall insurance program of the institution, and to other compensation programs or legal remedies available to injured subject. If possible, relevant documentation (e.g., copies of insurance policies) shall be provided. Insofar as possible, the attitudes of the insurance carriers in negotiating and implementing the program (including any problems encountered) shall be described.

During phase one of the program, the insurance was written as an endorsement to the institution's comprehensive general liability policy. The policy for the first year stated only that it covered participation in human experimentation for projects sponsored by the institution. The Workmen's Compensation model was specifically referred to in later versions of the policy and consequently the limitations of that plan became binding (a copy of the endorsement as it was worded for years 2 through 7 is attached hereto as Exhibit B). The initial plan provided first-dollar coverage which continued through year 6. In year 7 a $100,000 deductible clause was added to the policy.

In the second phase of the program, the coverage is included as a part of the University's general liability self-insurance program. The compensation policy (a copy of which is attached hereto as Exhibit C) has been adopted by the University's Board
of Regents, and any claims under the program are paid from reserves which have been deposited in a special self-insurance fund.

During both phases of the program, its distinguishing feature—as compared to other University liability insurance programs—has been its use of the "no-fault" concept; that is, unlike the traditional tort claim process in which the claimant must demonstrate University negligence in order to be entitled to damages, questions of fault or negligence do not enter into the determination of eligibility for compensation. Rather, the claimant must only demonstrate that he or she has suffered an adverse effect as a result of participation in a University-sponsored study.

The program is voluntary from the viewpoint of the subject, who may elect to follow a traditional tort remedy if he or she prefers. Thus, the individual may (or may not) recover more in the way of damages by filing suit, but only if University negligence can be established. By agreeing to accept the benefits provided under the program, the individual avoids the necessity of proving negligence and both parties avoid the cost of litigation.

During most of the first phase of the program, the University encountered no difficulty in maintaining the compensation coverage as part of its comprehensive general liability policy, which is presumably a reflection of the minimal claim experience during that period. The University had the same insurance carrier in years 1 through 7 (Aetna Casualty and Surety Company), and the coverage was included in the annual renewal of the insurance policy, with no real discussion at all in the later years. However, in seeking alternative quotations from competing carriers, the University did find increasing unwillingness to provide the coverage, and by year 7, one bidder (Insurance Company of North America) specifically excluded it from their quotation. It should be stressed, however, that the University's decision to begin self-insuring the program in year 8 was in no sense a consequence of the above-described trend, but was simply a part of the University's over-all transition from commercial insurance to self-insurance for most of its major liability exposures.

The costs of the compensation program and how such costs are determined (e.g., a flat rate, a charge per subject or per subject day of exposure). Are particular protocols rated for risk? If so, do these ratings play any role in the assessment of insurance premiums? Are risky projects excluded from coverage altogether?

During year 1 the cost was 50c per subject. In years 2 through 7 the insurance was a flat rate, estimated to be $35,000—estimated because the figure was not distinguishable from the total cost of the over-all insurance program of the University. How the initial insurer determined the rate is not known.

Protocols are not rated for risk for insurance purposes. For several months in the early 1970s, one of the University's institu-
tional review boards rated the risk of each protocol reviewed (over 80) in an effort to reduce the review time required for annual renewals. This effort did not succeed as it was found that perceptions of risk of the board members varied significantly, even though it was considered a homogeneous group. Assessment of risk has not been a requirement of the insurors, although the average length of time each subject was exposed to risk was provided prior to issuance of the initial policy (see above). Risky projects are not excluded from coverage as these are the ones which contributed most to the concerns which led to the initial procurement of the adverse effects insurance. Adverse effects occurring in risky projects involving patients, however, require special attention in order to establish that the effect is related to a procedure which would not be performed as a normal part of patient management and is not related to the natural course of a disease or of an accident.

Experience with the compensation program

• Number and nature of claims filed

Thirteen claims have been filed against the adverse effects insurance. These are described under REPORT 1 (1 claim); REPORT 5 (4 claims); REPORT 10 (1 claim); REPORT 13 (1 claim); REPORTS 15 (2 claims), 16 (1 claim), 17 (1 claim), 18 (1 claim); and REPORT 21 (1 claim). By the end of year nine, a total of 17 claims had been filed.

• Resolution of those claims within the program

The following indicates the resolution of each claim:

REPORT 1. The insurance company disallowed the claim on a technicality, although other factors could have dictated the same outcome. The company stated "... it would appear that the ultimate amputation of [the claimant's] right leg was the direct result of cardiac catheterization procedure performed in connection with the program within which [the patient] was enrolled and for which apparently a grant had been made to cover all costs. ..." It was not clear whether the grant involved (to the Clinical Research Center) should cover the adverse effect as no stipulation had been made in the insurance coverage for research activities supported thusly. The report was filed some months after the adverse effect. Further, the adverse effect was the result of a standard diagnostic procedure which was indicated even if the patient had not been in the study. Also relevant to the insuror's decision was the fact that a different firm had been selected to provide the University's insurance during the next year. This was the first claim against the adverse effects insurance and the only claim disallowed in the first year history. In the absence of an insurance settlement, the Clinical Research Center covered the costs.

REPORT 5. Three claimants were reimbursed $1,250 for their expenses; the fourth claimant received $1,550.
REPORT 10. Expenses of $410 were paid.
REPORT 13. Expenses of $38 were paid.
REPORT 15. Expenses of $2 and $52 were paid; the costs of hospitalization were covered by the Clinical Research Center.
REPORT 16. Expenses of $25 were paid.
REPORT 17. Expenses of $48 were paid.
REPORT 18. Expenses of $40 were paid.
REPORT 21. Expenses of $249 were paid.

By the end of year nine, a total of seventeen claims had been paid, the largest involving a settlement of $10,000 for adverse effect related to contamination of equipment.

- Disputes regarding those resolutions
  Only the project described in REPORT 1 involved a dispute and in view of the circumstances an appeal was not undertaken.

- Adverse effects for which medical care or financial compensation were provided outside the formal compensation program. the reasons therefore, and how such care is financed or accounted for.

It is known that some medical care and other professional services are provided to subjects who experience both anticipated and unanticipated adverse effects for which no claim is made against the adverse effects compensation program. This fact is reflected in the Status Reports described above. How such care is financed or accounted for is not reported to a central office, therefore this information is not available. The following means are likely: time donated by the health professional; costs absorbed by a grant or contract, as appropriate, e.g. the Clinical Research Center, and reciprocal services provided within the health professions.

- Mechanisms for reporting the incidence of adverse effects to a central office at the institution

Upon approval of a research project covered by the adverse effects insurance, the investigator is informed of the procedure to follow should an adverse effect occur. That is, in the event of an adverse effect which may result in a claim, an Adverse Effect Report should be filed. Further, during the eighth month of the one-year approval period (whether new or renewal), the investigator is sent a Status Report form which requests information on the number and types of adverse effects and on how they were handled. The Status Report covers one year and is requested for all projects including those which have concluded.

Information provided to prospective subjects regarding compensation during the consent process, and any differences in this respect between different projects or types of research. What are the perceived responses of potential subjects to this information?
Do subjects informed of compensation program seem to behave differently from subjects not so informed?

Subjects are not specifically informed about the self-insurance program for adverse effects. As appropriate, they are informed in the consent form that in the event of a physical injury (or illness) as a direct result of study procedures, they will be cared for by a member of the investigating team at no cost (or will be referred for appropriate treatment at no cost). The responsibility for reporting adverse effects and for recovering costs is placed on the investigator. This procedure works effectively because subjects do not then have the added burden of making a report and the concern of recovering expenses.

These procedures for claims against the insurance were established in 1972 and take into account the variations in the Workmen's Compensation model, the annual renewal of insurance required until June 1979, and the cumulative experience on this matter over time.

The rate of pay or remuneration for research subjects and the basis on which this is computed. In particular, is the degree of risk a factor in the calculation?

The University has no established rate of pay for research subjects. The institutional review board considers each application on its merits, with a special concern for undue inducement. The application form submitted by investigators requests specific information on inducements, e.g., payments, services, extra course credit. To date only one alleged adverse effect has been reported which may have been related to the $150 payment to participants. REPORT 12 relates the incident.

Informal comments from investigators indicate that the ability to recruit subjects, which is seldom related to the risk involved, is the factor which influences financial inducements. Blood withdrawal, for example, may provide $10 for a fifty milliliter sample because of the competition for donors.

Financial compensation for participation in research is still not widespread at this institution.

In addition, drawing upon personal experience and knowledge, contractor will advise the Commission regarding preferred or most efficient methods for providing compensation for individuals injured as a result of participating in Federally conducted, supported, or regulated research.*

Whether it is feasible to provide compensation for psychological, social or legal injury and, if so, how such injuries should be defined.

*The following comments represent the opinions of the authors and do not necessarily reflect the opinion of others within the institution. No institutional position has been taken on any of these issues.
While it may be feasible to provide compensation for psychological, social, or legal injury, in general, such a program would go beyond the recognized needs of research. The reports of adverse effects contained herein support this conclusion. The essential element in minimizing problems in these areas is adequate informed consent, which includes all significant risks. The risk of subpoena of research data, for example, is of importance to individuals disclosing personal information on illegal activities.

It may be desirable, however, to arrange a compensation program which makes provision for exceptional claims involving minors and others not competent to give informed consent. Special consideration might be given to meeting their needs in circumstances where an adverse reaction can be directly associated with study procedures. Such consideration suggests that screening procedures for prospective subjects need to be given unusual attention.

What limits should be placed

- **Amount of compensation provided**
  
  In general, institutional policy should determine what limits, if any, should be placed on the amount of compensation provided. As a minimum, however, compensation should be provided for emergency medical care necessitated by an adverse effect resulting from participation in human subjects research.

- **Length of time following participation in research during which claims may be filed**
  
  One year following participation in a research project is generally a reasonable limitation to place on filing of claims; however, reasonable exceptions to such a limit should be allowed. REPORT 14 provides information on a situation for which there should be no time limit. Institutional policy should determine this matter.

- **Persons eligible for payment [e.g., survivors of wage-earner, immediate family, e.g., parents, children of deceased subject who was not a wage-earner; third parties directly and adversely affected by subject’s participation]**

  The basic purpose of the compensation program should be to prevent economic loss to the subject and those who are or may reasonably be expected to become financially dependent upon the subject. Therefore, immediate family members and dependents of a wage-earner who becomes permanently incompetent or is fatally injured as a result of participation in a research project should be eligible for payment; parents of a minor deceased subject or minor children of a deceased subject who is not a wage-earner should also be eligible. Third parties should not be eligible for payments. Details of such coverage should be the responsibility of each institution conducting human research.
Desirability of a nationally uniform policy on compensation of subjects injured in research.

A national policy setting minimum requirements for coverage which individual institutions could voluntarily meet through self-insurance, procured private insurance, or procured national insurance would be acceptable. It is difficult to state that a national policy would be desirable, as a lack of information makes it difficult to assess the impact this would have on institutions performing limited research with few resources.

The type of mechanism which could best implement that policy:
A federal model similar to workers' compensation;
Private insurance through existing insurance companies;
Self-insurance;
Joint insurance pools in which individual research institutions could participate; or
Some other model or combination of approaches.

Assuming a national policy with minimum requirements for insurance, the ideal approach would be to allow each institution to select a suitable plan utilizing self-insurance; joint insurance pools; private insurance; or a federal plan; or a combination thereof. The freedom to select a plan is important in that many institutions will wish to cover injuries for all human research, including that which is not funded by the Federal government, and in that variations in the governance of institutions make a uniform requirement difficult if not impossible to implement. A model program might include procured private insurance with a deductible clause, the cost of which could be covered, if needed, by self-insurance; with a back-up of Federal insurance if the institution judges that the insurer has denied a legitimate claim and the claim exceeds the institution's deductible allowance.

A Federal compensation plan then is desirable, not as a mandatory plan but as an option available for sole coverage or as a backup to another plan. If a Federal model is patterned after Workmen's Compensation, special consideration should be given to unemployed subjects, children, and the elderly.

The burdens imposed on researchers and the institution by the existence of the compensation system and the responses to these burdens over time (e.g., to the extent concerns were expressed at the outset, what has been the effect of participating in the program over a period of years?).

The burdens of the compensation system have been negligible compared to the enormous relief many have felt by the establishment of an insurance plan for human subjects. Indicative of the concern for risks to subjects was the high response rate (80%) to the survey on adverse effects conducted in 1971 (see above). By placing the responsibility for reporting adverse effects
on the investigators, the potential for falsified claims has been reduced to zero. Investigators who are aware of the funding source for the insurance (primarily through indirect costs recovered by the University for grants and contracts) have expressed enthusiasm for this investment. The time-consuming aspects of the program have been the establishment of the initial plan, consideration of the coverage for self-insurance, and responding to inquiries from other institutions.

Perceived ethical obligations of researchers, their sponsoring institutions, or the funding agency, to subjects injured as a result of participation in the research. To what extent are these obligations affected by the presence of absence of negligent behavior by the researcher?

Researchers, sponsoring institutions, and companies which may benefit from the testing of products have an ethical obligation to the subjects of their research. The responsibilities of individual researchers, however, should be limited to providing subjects with a full disclosure of procedures and risks in their oral explanations and in the written consent forms and to providing immediate professional attention, as appropriate, in response to an adverse effect. Reimbursement of expenses and other related payments should be borne by sponsoring institutions and companies. Negligent behavior on the part of researchers should not be provided for through a no-fault compensation program. Professional liability insurance and general liability insurance should provide this type of coverage.
Attachment A

51.08.100 "Injury," "Injury" means a sudden and tangible happening, of a traumatic nature, producing an immediate or prompt result, and occurring from without, and such physical conditions as result therefrom. [1961 c 23 section 51.08.100. Prior: 1959 c 308 section 3; 1957 c 70 section 12; prior: 1939 c 41 section 2, part; 1929 c 132 section 1, part; 1927 c 310 section 2, part; 1921 c 182 section 2, part; 1919 c 131 section 2, part; 1917 c 120 section 1, part; 1911 c 74 section 3, part; RRS section 7675, part.]

51.28.050 Time limitation for filing application or enforcing claim for injury. No application shall be valid or claim thereunder enforceable unless filed within one year after the day upon which the injury occurred or the rights of dependents or beneficiaries accrued. [1961 c 23 section 51.28.050. Prior: 1927 c 310 section 6, part; 1921 c 182 section 7, part; 1911 c 74 section 12, part; RRS section 7666, part.]

51.28.055 Time limitation for filing claim for occupational disease. Claims for occupational disease or infection to be valid and compensable must be filed within one year following the date the worker had notice from a physician of the existence of his or her occupational disease, without reference to its date of origin. [1977 ex.s. c 350 section 34; 1961 c 23 section 51.28.055. Prior: 1959 c 308 section 18; prior: 1957 c 70 section 16 part; 1951 c 236 section 1, part.]

Attachment B

RESEARCH PROGRAM VOLUNTEERS ADVERSE EFFECTS

IT IS AGREED THAT:

(1) If any volunteer participating in an authorized research program conducted by the named insured shall sustain injury, including death resulting therefrom, while participating in such program, the company shall pay on behalf of the named insured an amount equal to the compensation and other benefits which would have been payable under the Washington Workmens Compensation Law had the injured volunteer and the named insured been subject to such law with respect to this program.

(2) The coverage afforded by this endorsement does not apply to injury or death which gives rise to a valid claim under any workmens compensation or occupational disease law.

(3) The benefits payable on account of such injury shall be paid to such person or persons as would have been entitled thereto
under the Washington Workmens Compensation Law, provided, however, that as a condition precedent to any such payment, the injured volunteer, or in the event of his incapacity, his legal representative, or, in the event of his death, his legal representative or the person or persons entitled to sue therefore, shall (1) execute such full and binding release of all claims against the insured and the company on account of such injury or death as may be required by the Company, and (2) assign to the company all claims or judgments or the proceeds thereof which he or they may have or recover against any person who or organization which is or may be liable on account of such injury or death and execute such other documents as the company may require to enable it to enforce such rights or collect such rights under any such assignment in its own name or in the name of the injured volunteer, or to make such negotiations and settlement as may be deemed expedient by the company but the company shall not be obligated to enforce such rights. In the event of any recovery or settlement the company shall pay the proceeds thereof, less payments hereunder and all expenses incident to such recovery or settlement to the person or persons entitled thereto.

(4) If any person entitled to payment under the coverage afforded by this endorsement shall refuse to accept such payment and to comply with the terms and conditions set forth above or if any person shall commence any proceedings at law, in equity or in admiralty, except for such payment, seeking damages from the insured or the company on account of such injury, the company’s liability hereunder with respect to such injury is thereupon terminated.

Attachment C
PROPOSED POLICY ON COMPENSATION
FOR ADVERSE EFFECTS TO HUMAN SUBJECTS
Addition to University Handbook
I. Volume I, Ch. VI (new):
A. APPLICATION OF PROGRAM

The University’s adverse effects compensation program is intended to apply to projects carried out by University personnel and under University sponsorship. To be covered, the project must also be one which has been approved in writing by the University’s Human Subjects Review Committee. The program applies only to adverse effects resulting from the study procedure itself.
B. SCOPE OF COMPENSATION

Compensation under the program is intended to be on a "no-fault" basis (i.e., the claimant need not demonstrate University fault or negligence), and is designed as a substitute for the traditional tort system. It is voluntary from the viewpoint of the claimant, who must agree to give up his or her right to pursue a traditional tort action in order to receive the benefits provided under the program.

The benefits to be provided are as follows:

1. All medical expenses immediately and directly associated with the adverse effect, up to a maximum of $10,000.

2. Such additional expenses or compensation as may be agreed to by the parties.

If the claimant is unwilling to give up his or her right to sue, then the matter will be handled as a traditional tort claim and will be settled or defended on that basis.

C. CLAIM PROCEDURE

If an investigator believes an adverse effect has occurred, he/she shall immediately prepare a report summarizing the background, nature and result of the adverse effect. The report shall be submitted to the Human Subjects Office and the Office of Risk Management, who may consult with representatives of the Attorney General's Division and the Human Subjects Review Committee which reviewed the project involved, in making a determination as to the applicability of the compensation program. If the situation is one for which compensation is appropriate, the Office of Risk Management will arrange for paying the applicable benefits and securing a release from the subject.

If a subject believes an adverse effect has occurred, he or she may independently prepare a report containing the information mentioned above to be submitted to the Human Subjects Office and Office of Risk Management, and a determination as to applicability of the compensation program will be made. If compensation is appropriate, it will be arranged as described above; if it is not, the subject will be so notified. Any such report must be submitted within one year of the occurrence of the adverse effect.
Incidence of Injury During Clinical Pharmacology Research and Indemnification of Injured Research Subjects at the Quincy Research Center

John D. Arnold, M.D.*

Incidence of Injuries

Number of Research Protocols Covered Since the Start of the Compensation Program

Research subjects participating in more than 230 protocols have been covered under the compensation program since its beginning in 1975 (Table I). Roughly two-thirds of the covered protocols have enrolled healthy adult male volunteers, while remaining protocols have enrolled adult male and female volunteers with a variety of pre-existing medical conditions. Representative types of drugs studied within the various protocols have typically been analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antihypertensives, neuroleptics (psychotropic), muscle relaxants, antiarrhythmics and even pesticidal agents. Types of protocols have typically been those having objectives of drug safety, tolerance, pharmacokinetics, and efficacy characteristics within single- and multiple-dose designs, while protocols having objectives of methodology testing, drug excretion characteristics, and the comparison of drugs manufactured by different processes have also been undertaken. Many protocols with safety objectives conducted at the Quincy Research Center have introduced investigational drugs into human subjects for the first time.

Number of Research Participants, Demographic Characteristics, Protocol Completion, and Duration of Participation

More than 5000 normal and outpatient volunteers in roughly equal numbers have participated in Phase I and Phase II through

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August 1980
Compensating through evaluation protocols

Particular protocols and participants' have been derived protocols. Moreover, complaints freely (86.57%) have been (Table I). Participants' have been free, for the most part, come from the general population of Kansas City, Missouri, and surrounding areas.

In general, Phase I participants have been males, 18 to 50 years of age, have not deviated by more than ±10% from the ideal weight for their respective heights and frame sizes, and have been without clinically significant disease in any organ or physiological system at the onset of their research participation. Additional inclusion requirements for various Phase I protocols have typically consisted of no history or current evidence of alcohol or drug abuse, no recent (7 to 30 days) history of taking prescription, over-the-counter (OTC), or investigational medication, and no clinically significant laboratory test results which fall out of the investigator's established normal ranges for the various parameters. Women of child-bearing potential are routinely excluded from both Phase I and Phase II through IV protocols.

Participants in Phase II through IV drug efficacy research have typically been males and females, 18 to 70 years of age with the majority of participants in the 40 to 70 year age range (although one protocol assessed the effectiveness of an anti-allergy medication in children), and have started protocol procedures with a variety of pre-existing health conditions as required by their respective protocols. Various protocols have selected participants who have been diagnosed as having rheumatoid arthritis, osteoarthritis, acute and chronic pain, hypertension, acute and chronic allergies, coryza (cold or flu symptoms), gastrointestinal disturbances, and other clinical significant medical conditions. In many instances, participants have been required by protocol to terminate other drug therapies previously prescribed to control their medical conditions.

Concomitant medications have been and continue to be freely available when necessary during the conduct of research protocols for the management of intercurrent illnesses and complaints secondary to participants' primary medical conditions. Moreover, strict monitoring of participants' health status has been routinely conducted throughout the course of all research protocols, and decisions by the investigator regarding participants' continuation in and completion of protocols have derived solely from ongoing evaluation of participants' state of health.

Data on protocol completion by research participants (Table I) indicate a slightly greater completion rate by normal volunteers (90.41%) in Phase I protocols than by outpatients (86.57%) in Phase II through IV protocols. Numbers of non-completing participants due to reasons of protocol violation, non-compliance, personal reasons and others were virtually identical for normal and outpatient participants, while outpatients not completing protocols due to clinically significant side effects or
other medical problems were more than twice as great in number as their normal counterparts (154 versus 69 non-completers, respectively). Specific clinical events resulting in early termination of normal and outpatient participants from protocols are listed in Table III and are discussed in detail under Descriptive Data on Clinical Events below.

Table I additionally indicates that the duration of research subject participation in compensable protocols was 81,490.5 subject days, including 35,881.5 subject days for Phase I normal participants and 45,609 subject days for Phase II through IV outpatient participants (outpatient duration data were based on 59 of 78 protocols and on 1659 of 2478 participants evaluated as of the date of issue of the present survey; data from remaining protocols and participants are currently under evaluation). The average number of total subject days per protocol was more than three and one-half times as great for Phase II through IV outpatients as for Phase I normals (773.03 versus 239.21 total subject days per protocol, respectively). Moreover, the average number of days per subject per protocol was almost twice as great for outpatient participants as for normal participants (25.93 versus 13.83 days per subject per protocol, respectively). Based on the available data, it is possible to project with some confidence that complete evaluation of remaining outpatient protocols will support the conclusion that the total duration of research participation for outpatients is almost twice as great as that for normal participants.

Descriptive Data on Clinical Events

Clinical events defined. Clinical events, as defined within the context of the present survey, refer to any clinical signs and symptoms reported by research participants or observed by medical staff from the point in time at which participants began pre-protocol procedures until their discharge from respective protocols. Criteria for inclusion of reported or observed events within the present survey were that events (1) must have been recorded in participants' permanent case reports or (2) must have been documented, if occurring after protocol completion, in investigator-sponsored correspondence or in Food and Drug Administration adverse reaction reports (form FD 1639). Primary sources of clinical event documentation, due to the consideration numbers of evaluable protocols, were the clinical investigator's final reports, which traditionally provide a second source of complete event documentation without regard to event triviality or pre-existence and which reliably reflect events recorded in participants' case reports. In the event final reports were unavailable, and for protocols for which particularly significant or peculiar events were noted (for example, refer to Psychological and Social Injuries below), participants' primary case reports
were examined. No further limitations were imposed on the inclusion of clinical events data within the present survey.

Abnormal results from clinical laboratory evaluations (that is, those that fell out of the investigator's normal ranges for laboratory parameters) were not expressly included per se within the definition of clinical events employed in the present survey. Although constituting a potentially rich source of information regarding specific physiological systems responses to drug administration and participation in pharmacology research, laboratory anomalies were not examined due to their volume unless directly instrumental in such participant sequelae as early participant termination from protocols and diagnoses of undiscovered disease states such as hepatitis. A vast majority of abnormal laboratory results did not result in participant sequelae such as these and are, thus, not represented within the survey.

Noteworthy within contexts of ethical obligations to research participants and scientific obligations in the pursuit of high quality research, as perceived by the Quincy Research Center, is the need for strong commitments by clinical investigators to follow-up to resolution any abnormal test results or adverse events experienced by participants. Without regard to test results or clinical event triviality or etiology, all such occurrences have been followed up at this center until stabilized resolution has been achieved or until additional medical sequelae such as hospitalization or additional care and consultation have been required. The Quincy Research Center has provided, and has assumed responsibility for costs incurred as a result of, follow-up clinical laboratory evaluations, therapeutic intervention, and immediate medical care conducted by medical and laboratory staff at the center. These self-insurance costs are calculable but have not been completed within the limitations of available time and resources for the present survey.

It should also be noted that no conflicts between the investigator and research participants are allowed to remain unresolved regarding responsibilities for additional, non-immediate, medical work not required by protocols. When clinical events have been determined to be related neither to drug administration or to protocol participation, participants' private health insurance has been requested to cover these additional costs. When events have been shown to have some degree of drug- or participation-relatedness, the center has assumed responsibility for costs. When events have been neither drug- nor participation-related and the participant has had no private insurance, compassionate assumption of costs by the center has occurred. In some instances, such costs assumed by the center have been reimbursed by sponsoring pharmaceutical companies.

Original data collection procedures. In general, original data collection procedures differed slightly for normal and out-
patient participants. Phase I protocols with objectives of drug safety, tolerance, pharmacokinetics and others have been conducted in normal participants who have remained cloistered at the Quincy Research Center for the duration of their respective protocols. Protocol durations have typically ranged from 4 to 6 hours for some bioavailability studies to as much as 10 weeks for more complicated studies requiring chronic dosing. While inhouse, normal participants remain under 24-hour observation by professional medical staff. Overt clinical events are, therefore, immediately observable and verifiable. By contrast, most Phase II through IV protocols are conducted on the basis of outpatient participant visits to the testing facility at periodic intervals, typically weekly or bi-monthly although some exceptions occur, over durations of up to two years. Clinical event documentation for outpatients relies, therefore, on participant recall of events during the previous interval and, for some protocols, daily event diaries completed by participants. Confirmation of these events is not possible unless accompanied by overt abnormalities noted during participant visits via clinical laboratory work, physical examinations, or specific physiological systems reviews.

Evaluation strategies. For the purposes of the present survey, specific strategies with regard to clinical event evaluation were necessary. To insure comparability of data reflecting incidence of clinical events with data on subjects' duration of participation, frequencies of clinical events were tabulated on an event per day basis. Thus, if a research participant complained of nausea, vomiting, two headaches, and four loose stools during a single non-directive interview for occurrence of clinical events, frequency counts for the four separate event categories were incremented by 1.1, 2, and 4 instances, respectively. If a participant complained of an intermittent headache throughout a 20-day trial, frequency counts for headache were incremented by 20 instances.

Secondly, comprehensive protocol evaluation, including all data categories as listed in Table I through VII, has been conducted to the extent possible as of the date of issue of the present survey. Several protocols, particularly those employing outpatient participants, have yielded less than complete sets of data. Thus, while 147 of 153 (96.1%) completed Phase I protocols and 2573 of 2596 (99.1%) normal participants have yielded highly specific data on the incidence of clinical events, 49 of 78 (62.8%) completed Phase II through IV protocols and 118 of 2478 (4.8%) outpatient participants have yielded clinical events data (Table II). Where appropriate, numbers of protocols, participants, and total subject days upon which event incidence data are based are clearly indicated. Results of the present survey may be viewed as virtually complete and conclusive for Phase I normal participants but as yet tentative and, therefore, only suggestive for Phase II through IV outpatient participants. Comparisons between nor-
Compensating for Research Injuries: Appendix I

mals and outpatients have been made for heuristic, rather than definitive, purposes.

Additionally, the development of a comprehensive data base and resultant breakdown of clinical events into separate physical or physiological categories by treatment groups or periods (i.e., drug vs. placebo) has not been possible within the context of the present survey. Where the occurrence of clinical events (e.g., nausea, vomiting, hepatitis, elective surgery) resulted in such participant sequelae as early termination from protocols, death, hospitalization, participant referrals for additional medical care and consultation, or therapeutic intervention, or such protocol sequelae as early termination of the protocol or alteration of the experimental design and/or drug administration schedule, these clinical events have been specified. Otherwise, simple frequency counts of undifferentiated clinical events were made.

Clinical events: incidence and descriptive data. As Table II indicates, a total of 12,391 clinical events have been reported by 3772 normal and outpatient participants in 196 evaluated protocols since the start of the compensation program at the Quincy Research Center. Normal and outpatient participants taken together, clinical events incidence data are available from 65,089 subject days of participation.

Based on the available data, average numbers of clinical events per protocol were almost twice as great in outpatients as in normals (98.02 vs. 51.62 events per protocol, respectively), while numbers of events per participant were 35% greater in outpatients than in normals (4.01 vs. 2.95 events per participant, respectively). Interestingly, additional descriptive data revealed that, on the average, a single clinical event was reported by normal participants for about every 5 subject days of participation, while a single outpatient event was reported for about every 6 subject days of participation.

Significant clinical events with sequelae. Table II [item C] indicates the numbers of more significant clinical events noted during and subsequent to the conduct of research protocols which resulted in various participant and protocol sequelae. In general, these data support the conclusion that the conduct of Phase II through IV protocols is inherently beset by greater incidences of primary disease states in outpatient participants by reason of efficacy testing objectives which require pre-existing disease states in selected participants, in all likelihood, by reason of the greater average duration of research participation, and by reason of the more advanced age of these participants. It is probable that the presence of these primary disease states was instrumental in producing greater numbers of early participant termination from protocols, death, and hospitalization. Secondly, descriptive data on participant referrals for additional medical
care and consultation as well as data on early termination of protocols and protocol design alteration tentatively support the conclusion that many clinical events occurring during the conduct of Phase I protocols result from toxicity of new investigational drug entities at this early stage of drug research in human subjects.

Although normal and outpatients volunteers in roughly equal numbers both (1) participated in research protocols and (2) terminated early from protocol participation by reason of non-compliance, protocol violation, etc., more than twice as many outpatients as normals failed to complete their respective protocols by reason of the occurrence of clinically significant side effects or other medical problems (Table I). Table III lists numbers of normal and outpatient participants who terminated from protocols early due to similar clinical events, due to dissimilar clinical events, and due to as yet undefined clinically significant side effects or other medical problems. Although definitive conclusions regarding participant termination data await the full description of undefined events, the trend in the data appears to clearly indicate the prevalence of complications for the conduct of outpatient protocols arising from the presence of primary, probably pre-existing, disease states. Discovery during clinical trials of such outpatient complications as the presence of malignancies, events requiring elective surgeries, diverticulosis, poly-myalgia, biliary colic, hypertensive crisis, congestive heart failure, flare arthritis, the need for bilateral knee replacement, and cerebrovascular accident (stroke), and the relative paucity of similar events serving to complicate Phase I trials in normal participants, appears to define a clear trend of greater complications from disease states neither drug- nor participation-related.

Data reflecting the greater numbers of serious clinical events in outpatients than in normals resulting in death (Table IV) or hospitalization (Table V), while of low apparent incidence in outpatients (0.24% and 1.43%, respectively), document the extent of complications arising from the presence of primary disease states. All participants who expired during the conduct of their respective protocols had received investigational medications for periods of time ranging from approximately 3 days (one patient who committed suicide: no evidence is available to indicate that this patient actually took drug) to more than 2 years. None of these events were thought to be drug-related by the investigator, the pharmaceutical sponsors for respective protocols, or consultant physicians and pathologists not otherwise associated with the testing facility. The available data suggest that the incidence of occurrence of death from probably pre-existing disease states may be as high as one death for every 12 protocols or 413 outpatients.
Events requiring outpatient hospitalization also appear to reflect the presence of primary disease states in older participants, significant medical events to which the great majority of younger, normal, Phase I participants are not subject. Only 7 of 30 specified events requiring hospitalization of outpatients (5 instances of gastrointestinal problems and single instances of hematuria and syncope associated with black stools) could conceivably, though not definitely, be related to drug administration or to participation in protocols. By contrast, 3 of the 5 events resulting in hospitalization of normal participants (single instances of drug rechallenge, extrapyramidal symptomatology, and seizure) could have conceivably been drug- or participation-related. Available data suggest that the incidence of events requiring hospitalization of outpatients may be as high as one hospitalization for every 2.17 protocols or 68.9 outpatients. By contrast, hospitalization of normals appears to have occurred at an incidence of one hospitalization for every 30.2 protocols or 519.2 normal participants.

Single instances each of outpatient participants' disability and loss of work time were noted during the survey, while no similar events were noted for normal participants (Table II). Clinically significant opacities were detected in both eyes of one outpatient; this event was subsequently followed by the award of a temporary total disability status to the individual by the Veterans Administration and was not drug-related. One outpatient's loss of work time was due to shakiness and unsteadiness upon standing, an elevation in heart rate, and lightheadedness. These events were not thought to be drug-related.

A second suggestion is apparent from data on significant clinical events with sequelae. Descriptive data regarding referrals of participants for additional medical care as a result of significant clinical events indicate that referrals were greater in number for normal participants (53 referrals) than for outpatients (28 referrals). If the direction and magnitude of this comparison persist through completion of the survey of research protocols, the data may support the intuitive conclusion that Phase I protocols expose normal participants to greater risks of possible toxicity reactions to new investigational drug entities, resulting in the greater incidence of clinical events requiring additional medical care and consultation for normal participants than for outpatient participants. Of possible heuristic value is the finding that 10 of the 28 outpatient referrals indicated in Tables II and IV were noted during evaluation of the 49 completed outpatient protocols (including 1199 outpatients) which have provided specific incidence and descriptive data on clinical events; of the 18 remaining referrals, 10 referrals have been noted during preliminary evaluation of current outpatient protocols. Thus, if the same incidence rate of occurrence of outpatient referrals persists throughout remaining protocol evaluations, few additional such referrals would be expected.
Stronger support for the suggestion of greater Phase I drug toxicity effects is apparent from descriptive data on clinical events resulting in early termination of research protocols and in intra-study alteration of protocol designs and/or drug administration schedules (Table II). Eleven (11) of 153 Phase I protocols were either terminated or altered due to significant drug-related clinical events (7.2% of completed protocols), while a single Phase III protocol was similarly terminated (1.3%). Clinical events producing these protocol sequelae included the appearance of bizarre behavior and behavioral patterns in one instance associated with severe headaches, nausea, vomiting, and gastrointestinal disturbances requiring significant therapeutic intervention (3 protocols; refer to Psychological and Social Injuries below), severe orthostatic hypotension (2 protocols), complexes of clinical events including sedation, dizziness, lightheadedness and, in one protocol, associated nausea and significant changes in cardiovascular parameters (2 protocols), and single instances each of significant anticholinesterase activity (due to dermal application of a pesticidal agent under conditions of high temperature and humidity), significant inhibition of platelet aggregation activity, severe dystonia, and severe gastrointestinal disturbances including diarrhea, nausea, and vomiting. Early termination of the single Phase III protocol occurred due to severe gastrointestinal disturbances. Interestingly, early termination or alteration of Phase I protocols did not appear to be associated with instances of hospitalization of normal participants since only a single subject who had participated in an altered protocol was eventually hospitalized; the reason for this action was to rechallenge the subject with drug doses previously administered to him during the protocol. Hospital charges for this drug rechallenge (more than $1200) were assumed by the pharmaceutical company that sponsored the original protocol. By contrast, 34 events requiring therapeutic intervention and 4 events requiring additional medical care and consultation were noted from terminated or altered Phase I protocols. One outpatient from the single terminated Phase III protocol required both additional medical care and consultation as well as hospitalization for ulcer.

Table VII lists significant normal and outpatient clinical events for which, in the investigator's judgment, therapeutic intervention was required. No definitive conclusions may, as yet, be drawn from these data. It may be noted, however, that therapeutic medications drawn from the investigator's clinical supplies were employed to resolve these events and that participants were not charged for these costs.

Psychological and Social Injury
A wealth of objectively definable and measurable physiological information is currently available which may be brought to bear on the problems of defining actual and predicting
potential physical injury to research participants. Moreover, much is known regarding therapeutic control of such injuries. By contrast, little information is available to facilitate definitions of, and indicate therapies for, psychological and social injury to participants in research.

Throughout the recent 40-year period of rapid and substantial growth in the pharmaceutical industry, the successful development of new drugs and therapies to alleviate human suffering and control disease states has been predicated primarily on safety and tolerability characteristics of new drug entities as well as their efficacy. Current operational definitions of drug safety and tolerance draw heavily from both objective physiological evaluations, including results of clinical laboratory examination of blood, urine, fecal, and tissue specimens, and physicians' findings on physical, electrocardiographic, electroencephalographic, ophthalmologic, audiographic, and vestibular and nervous system evaluations, and subjective reports by research participants of adverse and other clinical reactions to drug administration. Comparisons of objective results with existing physiological data bases and normal ranges have been, in part, instrumental in determining safety and tolerance characteristics. Comparisons in attempts to infer drug safety and tolerance characteristics from subjective participant data, however, have been limited due to lack of comprehensive data bases and reference, or normal, values. Thus, in light of current objectives regarding indemnification programs for injured research subjects, a strong need exists to develop such reference data bases for clinical events experienced by subjects as well as the conceivably more subtle and extensive psychological and social effects of investigational drug administration and research participation.

Several incidents documented at the Quincy Research Center since 1975 may serve to indicate areas of concern that are conceivably psychological and/or social in implications. Incidents have been identified that appear to derive directly from drug administration or indirectly from participation in research in a cloistered environment. Contextual foci of concern regarding direct and indirect effects of protocol participation are individual research participants themselves, clinical investigators and staff at research institutions, immediate families of research participants, and society in general.

During the conduct of a phase I crossover bioavailability study of 3 preparations of the same potent anti-psychotic medication, in addition to subject complaints of mild to severe sedation, many complaints related to anxiety or depression (including restlessness, nervousness, tenseness, and jittery and fidgety behavior) were noted throughout the study. Moreover, several instances of strange behavior or behavior possibly indicating confused and/or disoriented thinking or abnormal mental states were noted. Nine subjects could not complete the study due to
these effects, and 5 subjects were given a Benadryl antidote for selected symptoms. One subject became impatient and angry within 2 hours post-dose and became anxious and left the center shortly thereafter against the strongest of medical advice stating "I've got to go." A second subject reported headache, complained of being cold, became very angry and irritable, and fled the center against medical advice on his motorcycle within two and a half hours after drug administration. This subject was located by phone at home later that evening; he explained that he did not know what came over him, that he had become very angry and felt compelled to leave the center. A third subject stated that he became very angry within 2 hours after drug administration and felt that he "wanted to hit someone" but did not know why. This subject was given the Benadryl antidote but failed to return to complete the protocol. A fourth subject complained of feeling drowsy, jittery, uncoordinated, ill at ease, and subsequently became severely sleepy and fell asleep in bed with a cigarette burning in his hand. A fifth subject, within 2 hours post-drug, complained of severe anxiety and involuntary sexual arousal requiring masturbation for relief. The medical staff noticed involuntary torticollis (without muscle spasms) and trunkal dystonia, and the subject later stated "no one understands what is happening to me" and failed to return to the center to complete the protocol. A sixth subject voiced no complaints after the initial dosing but was found to have disappeared from the center sometime during the day. A phone call made to the subject's home was answered by his mother who was very anxious and would not allow staff to speak with him. The subject had told his mother that "the drug was just too much" for him.

The above example is extreme and does not represent the vast majority of protocols conducted at QRC but illustrates direct drug effects that have both physiological and psychological components. Of concern both for ethical and, hypothetically, compensation purposes were the research participants themselves (due to anxiety, depression, other individual symptoms, and falling asleep in bed while smoking), the investigator and staff of the center (due to one subject's potentially aggressive behavior), the immediate family of one participant (due to the perception of actual or potential harm to the participant from investigational drug ingestion), and society in general (due to one subject's fleeing the center via motorcycle).

The conduct of two additional protocols employing normal participants and a benzodiazepine compound known to have potent sedative, hypnotic, and anti-convulsant properties illustrates additional events which have potential psychological and social implications. Within one protocol, one man who received drug exhibited unspecified bizarre behavior, was uncooperative and hostile, and had to be isolated from the other participants in this study reportedly due to their resentment of his behavior. Two additional subjects showed high anxiety levels during par-
Compensating for Research Injuries: Appendix I

Participation that were attributed to marital problems and stressful, personal relationships. One of these men had shown considerable adaptation problems at the onset of the study and also seemed to show separation anxiety prior to his discharge from the center. During the study, he was restless and over-reactive and seemed to experience considerable difficulty in controlling his impulses. The other man showed many signs of social mal-adjustment, felt isolated, had low self-esteem, and seemed depressed. Three other subjects reported weird or vivid dreams, while one subject lost consciousness at 60 hours post-drug and had a tonic-clonic seizure which lasted about four minutes. Follow-up evaluation revealed no repetition of the event or any other abnormality.

Five days after completion of the second protocol, one subject who had received drug was in a bar and had been drinking an unspecified amount of alcohol when he became uncomfortable and began to stagger. Within the next half hour, the man had two seizure episodes and was confused and disoriented but responsive in the interim. Electroencephalographic evaluation was found to be normal without epileptiform activity. These incidents represent particularly difficult problems both for the subject and for the clinical investigator. First, this episode occurred after the man had been discharged from the center. Its description thus depended on the recollection of the subject and on the observations of his companions. Second, the seizure occurred five days after this person had stopped taking the investigational medication, and the investigator could not obtain any reliable information regarding products other than ethanol which the subject might have taken during this period. Third, the seizure apparently occurred while this man was drinking, but the amount of alcohol ingested was unknown. The delay between discontinuation of the investigational medication and the seizure, and the occurrence of the seizure while drinking, would suggest that the seizure probably was neither a withdrawal reaction nor a direct drug effect. The lack of reliability of the observation and the many uncertainties surrounding its possible causes make it difficult to draw a firm conclusion regarding this episode. Nonetheless, the episode is of considerable concern because it occurred in relatively close temporal association with the ingestion of investigational drugs. The episode also dramatically illustrates a situation that may be termed the "long chain of events" problem faced by clinical pharmacology investigators potentially in every instance in which investigational materials are given to research subjects. This problem is not new to clinical investigators.

Additional incidents document strongly social implications for research participants’ lives and lifestyles outside the confines of the testing facility and often force consideration of the “long chain of events” problem within the context of both ethical and compensation obligations to research subjects. While there are
substantial advantages to the use of cloistered, non-institutionalized, normal volunteers during early stages of drug research, as described elsewhere (John D. Arnold, M.D., Alternatives to the Use of Prisoners in Research in the United States. Paper prepared at the request of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research), incidents described below reveal the potential for grave social risks and injury due to "career" normal participants' habituation to the research job and the possibly-related development of certain risky lifestyles. In general, the class of normal volunteers who participate in research at the center are either chronically or periodically unemployed, do not have bank accounts, are typically accustomed to dealing with financial matters in cash only, and, upon their discharge from protocols, typically cash their honorarium checks immediately at local banks. A situation such as this renders discharged participants particularly vulnerable to assaults and crimes against them both from individuals unknown to them and from acquaintances who have also participated in research at the center. One such instance of the latter type, in which one participant was killed during a robbery attempt by another participant within hours after their discharge from the same protocol, caught the center by complete surprise.

As a result and in an attempt to cut the "long chain of events" of potential indirect responsibility of the center for future occurrences such as this, participant selection procedures were modified to more effectively screen out volunteers having abnormal or incompatible current mental states of health regarding research in a cloistered environment and anti-social tendencies or behaviors and personality disorders.

Several incidents documented during or subsequent to the conduct of Phase II through IV protocols employing outpatient volunteers may be no less dramatic than those cited above and indicate different areas of considerable concern to the clinical investigator, one of the most predominant of which is associated with outpatients' primary disease states (physical and, presumably, otherwise). As described under Significant clinical events with sequelae, two outpatient participants who had received investigational medications took their own lives. According to expert medical opinion, these events were, in all probability, not related to drug administration; however, the presence of the pharmaceutical companies, the drug testing facility, and the presumed ingestion of investigational medications in chains of events leading to these two suicides are unmistakable. Thus, although rigorous and multi-faceted participant selection procedures are routinely employed by the Quincy Research Center to enroll only those volunteers, both outpatients and normals, determined to be most fit for research participation, the pre-protocol detection of precursor or pre-existing disease or mental states such as these may quite simply exceed the capabilities of any selection process.
Additional notable outpatient incidents included a threat of suicide, a statement by one outpatient to the effect that she thought she was being poisoned by the investigational drug she was taking, an antagonistic letter written to the clinical investigator demanding reimbursement for medical expenses and mileage incurred by reason of a secondary disease state, and concern overtly expressed by the family of one outpatient regarding the patient's use of investigational drugs.

Summary and Discussion: Incidence of Injuries

More than 230 research protocols with more than 5000 normal and outpatient participants have been completed at the Quincy Research Center since indemnification coverage for injured participants via self-insurance or standard workmen's compensation was instituted in 1975. Roughly equal numbers of normals and outpatients have participated in research consisting of almost twice as many Phase I protocols having safety, tolerance, and pharmacokinetic objectives as Phase II through IV protocols having drug efficacy and other objectives. Thus, the average number of participants per protocol was almost twice as great for outpatient protocols as for normal protocols. Additionally, the duration of outpatient participation in total subject days was found to be, via projection, almost twice as great as that noted for normal participants.

The incidence of protocol non-completion by participants was greater in outpatients than in normals (13.43% vs. 8.59%, respectively). Since virtually identical numbers of outpatient and normal participants did not complete their respective protocols for such reasons as protocol violation, non-compliance, loss of interest, and lack of drug efficacy (Phase II through IV protocols only), differences between subject populations in incidence of protocol non-completion were due to the greater occurrence of clinically significant side effects or other medical problems in outpatients than in normals. Additional data available to date tentatively suggested the greater prevalence of other medical problems rather than drug- or participation-related side effects in producing early outpatient termination from research protocols. By contrast, physical effects of drug administration or protocol participation appeared more prevalent as reasons for early normal participant termination of protocols.

Regarding data which represented the undifferentiated incidence of clinical events, three related findings were noteworthy. Numbers of clinical events noted per protocol were almost twice as great for outpatients as for normal protocols. It appears likely that this finding may reflect, for the most part, both the greater duration of outpatient participation in protocols and the greater number of outpatient participants per protocol. Secondly, the number of clinical events per participant was 35% greater, on the average, for outpatients than for normals, tentatively yet inte-
itively suggesting that duration of research exposure is indeed associated with the frequencies of occurrence of clinical events. Thirdly, clinical events did not appear to occur relatively more frequently in outpatients than in normals, since, on the average, one clinical event for approximately every 6 outpatient days of participation were noted, while one clinical event for approximately 5 normal days of participation were noted.

Based on undifferentiated incidence data on clinical events alone, one might easily draw the conclusion that normal and outpatient participants do not substantially differ in their clinical responses to investigational drug administration and/or research participation. Additional data extracted during the present survey, however, suggest that any conclusion of no differences in response of the two separate populations of participants would be erroneous. The available data on significant clinical events with participant and protocol sequelae support the conclusion that the incidence of drug- and participation-related events is higher in Phase I protocols employing normal participants by reason of heretofore undiscovered drug effects that are toxic to a greater or lesser extent to human subjects. By employing normal adult male subjects for the conduct of Phase I protocols, these events were more easily and immediately resolved via therapeutic intervention and additional physician consultation and resulted in a minimization of the amount of actual risk to participants and additional sequelae such as early termination from protocol and/or hospitalization. Thus, Phase I data indicate that normal male participants were able to tolerate the ultimate hazards of early Phase I drug testing without serious sequelae, as evidenced by findings of no deaths and few hospitalizations but increases in participant referrals for additional medical care and physician consultations. We believe the same drug-related complications would have been fatal or very serious in ill outpatients.

Additionally, available data supported the conclusion that the incidence of clinical events having probable etiologies of primary, pre-existing, disease states is higher in Phase II through IV protocols employing outpatients and that these complications inherently beset the clinical investigator and the conduct of outpatient protocols. The occurrence of serious and significant clinical events such as death and hospitalization was more numerous in outpatients.

In addition to incidence and descriptive data on the occurrence of clinical events during the conduct of normal and outpatient protocols, the present survey also suggested several areas of concern regarding the potential for psychological and/or social injuries as a result of drug administration and protocol participation. Several actual incidents conceivably having either direct or indirect psychological or social implications were explicitly described in an attempt to indicate the scope of these concerns and implications on the basis of experiences at this
center. No conclusions are warranted from these data due to the current lack of definition of circumstances constituting psychological or social injury, the lack of existing and comprehensive data bases and normal, or reference, “values,” and definite information regarding the potential for therapeutic control of such events. Nonetheless, it is felt that the occurrence of such events within the experience of the Quincy Research Center, given the numbers of protocols undertaken and participants enrolled, necessitates significant consideration within the context of the development of any nationally uniform program for indemnification of injured research subjects. Areas of concern are not only research participants themselves but also clinical investigators and staff at research institutions, immediate families of research participants, and society in general.

To date, it has been possible to resolve questions of liability for indemnification for serious clinical events, and no conflicts regarding causes of these events remain unresolved. When it was possible to determine that clinical events were neither drug- nor participation-related, participants' private health insurance coverage was invoked to assume responsibility for costs of significant sequelae. In the event private insurance was not available, compassionate assumption of responsibility for costs of sequelae was undertaken under the rubric of self-insurance by the Quincy Research Center. When it was possible, on the other hand, to determine that events were conceivably drug- or participation-related, the self-insurance program in effect at the center assumed responsibility for costs of sequelae. In some instances, sponsoring pharmaceutical companies have reimbursed the center for these costs. To date, staff at the center are aware of no instances in which the center's indemnification program has been used by participants in an exploitative manner.

Indemnification of Injured Research Subjects

Description of Compensation Program

The Quincy Research Center (QRC) provides medical care and indemnification for injured research subjects via a “two-tiered” combination of self-insurance and standard workmens' compensation coverage. Workmens' compensation coverage has been in effect since 1975 for Phase I normal participants and since 1978 for Phases II, III, and IV outpatients, while QRC has provided medical care under the self-insurance concept for all research participants since 1975.

The availability of standard workmens' compensation coverage for research participants is provided via the classification of these individuals as employees of QRC by virtue of subjects' meeting employment criteria as defined by Missouri State Workmens' Compensation law. By law, an employee is defined as a
person who is employed by the same employer for more than five and one-half consecutive work days. QRC has applied for and received confirmation of employee status for research subjects who participate in studies of shorter length or in studies requiring outpatient visits at intervals.

As employees, research participants retain all rights and compensation privileges for employment-related injuries, diseases, disability, and death accorded employees under Missouri State Workmens' Compensation and Occupational Disease laws. Coverage available includes complete (i.e., $0 deductible) medical care and hospitalization for injuries suffered as a result of, or aggravated by, participation in clinical pharmacology trials. Disability income in the event of temporary or permanent injury resulting in loss of actual or potential wage-earning ability, and survivors' benefits should death occur. No dollar limitation on available coverage exists for medical care and hospitalization, while disability income and survivors' benefits are available at two-thirds the regular weekly income of the injured subject to a maximum of $125.00 per week. Moreover, under Missouri state law, workmens' compensation coverage provides for arbitration, and does not require litigation, in settlement of claims.

Under the standard workmens' compensation program as currently written for QRC, the premium costs of coverage are determined as a multiplicative function of a standard rate per $100 remunerated for separate classes of employees and the total annual dollar amount of remuneration for classes of employees. These standard rates for research subjects as employees are approximately twice as great as those for physicians and consultants, approximately five times as great as those for clerical office employees, slightly less than one-third as great as those for chauffeurs and drivers, and approximately equal to those for analytical chemists. The approximate equivalence of research participant employees and analytical chemists was established via consistency in terminology describing characteristics of analytical chemists for compensation purposes and characteristics of research participants as recommended by the Missouri State Insurance Commission.

Definition of research qualifying for coverage. Within the workmens' compensation program in effect at QRC, no explicit differentiation regarding availability or costs of coverage is made for different categories of research subject (e.g., Phase I normal vs. Phases II, III, and IV outpatients), different categories of research (i.e., therapeutic vs. non-therapeutic, biomedical vs. behavioral) or for different categories of investigational treatment effects (e.g., anticipated vs. unanticipated). Thus, there are no explicit categorical exclusions to coverage for research-related injuries.
Events for which compensation is provided. The workmen's compensation program provides for compensation for physical injury, disability and death via accident or disease caused or exacerbated by, or during the conduct of, employment-related activities. No explicit provisions, nor exclusions, are made within the workmen's compensation system for injuries that could conceivably be described as psychological or social in nature. The Missouri State Workmen's Compensation law includes a statute, however, that requires that all provisions of the law shall be liberally construed with a view to the public welfare. According to the insurance carrier, definitions of and actuarial data regarding psychological injuries are lacking; nonetheless, awards for psychological injuries under the Missouri State Workmen's Compensation system have been made. By contrast, "pain and suffering" or other non-economic loss is, in the opinion of the insurance consultant, not compensable.

Time limitations on filing of claims. Claims requesting compensation for employment-related injuries must be filed within 2 years or in some cases within 5 years of the date of discovery of the injury. This statute of limitations becomes effective August, 1980.

Other restrictions or limitations on recovery. Death resulting from employment-related injury or sequelae is compensable if occurring within 300 weeks after the injury; if the basis of a claim for compensation for death is occupational disease, the 300-week limitation is not applicable. Gross misinformation or falsification of medical history by subjects or disregard of the physician researcher's directives regarding concomitant use of alcohol or other drugs renders questionable the compensability of a resultant injury. Compensability of claims made under such circumstances is determined by Missouri state compensation authorities. In the absence of mitigating circumstances, compensation is not available for self-inflicted injury or disease or for death or disability caused, continued, or aggravated by unreasonable refusal of medical or surgical care. Where injury or disease is caused or aggravated by failure of the employer to comply with state safety statutes, 15% additional compensation is required. Where such events occur as a result of willful failure of the employee to use safety devices or obey reasonably enforced safety regulations, a 15% reduction in compensation is required.

Although QRC does not routinely allow participation in clinical pharmacology trials by females of child-bearing potential, Missouri state compensation laws do not explicitly exclude these individuals from coverage.

Methods for computing compensation amounts for specific injuries or classes of research participants. Methods of
computing amounts to be paid to injured research subjects as employees of QRC are set by state law once subjects' specific type-of-employee classification has been determined. Amounts paid to injured research subjects are thereby determined within the framework of the state workmens' compensation system and in an identical fashion to that in determining compensation for injured professional and ancillary QRC personnel. Children employed as research subjects are compensated as adults under state workmens' compensation laws except that consideration of additional compensation is provided by law for the increased earning power of the minor until attainment of the age of twenty-one and in all cases where the minor has been knowingly employed in violation of state child labor laws. In the latter case, fifty percent additional compensation is allowed.

The Missouri State Workmens' Compensation law provides for no separate compensation system for students, the elderly, other non-wage earners, or for seriously ill patients. For all employees, compensability of pre-existing illnesses depends upon whether or not these events are aggravated or exacerbated by reason of employment or participation in research at QRC.

Description of Legal and Insurance Aspects of Compensation Program

The standard workmens' compensation policy provides all compensation and other benefits required of QRC by the Missouri State Workmens' Compensation law. In the opinion of the insurance consultant, the private insurance industry currently has capabilities and resources to provide compensation plans which meet any current or potential federal standards regarding experimentation on human volunteers. Specifically, once it was determined that research subjects and the clinical investigator jointly met minimum criteria defining employer-employee relationships, the development of an indemnification program became a relatively simple matter within the framework of state workmens' compensation and occupational disease statutes. As such, the availability of workmens' compensation coverage for research subjects conforms to requirements of present guidelines on research in human subjects and satisfies ethical obligations of investigators to participants, positions investigators within the law should the judicial system later confirm the validity of the employer-employee relationship between investigator and research subject, provides a release for QRC and the insurance carrier from liability for claims for injuries, disability, or death compensable under the program, and provides for settlement of claims via arbitration, thereby limiting litigation.

Costs of the Compensation Program and How Costs are Determined

Under workmens' compensation coverage, yearly premium rates are based on the total annual remuneration by QRC for
separate classifications of employee, premium rates per $100 re-
muneration established for separate classifications of employee
by the Missouri State Insurance Commission, and an "experience
modification" factor which can adjust insurance premiums
according to the ratio of premiums paid the carrier to losses by
the carrier resulting from payment of claims. Within the work-
mens' compensation program, comparative risks of separate pro-
tocols or procedures play no role in the assessment of insurance
premiums. Particularly risky protocols are covered no differently
than minimum risk protocols.

Experience with the Compensation Program
Since workmens' compensation coverage was originated in
1975 for Phase I "normal" volunteers and in 1978 for Phase II
"patients," no claims have been filed with the Missouri State
Workmens' Compensation Commission for subject indemnifica-
tion. By contrast, since 1977, thirteen workmens' compensation
claims have been filed for injuries to traditionally-defined pro-
fessional and ancillary employees. Instead, QRC has chosen to
provide medical care for injured subjects outside the compensa-
tion program and under the rubric of self-insurance; costs
incurred under self-insurance have been accounted for under
general overhead. These costs are calculable but have not been
completed due to time and resource limitations for the present
survey. Limited data available from early 1977 to date show that
self-insurance costs for Phase I protocols were $1977.64, while
those for Phase II through IV protocols were $1110.87.

For the large majority of subjects who have required medical
care for events occurring during or shortly after participation in
clinical pharmacology trials, these events have typically been of
little real harm to subjects, have not required hospitalization or
extended medical care, have proved to be of little or no threat to
subjects' ability to return to regular employment, and have typi-
cally been easily and immediately resolved by professional med-
ical staff at QRC or by consulting physicians. Contributing factors
to the success of the self-insurance approach have been (1) strong
commitments to subjects' welfare which in all cases have estab-
lished that ethical obligations to research participants are no less
important than those to traditionally-defined employees and are
no less important than scientific obligations in the pursuit of
quality research, and (2) the immediacy and specificity of resolu-
tion of these events.

Information Provided to Prospective Subjects Re-
garding Availability of Compensation for Injuries
As now provided for under FDA guidelines regarding in-
formed consent of volunteers for participation in research, QRC
informs prospective subjects of the availability of medical treat-
ment, a compensation plan for coverage of medical expenses.
and reimbursement of lost wages in accordance with Workmens' Compensation provisions, as follows.

Should medical problems arise out of the study, treatment is available and necessary expenses will be paid in accordance with Missouri's Workmens' Compensation law. Loss of wages that results from these problems would also be reimbursed in accordance with Workmens' Compensation provisions.

This information is provided to all volunteers regardless of differences in types of research.

Few participants ever respond in any way to this information, and, of those that do respond, the most frequent question is "will I get hurt?".

Statements reflecting availability of medical treatment and coverage for medical expenses have been made to research volunteers since the earliest days of QRC operations; therefore, it has not been possible to observe behavioral differences in informed subjects and patients versus those not so informed.

Rates of Remuneration for Research Subjects

Research subjects are paid "honorariums" for their participation in clinical trials at QRC which differ in amount depending on (1) degree of responsibility of the subject to the research program, (2) implicitly, the kinds and frequencies of procedures subjects must undergo during trials, and (3) current understanding of the safety and tolerance of investigational drugs to be administered. Elevations in honorariums for Phase I normal subjects are typically provided in attempts to ensure subjects' compliance with and completion of procedurally complicated and lengthy protocols, protocols assessing bioavailability and pharmacokinetic parameters where the invasiveness of procedures employed is substantial, protocols which for the first time assess safety and tolerance of new investigational drugs that have never before been administered to human subjects, and protocols for which, in general, the ratio of benefits accrued by subjects to inherent procedural and conceivably drug-related risks involved is low. By contrast, honorariums are lower for Phase II through IV studies of investigational drug efficacy and comparative efficacy assessments between drug products already FDA-approved and marketed. Reasons for this include the availability of greater amounts of data describing safety and tolerance characteristics of drugs in Phase II through IV testing, the lack of a need to cloister outpatients during the conduct of protocols, and the lesser extent to which outpatients must submit to invasive procedures.
TABLE I. Numbers of Compensable Research Protocols and Research Participants
In Clinical Pharmacology Research:
at the Quincy Research Center, Kansas City, Missouri 64127

<table>
<thead>
<tr>
<th>Descriptive Data: Protocols and Participants</th>
<th>Phase I Protocols</th>
<th>Phase II, III, and IV Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>in &quot;Normal&quot; Volunteers</td>
<td>in &quot;Patients&quot; and &quot;Outpatients&quot;</td>
</tr>
<tr>
<td>A. Number of protocols covered under compensation program:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Completed:</td>
<td>180</td>
<td>97</td>
</tr>
<tr>
<td>2. Current or pending:</td>
<td>153</td>
<td>78</td>
</tr>
<tr>
<td>B. Number of research participants (number of protocols):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Average number of participants per protocol:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Protocol completion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number/percentage of participants completing protocols:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number/percentage of participants not completing protocols:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Protocol non-completion: reasons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number/percentage due to protocol violation, non-compliance, lack of efficacy, personal reasons (loss of interest, etc.):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number/percentage due to clinically significant side effects or other medical problems (physical and otherwise):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Duration of participation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of protocols/participants providing duration data:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of subject days of participation:</td>
<td>35,881.5</td>
<td>45,609</td>
</tr>
<tr>
<td>Average number of total subject days per protocol:</td>
<td>239.21</td>
<td>773.03</td>
</tr>
<tr>
<td>Average number of days per subject per protocol:</td>
<td>13.88</td>
<td>25.93</td>
</tr>
</tbody>
</table>

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### TABLE II. Incidence of Clinical Events (Adverse and Otherwise)
Noted during the Conduct of Clinical Pharmacology Research at the Quincy Research Center, Kansas City, Missouri 64127

<table>
<thead>
<tr>
<th>A. Incidence data on clinical events</th>
<th>Phase I</th>
<th>Phase II, III, IV</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Number of clinical events reported by participants/observed by QRC staff:</td>
<td>7588</td>
<td>4803</td>
<td>12,391</td>
</tr>
<tr>
<td>2. Number of protocols for which incidence data are available:</td>
<td>147</td>
<td>49</td>
<td>196</td>
</tr>
<tr>
<td>3. Number of participants for which incidence data are available:</td>
<td>2573</td>
<td>1199</td>
<td>3772</td>
</tr>
<tr>
<td>4. Number of total subject days for which incidence data are available:</td>
<td>35,016</td>
<td>29,473</td>
<td>65,089</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Descriptive data on clinical events</th>
<th>Phase I</th>
<th>Phase II, III, IV</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Average number of clinical events per protocol:</td>
<td>51.62</td>
<td>98.02</td>
<td>63.22</td>
</tr>
<tr>
<td>2. Average number of clinical events per participant:</td>
<td>2.95</td>
<td>4.01</td>
<td>3.28</td>
</tr>
<tr>
<td>3. Average number of clinical events per subject day:</td>
<td>.213</td>
<td>.163</td>
<td>.180</td>
</tr>
</tbody>
</table>
TABLE II. Incidence of Clinical Events (Adverse and Otherwise)
Noted during the Conduct of Clinical Pharmacology Research
at the Quincy Research Center, Kansas City, Missouri 64127 (cont.)

<table>
<thead>
<tr>
<th>C. Significant clinical events with sequelae</th>
<th>Phases 1</th>
<th>Phases II, III, IV</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of significant events noted during and subsequent to the conduct of research protocols which resulted in:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Participant sequelae, including:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Participant early termination from protocol (Table III):</td>
<td>69</td>
<td>154</td>
<td>223</td>
</tr>
<tr>
<td>(2) Participant death (Table IV):</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>(3) Participant hospitalization (Table V):</td>
<td>5</td>
<td>30</td>
<td>41</td>
</tr>
<tr>
<td>(4) Participant disability:</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(5) Participant loss of work time:</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(6) Participant referrals for additional medical and/or professional consultation (Table VI):</td>
<td>53</td>
<td>28</td>
<td>81</td>
</tr>
<tr>
<td>(7) Therapeutic intervention provided by the Quincy Research Center during the course of the event (Table VII):</td>
<td>180</td>
<td>176</td>
<td>356</td>
</tr>
<tr>
<td>b. Protocol sequelae, including:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Early termination of research protocol:</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>(2) Alteration of experimental design and/or drug administration schedule</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

* Event categories are not necessarily mutually exclusive.

Note: Phase 1 data were based on evaluation of 147 of 153 completed protocols. Phase II, III, and IV data, except for those reflecting early participant termination from protocols, were based on an incomplete evaluation of both completed and current protocols.
TABLE III: Clinical Events Resulting in Early Termination of Research Subjects from Protocol Participation

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II, III, IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Unspecified significant side effects</td>
</tr>
<tr>
<td>6</td>
<td>Unspecified other medical problems</td>
</tr>
<tr>
<td>2</td>
<td>Rash</td>
</tr>
<tr>
<td>4</td>
<td>GI disturbances, nausea, vomiting, diarrhea, bloody stools, indigestion</td>
</tr>
<tr>
<td>1</td>
<td>Ulcer</td>
</tr>
<tr>
<td>3</td>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td>1</td>
<td>Elevated blood pressures</td>
</tr>
<tr>
<td>1</td>
<td>Bronchitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase I</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase II, III, IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

Phase I Total = 69
Phase II, III, IV Total = 154
TABLE IV. Clinical Events Resulting in Death of Research Participants

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II—IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2 Suicide</td>
</tr>
<tr>
<td></td>
<td>1 Acute myeloblastic leukemia</td>
</tr>
<tr>
<td></td>
<td>1 Breast cancer</td>
</tr>
<tr>
<td></td>
<td>1 Cerebrovascular Accident (CVA)</td>
</tr>
<tr>
<td></td>
<td>1 Colostomy and perforated bowel from a fecalith</td>
</tr>
<tr>
<td>Totals</td>
<td>0</td>
</tr>
</tbody>
</table>

* All patients had received investigational drug.

TABLE V. Clinical Events Requiring Hospitalization

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Flu</td>
<td>6 Unspecified medical problems</td>
</tr>
<tr>
<td>1 Appendectomy</td>
<td>5 Gastrointestinal problems</td>
</tr>
<tr>
<td>1 Drug rechallenge</td>
<td>3 Cancer</td>
</tr>
<tr>
<td>1 Extrapyramidal symptoms</td>
<td>3 Fractures</td>
</tr>
<tr>
<td>1 Seizure</td>
<td>2 X-ray, mammography</td>
</tr>
<tr>
<td>1 Unspecified medical problems</td>
<td>2 Bladder/urinary tract infections</td>
</tr>
<tr>
<td>1 Atopic asthma</td>
<td>1 Hematuria</td>
</tr>
<tr>
<td>1 Bilateral knee replacement</td>
<td>1 Cerebrovascular accident (CVA)</td>
</tr>
<tr>
<td>1 Manic-depressive disorder</td>
<td>1 Gallbladder surgery</td>
</tr>
<tr>
<td>1 Bilary colic</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>1 Eye surgery</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>1 Hand surgery</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>1 Breast surgery</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>1 Prostate surgery</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>1 Knee surgery</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>1 Myocardial infarct</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>1 Syncope, black stools</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>1 Diverticulosis</td>
<td>1 Biliary colic</td>
</tr>
<tr>
<td>Totals: 5</td>
<td>36</td>
</tr>
</tbody>
</table>
TABLE VI. Clinical Events Requiring Additional Physician Consultation

<table>
<thead>
<tr>
<th>Events</th>
<th>Phase I</th>
<th>Phase II—IV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecified</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>EENT</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Dermatologist</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>OB/GYN</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dentist</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Radiologist</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>EEG</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rash, itch</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Cold symptoms, cough</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Ulcer, colitis</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Leg cramps</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ringing in ears</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Weak, shaky, jittery, exhaustion, dizzy</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other GI, stomach problems</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Other aches, pains</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Seizure activity</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory difficulties</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hot sweats</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thumb tendonitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Falls</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Spider bite</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Eye lidament distension</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>53</td>
<td>28</td>
</tr>
</tbody>
</table>

* Based on rather limited evaluation as of date of this survey.
Additional evaluation continues.
### TABLE VII. Clinical Events Requiring Therapeutic Intervention

<table>
<thead>
<tr>
<th>Events</th>
<th>Phase I</th>
<th>Phase II—IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecified</td>
<td>116</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td>Toothache</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Rash, itch</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Cold, flu, sore throat, cough, nasal congestion, chills</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Nausea, vomiting, stomach/abdominal pain/upset, diarrhea, gas, constipation, hard stools, heartburn</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Hypertension, tachycardia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Muscle aches, pains</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Swollen lymph nodes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hayfever</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Gout</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Eyes watering</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Menopause</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Weakness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Erythrasma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Earache</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Bad taste in mouth</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Leg swollen, pain</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Toe injury</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Arthritis pain</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Twisted ankle</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Drowsy, yawning, fatigue</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Extrapyramidal symptomatology</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hack.che</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>186</strong></td>
<td><strong>176</strong></td>
</tr>
</tbody>
</table>
Report on Survey Concerning Availability of Compensation for Injuries Resulting from Participation in Biomedical Research

Pharmaceutical Manufacturers Association*

This survey of PMA members was conducted in order to obtain requested information for the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. The companies responding represent a good cross section of large, medium and small sized companies. Of those firms which responded to the PMA Annual Survey Report, the 45 companies responding to this survey represent 57 percent of the total expenditure of PMA firms on clinical research. A compilation of survey results follows.

(1) *Does your company conduct or sponsor clinical research?*

Of the one hundred and forty-nine companies surveyed, forty-nine responded. Of these, forty-five indicated that their firms either conducted or sponsored clinical research. Four indicated that they do not conduct clinical research.

(2) *In what clinical settings has your clinical research been carried out during the past three years?*

The companies utilized a number of different settings, including combinations of settings, for their clinical research. Hospitals and clinics were the most widely used settings, as the following graph indicates.

<table>
<thead>
<tr>
<th>Clinical Settings</th>
<th>Number of Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals</td>
<td>43</td>
</tr>
<tr>
<td>Clinics</td>
<td>42</td>
</tr>
<tr>
<td>Private Practice</td>
<td>35</td>
</tr>
<tr>
<td>Company Employees</td>
<td>20</td>
</tr>
<tr>
<td>State Prisoners</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
</tr>
</tbody>
</table>

* Lewis A. Engman, President
Washington, D.C.
December 1980
Some of the other settings mentioned included a contract laboratory residential facility, a privately owned clinical laboratory, a private clinical pharmacology unit, a university medical school, and a dialysis center.

(3a.) Does your company have a program for compensating subjects who might be injured during clinical research (including drugs and/or devices) and must subjects file a formal claim? Twenty-six of the respondents have some kind of formal program for compensating subjects who might be injured during clinical research. Nineteen firms have no such programs. Only fourteen of the twenty-six companies with programs require the subject to file a formal claim against the company before being considered for compensation.

(3b.) Describe your program, indicating what is covered (e.g. medical and hospital care for observation and evaluation, medical and hospital care for treatment, financial compensation for loss of work, etc.) and whether all study subjects are covered including those who received control treatment or just those who receive investigational treatment.

Some of the characteristics of the twenty-six programs include the following:

- Ten programs cover medical and hospital care for evaluation and/or observation.
- Thirteen of the programs provide medical and hospital care for treatment.
- Eleven of the companies provide compensation for those receiving investigational treatment while eight cover those receiving control treatment.
- Seven firms did not specify the benefits of their programs, but they did state that coverage is provided according to the terms of their liability insurance.
- One company indicated that their program provides compensation for loss of work.
- One company indicated that compensation for medical and hospital care is only paid when it has been awarded by a court of law.
- One company indicated that compensation for medical care will be provided if it is notified within 30 days following completion of the study.

There were some restrictions on the provision of benefits. Five companies do not provide coverage unless the firm's product is determined to be the causative factor in the injury or illness. One of the five stated that side effects or reactions need only have been "reasonably incurred" as a result of administration of the drug. Another company covers hospital and medical care when the subject has no existing health coverage and the illness or injury was not a result of patient negligence.
Compensation in Pharmaceutical Research

One company with a similar stipulation also specified that the subject would not be covered if he/she were covered by any government program providing health care. This company does not, however, require a finding of patient negligence.

(3c.) *Is your program covered by an insurance carrier?* Not all companies have coverage through an insurance carrier. Nine firms indicated they have total insurance coverage. Sixteen companies have partial coverage and six have none. One company, covered partially by an insurance carrier, also has a self-insured program. One of those not covered by an insurance carrier did state that their program was self-insured.

(4) *How many formal and informal claims have been made against your company within the past three years? Include only claims for serious adverse effects directly resulting from the administration of the test article, which required that the subject be hospitalized or receive medical treatment beyond that which was called for in the protocol.*

A numerical breakdown of claims, both formal and informal, filed against those respondent companies involved in clinical research follows:

**Formal Claims***

<table>
<thead>
<tr>
<th>Number of Claims</th>
<th>Number of Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*NOTE: Only four formal claims in the past three years—during which time 75,000-100,000+ individuals participated in clinical research.*

**Informal Claims**

<table>
<thead>
<tr>
<th>Number of Claims</th>
<th>Number of Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

(5) *Please describe the nature of any claims made within the past three years.*

Most of the claims filed against the companies were not of a serious nature. (As a reminder, forty companies said they had no formal claims against them; thirty-two companies had no informal claims.) In fact, the most serious injury specified was found to be the fault of the physician involved in the study, not the
company. The results of some of the claims filed in the past three years follow:

Of the four formal claims, three resulted in lawsuits. The final decision was not indicated for one case. In another, the company was found to be not liable for the resulting injury. In the other, the company was dismissed from the case and the investigator settled before trial. The last of the formal claims was terminated by payment of a small sum covering certain alleged hospital expenses.

Two companies specified that claims resulted in hospitalization. In one instance, the company was not billed. In the other, the company was requested by the investigator to make payment, and the firm complied.

In four cases, the companies were required to pay for other medical expenses (including hospital, diagnostic, physician, and other services).

One case involved a request by the subject for termination of pregnancy during oral contraceptive studies. (The procedure was anticipated and included in protocol.)

(6) Please estimate the total number of subjects participating in clinical investigations conducted or sponsored by your company during the past three years.

A breakdown of the TOTAL NUMBER OF SUBJECTS (75,000-100,000+) participating in clinical investigations conducted by or sponsored by respondent companies during the past three years follows:

Phase I:

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Number of Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-99</td>
<td>10</td>
</tr>
<tr>
<td>100-249</td>
<td>13</td>
</tr>
<tr>
<td>250-499</td>
<td>9</td>
</tr>
<tr>
<td>500+</td>
<td>7</td>
</tr>
</tbody>
</table>

Phase II

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Number of Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-249</td>
<td>9</td>
</tr>
<tr>
<td>250-499</td>
<td>10</td>
</tr>
<tr>
<td>500-999</td>
<td>6</td>
</tr>
<tr>
<td>1000+</td>
<td>15</td>
</tr>
</tbody>
</table>
Phase III:

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Number of Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–249</td>
<td>3</td>
</tr>
<tr>
<td>250–499</td>
<td>5</td>
</tr>
<tr>
<td>500–399</td>
<td>7</td>
</tr>
<tr>
<td>1000–1999</td>
<td>4</td>
</tr>
<tr>
<td>2000+</td>
<td>20</td>
</tr>
</tbody>
</table>

There were some additional comments regarding the number of subjects participating in the investigations.

One company indicated that its studies were done on blood samples only.

One company wishing to specify its proportionately larger number of respondents specified its own range: 700+ participants for Phase I, 3000+ participants for Phase II, and 6000+ participants for Phase III.

One company indicated that 0–249 subjects participated in studies to support marketed products.*

One company stated that investigation was done only on patients requiring surgery. This investigation was not done in phases and involved 500–999 subjects.*

One company stated that they used 70 subjects in bioavailability studies.*

* These subjects were not counted in the totals listed above.
Introduction

A meaningful description of the system for compensation of subjects participating in medical research in Sweden would not be meaningful without a review in some detail of other compensation systems related to health care in Sweden. The reason is that the relative simplicity of the system for compensation of research subjects available in this country is closely related to the existence of a network of insurance programmes which taken together give a high degree of coverage of economical losses in case of sickness and disability.

The general health insurance. The most important part of this network is the compulsory general health insurance (GHI) which includes essentially all inhabitants of Sweden. This system gives a very substantial contribution to the coverage of the total need of compensation for any sick or injured person whatever the cause might be. The average value of this contribution which includes future cost of short-time and long-time health care and rehabilitation and compensation of up to 90% of income losses etc., is very difficult to estimate but might amount to about 80% of the total cost of full compensation according to general accepted insurance principles. Thus, the estimated average costs which should be covered from other sources amount to about 20% of the total cost only. The above mentioned fact has indeed facilitated the construction of other insurance schemes related to health care now in operation on the Swedish market. The most important of these schemes are the workers compensation

*Head of the Department of Internal Medicine, University Hospital, Uppsala Sweden; Medical Advisor to the Skandia Insurance Company Stockholm.
August 1980

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scheme (not further dealt with in this report), the general patient insurance and the general drug insurance.

The General Patient Insurance (GPI). The general patient insurance (GPI) scheme which has been in operation since 1975 as well as the general drug insurance (GDI) scheme which was introduced July 1, 1978, are both constructed as so-called “no fault” insurances. The GPI-system gives coverage for unexpected complications in health care and dental care (“malpractice”) whether delivered at hospitals or health care or dental care centers run by the state or the local authorities or by private doctors or dentists.

The total cost per year for this scheme amounts to about 25 million SwCr and the average number of patients qualified for compensation has amounted to about 1,500 persons annually.

The upper limit of compensation per individual is 2 million SwCr. The compensation rates are in the individual cases settled by the insurance authority under the supervision of a governmental committee. Policy holders of the GPI scheme are the health authorities or the private doctors or dentists responsible for the delivery of health care. The insurer is an Insurance consortium consisting of the main Swedish insurance companies.

The General Drug Insurance (GDI). Since adverse effects of drugs (given according to recommendations of the producer as approved by the National Board of Health and Social Welfare) are not included in the GPI system, the GDI-scheme was later introduced on the basis of an agreement between the Insurance consortium and Swedish and foreign drug companies operating on the Swedish market (policy holders). The construction of the GDI-scheme is very similar to the GPI-scheme. The total cost of the scheme is so far not exceeding 10 million SwCr per year. During the first two years the number of claims has amounted to about 100 per year which is much less than expected. Since the time limit for filing in claims is three years from the administration of the drug, this figure is expected to rise.

The upper limit for compensation per injured person is 2 million SwCr and the upper limit for injuries caused by each drug or type of drug is 75 million SwCr.

Need for a special insurance for research subjects. In connection with the discussions and negotiations which preceded the introduction of the GPI-scheme it became obvious that healthy persons volunteering as research subjects in medical research would not be included in the GPI-system. The same was true for patients in hospitals who agreed to participate as research subjects in diagnostic procedures or other investigations which were not related to the disease of the patient or of immediate value for him personally. Before introduction of the GDI-scheme all experiments in which drugs were involved were also left without insurance coverage. On the other hand, extended but justified diagnostic procedures as well as therapeutic trials in
individual cases would be covered by the GDI-scheme. After the introduction of the GDI-scheme phase II and phase III-studies of new drugs on patients are also considered to be covered by this scheme.

Since most research subjects, however, were not included in the above mentioned insurance scheme a number of Swedish investigators made inquiries to the private insurance companies about the possibility of their offering insurance schemes especially designed for this purpose. The Skandia Insurance Company which is holding about 50% of the Swedish insurance market reacted positively on these inquiries and has been able to offer such an insurance since 1975.

A description of the construction and hitherto experience of the Research Insurance (RI) scheme offered by the Skandia Insurance Company is given in the following. An attempt will be made to follow the various issues outlined in the Commission’s “work scope.” Since the experience of the RI-scheme is somewhat limited so far, and particularly since extremely few adverse effects have occurred, some of the issues of the “work scope” can not be elucidated by the present experience of the RI-scheme.

Incidence of Injuries

A review of Skandia’s RI-scheme which got a slow start during the autumn 1975, has shown that up to July 1, 1980, 157 protocols have been covered by this insurance (Table I). As also indicated in the table most of the protocols contain low risk procedures (Code 1-4) according to the method employed for the assessment of risks described under II:6. Twenty protocols involving high risk procedures (Code 5-10) have also been covered by the RI-scheme.

Table I. The research insurance scheme 1975-1980. The table indicates the total number of protocols and research subjects covered by the RI-scheme, the number of adverse effects observed as well as the range of rates (SwCr. of the programme). Code 1-10 refers to the system used for assessment of the risks of various research procedures as described under II:A:6.

<table>
<thead>
<tr>
<th>Code</th>
<th>Number of Protocols</th>
<th>Number of subjects</th>
<th>Adverse effects</th>
<th>Range of rates SwCr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>157</td>
<td>8,201</td>
<td>3</td>
<td>500-7,800</td>
</tr>
<tr>
<td>Code 1</td>
<td>42</td>
<td>3,727</td>
<td>-</td>
<td>500-5,300</td>
</tr>
<tr>
<td>Code 2</td>
<td>77</td>
<td>3,192</td>
<td>3</td>
<td>500-7,800</td>
</tr>
<tr>
<td>Code 3</td>
<td>17</td>
<td>365</td>
<td>-</td>
<td>1,100-1,800</td>
</tr>
<tr>
<td>Code 4</td>
<td>1</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Code 5</td>
<td>15</td>
<td>437</td>
<td>-</td>
<td>1,500-5,000</td>
</tr>
<tr>
<td>Code 6</td>
<td>1</td>
<td>420</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Code 8</td>
<td>2</td>
<td>37</td>
<td>-</td>
<td>3,000-5,000</td>
</tr>
<tr>
<td>Code 10</td>
<td>2</td>
<td>15</td>
<td>-</td>
<td>2,000</td>
</tr>
</tbody>
</table>
The number of research subjects who have participated in these protocols (according to the application forms) amount to 8,201 persons (Table I) of which 7,292 have been subject to low-risk procedures (Code 1-4) and 909 to high-risk procedures (Code 5-10).

A detailed picture of the demographic characteristics of the population of research subjects cannot be obtained from the application forms. As far as healthy volunteers are concerned, by tradition, however, those persons are recruited among groups of people which can be addressed collectively like fireman, registered blood-donors, healthy relatives to certain groups of patients, students and student nurses, etc.

The patients who have volunteered to participate as research subjects are carrying a broad variety of somatic and in some cases of psychiatric diagnoses related or unrelated to the actual field of research. In some cases the physical condition of the group of patients studied has been judged to be of importance for the assessment of the risks (e.g. exercise tests performed on patients with a history of a recent cardiac infarction).

According to a rough estimate about 75% of the research subjects have been healthy volunteers and 25% of the subjects have been patients who have volunteered to extended investigations. There is a tendency of an increased frequency of participation of patients in the more sophisticated research programs.

As indicated in the introduction and in Table I the incidence of adverse effects and claims for compensation among the research subjects have been exceedingly low. Only three cases of adverse effects have been reported so far. A short history of these cases will be given in the following.

**Case I. G. O. A 30-year old female who participated in a large series of studies conducted by a university clinic of gynecology and obstetrics on the systemic effect of hormones (oestrogen- and progesterone-derivatives) given as contraceptives by different routes of administration. The protocol contained a series of venous blood tests as well as an intravenous ACTH-infusion (Code 2).**

**Adverse effect:** A left sided pneumonia with a small abscess (Staphylococcus aureus?) occurred. The possibility of a bacterial embolus from an infected thrombophlebitis secondary to the ACTH-infusion could not be ruled out.

**Consequences for the patient:** 1 week of hospitalization, 5 weeks of sick-leave. Compensation from RI was given for loss of income. The hospital costs were covered by the GHI-scheme.

**Case II. R. M. A 46-year old man with a diagnosis of endogenous depression participated in a study conducted by a psychiatric clinic of a university hospital. Sampling of the spinal fluid at two occasions for biochemical studies was included in the protocol.**
Adverse effect: About 24 hours after the second spinal puncture the patient got headache, dizziness, vertigo and pain in the neck. These symptoms which were most pronounced in the afternoons lasted for 10 days. A connection between the spinal puncture and the appearance of the symptom could not be ruled out.

Consequences for the patient: Prolonged sick-leave for ten days. Compensation was given for loss of income.

Case III. B.L. A 50-year old female who participated in the same protocol as Case II as a healthy volunteer.

Adverse effect: A few hours after the spinal puncture she got severe headache.

Consequences for the patient: The patient was bed-ridden at home for four days and unable to work for another five days. Compensation was given for loss of income for nine days and for extra costs for the care of two children during the same time.

Comments. The limited number of research subjects covered by Skandias' RI-scheme during the five years the scheme has been in operation, possibly represent a minority only of the total number of persons who have participated in medical research in Sweden during this period of time. Many circumstances could possibly explain this finding. First of all it is obvious that all Swedish scientists have not so far recognized the necessity to offer the research subjects an acceptable insurance coverage. There may also exist other schemes offered by other insurance companies although on a very small scale.

Since medical research is a generally accepted responsibility of the university hospitals it is a general opinion within the Swedish medical profession that the insurance of research subjects should be included in the general patient insurance scheme. Negotiations between the CPI-consortium and the hospital authorities on this matter has also taken place recently and it is expected that these problems will be solved within the next few years.

As mentioned above, very few adverse effects, three in more than 8,000 research subjects, have occurred in this programme. This figure might rise to some extent since the time for filing claims in this scheme amounts to four years. On the other hand a higher incidence of adverse effects might perhaps not be expected since research subjects in general are very carefully supervised and monitored. The Swedish experience of related schemes also indicate a low incidence of adverse effects. Thus in the GPI-scheme about 2,000 and the GDI-scheme about 100 claims regarding adverse effects are made each year. The number of hospital admissions, medical consultations and dental consultations per year amounts to 1.5 million, 20 million and 4 million, respectively.
Compensation Program

A copy of the Insurance Conditions of the Research Insurance in Swedish (with an unauthorized translation of the present author) is added to this report as Attachment I.

Information on the details of the indemnity rules of the patient insurance scheme is given in a paper by C. M. Oldertz. Since both the compensation system for the GPI-scheme and the RI-scheme are based on the Swedish tort law most of the rules are common for both these schemes.

All medical research in Sweden in which healthy volunteers or patients participate as research subjects shall be performed according to the Helsinki declaration and must be approved by the ethics committee of the medical school to which the investigators belong. In addition testing of drugs on human beings must be approved by the National Board of Health and Welfare. With these conditions fulfilled all suggested projects have so far been regarded as qualified for the RI-scheme. No categorial exclusions have been made. As mentioned above the participation of patients posing special risks might, however, influence the premium of the insurance.

In accordance with the indemnity rules for the patient insurance* compensation is provided for physical injuries and its social consequences, for pain and suffering and for deformity and permanent disability, but in general not for psychological injuries.

The time limitation for filing of claims is 4 years for the RI-scheme.

As indicated in Attachment II, failure of the research subject to follow the directives of the investigator might disqualify the subject from being compensated for an adverse effect.

As to the amount to be paid for specific injuries similar rules as for the patient insurance is applicable with the exception that RI gives compensation from the first day of loss of working capacity.

The method used for assessment of risks of the various research protocols is as follows.

On the basis of the application form (Attachment II) and a detailed description of the research protocol (copy of grant application and application for approval by the ethics committee) the potential risks involved in the procedures to be used are estimated by a medical advisor to Skandia according to a ten-point scale as illustrated by Table II.


*Supra, note 1.
TABLE II. The RI-system for assessment of the risks of various research procedures.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Research procedures (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code 1</td>
<td>Sampling of venous blood, Administration of approved drugs in recommended doses, Intravenous and intra-muscular injections, Skin biopsies, etc.</td>
</tr>
<tr>
<td>Code 2</td>
<td>Sternal and spinal puncture, Intravenous or intra-arterial infusions, Muscle biopsies, Endoscopy and biopsies of the gastro-intestinal tract, etc.</td>
</tr>
<tr>
<td>Code 3</td>
<td>Biopsies of liver, lung, kidney, Catheterization of peripheral arteries, Angiography of abdominal organs, Testing of allergens, etc.</td>
</tr>
<tr>
<td>Code 5</td>
<td>Right heart catheterization, Angiography of coronary and pulmonary vessels, Exercise testing of patients with known coronary disease, etc.</td>
</tr>
<tr>
<td>Code 8</td>
<td>Transhepatic portal vein catheterization, Left heart catheterization by puncture of atrial septum, Exercise testing of patients with recent myocardial infarction.</td>
</tr>
<tr>
<td>Code 10</td>
<td>Combination of several procedures according to Code 5-8.</td>
</tr>
</tbody>
</table>

The result of this estimate is summarized on the form filled in by the medical advisor (Attachment II). On the basis of the particular code number given to the protocol the premium of the insurance is calculated.

The relation of the RI-scheme to other insurance systems in Sweden has been dealt with in the introductory remarks of this paper. A characteristic feature of the Swedish situation is that claims for economic compensation from patients for unexpected complications and adverse effects of medical care have by tradition been relatively scanty. Thus, contrary to the situation in certain other countries suing of doctors or drug companies etc. for those events have been a fairly uncommon procedure. One important reason is that the compulsory general health insurance has provided basic compensation for economic losses. Another reason is that suggested serious injuries of patients due to accident or negligence by medical personnel according to a special law has to be reported to the Committee on Medical Responsibility under the National Board of Health and Welfare. This procedure is described in a paper by the present author. Only in some of these cases when the review by the committee leads to a statement that an actual patient has not been treated in accordance with current medical science and experience, suing

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1 Harry Boström, Unexpected Complications in Internal Medicine in Sweden, in Unexpected Complications in Medical Care, Skandia International Symposia, Almquist & Wiksell International, Stockholm (1979) at p 141-7.
Compensating for Research Injuries: Appendix K

of the doctor or a member of the medical staff would be worthwhile.

With regard to the adverse effects of drugs the situation in Sweden changed markedly after the thalidomide catastrophe and several trials have recently been opened against drug companies providing anticonceptional pills, certain antibiotics, etc. Most of these trials have so far not been closed. Interestingly enough, no trials against doctors or drug companies have been opened by patients covered by the GPI-scheme, the GDI-scheme (and the RI-scheme) since the introduction of these insurance systems. The obvious reasons seem to be that the patient has in fact accepted the amount of compensation provided by the insurance and appreciated the rapid and non-bureaucratic procedure.

With regard to the cost of the compensation program the levels of premiums are indicated in Table 1. The premium for a certain protocol is calculated according to the following formula:

\[ P \cdot \text{Code number} \cdot \text{number of research subjects} \]

in which \( P \) denotes the basic premium for each research subject and the code number refers to the system for assessment of risks as described above. When the RI-scheme was started factor \( P \) was equal to 15 SwCr, but due to the effect of inflation \( P \) has later been multiplied by an inflation factor (at present 1.3).

The final premium calculated as mentioned above is modified by the rule that a minimum premium of 500 to 2,000 SwCr is charged depending on the assessed risk of the actual protocol. For low risk procedures (Code 1) to be applied to a large number of individual negotiations between the presumptive policy holder and the insurance company have in most cases resulted in marked reduction of the basic premium for each subject.

The hitherto experience with the RI-scheme has indicated that the aim of the program has been fulfilled. Due to the low number of adverse effects, no comparison of assessed risks to the actual incidence of injuries can, however, be made. The claims of the patients have been made to the policy holders (head of the actual institution of clinic) who have reported the event to the insurance authorities. This procedure seems to be adequate.

As a rule the research subjects have been informed about the insurance situation in connection with the informed consent requested by the research subjects according to the declaration of Helsinki. Since all these subjects more or less take it for granted that they will be given compensation if they should be injured by doctors or medical personnel, subjects whether informed or uninformed on the compensation program, are not expected to react differently.

The rates of pay for research subjects as a rule recorded in the application to the ethical committee are not taken into account in the assessment of risks of a certain protocol. The reason is that the rate of pay as a rule is given for loss of income during
the time the subjects have been at disposal for the investigator. The rate of pay might also be related to the degree of inconvenience caused by the procedures but more seldom to the actual risk involved.

The feasibility of the construction of insurance systems to provide compensation for individuals injured as a result of unexpected complication of medical care, adverse effects of drugs and adverse effects of certain research procedures is obvious to the present author with regard to the Swedish experience of this system. A prerequisite seems to be that these are constructed as "no fault insurances," give "full compensation" and that expectations of "overcompensations" (e.g. as a result of legal procedures) can be avoided:

This means that as far as physical injuries are concerned compensation for actual and future loss of income, costs of medical care and rehabilitation, indemnity for individual pain and suffering during the acute illness as well as compensation for deformity and permanent disability should be given. Compensation for social injury which may affect the research subject or his dependents should also be provided to a reasonable extent. Thus support should be given, for instance, for the buying of equipment to facilitate daily life at home and for transportation of disabled persons. Extra costs for care and upbringing of children should also be provided.

Since psychological and legal injuries, because of difficulties in definition and estimation of the degree of severity of these injuries, were excluded in the Swedish schemes, no experience is available on the feasibility of insurance coverage of such injuries.

As to the amount of compensation provided, this should be calculated to give full compensation according to current tort laws when added to support obtained from other sources, for instance private insurances and patient schemes.

A suitable length of time for filing claims following the participation in research procedures seems to be three to four years.

Persons eligible for payment in addition to the research subject should be dependents belonging to the immediate family. Children of a deceased subject should be compensated for the loss of support of the deceased patient up to a certain age according to current rules in the society. When these and other rules are set it seems to be of fundamental importance that the general rules of indemnity of the scheme is acceptable to the members of the society in which the scheme is supposed to operate.

The existence of Skandia's RI-scheme, which in fact due to the extremely low turnover of this insurance is considered to be more of a goodwill service to the scientific society than of a serious business, has been highly appreciated by the customers particularly those involved in research procedures which carry
high risks. The burden imposed on the investigator, which consists of filling in the application (Attachment I), providing a copy of the grant application or the application to the ethics committee and finally if an adverse effect is suspected, report to the insurance company, does not seem to be too heavy.

Since the premiums of the RI-scheme have been comparatively low it has been possible to include these costs in the ordinary budget of the actual research projects or of the institutions.

The obligations of the head of the institutions is not supposed to have changed as far as the ethical obligations are concerned. With or without an insurance plan it must be the responsibility of the head of the department to keep a watchful eye on the safety of the research procedures as well as the quality of the investigations and of the investigators.

In view of the great impact the Federal government of USA has on medical research all over the country due to its generous support of this research, a nationally uniform policy on compensation of research subjects seems highly desirable.

As to the type of mechanisms which would best implement such a policy, two of the suggested models seem most attractive to the present author. This is because of the fact that also in USA, in spite of the impressive amount of clinical research performed in this country, the turnover of an insurance program for research subjects is expected to be relatively low from the insurance business' point of view. Therefore, such an insurance scheme should be attached to existing agencies rather than new ones formed for this purpose only. Since the federal working compensation scheme seems to deal with problems not too different from those discussed in the present paper, an attachment of a presumptive RI-scheme in USA to this agency would not be inappropriate. (In fact the Swedish GPI- and GDI-systems are administered by the same agency, an insurance consortium, which also administers the workers compensation scheme.)

In case a federal engagement in the presumptive research insurance program would be considered non-desirable by the committee for political or other reasons, the problem should be handed over to the private insurance industry. Particularly those companies which have gained experience of administering "malpractice insurance schemes" can be expected to have access to the expertise needed for the administration of an insurance scheme for research subjects.
### Attachment I: INSURANCE CONDITIONS

Medical research with participating of volunteering research subjects not directly related to medical treatment.

1. The insurance is valid for the insured person and refers to the research activity described in the insurance policy as approved by the National Board of Health and Welfare, Ethical Committee or by Skandia.

2. Skandia undertakes to give compensation to the insured persons for any physical but not psychical injury which has affected him as a consequence of participation as research subject in medical research without direct connection to medical treatment. The compensation will be given according to the rules of the Swedish tort law provided the participation in the research project took place during the period of validity of the policy.

3. With the term physical injury is understood any injury or disease which is a direct consequence of the experimental procedure used and not can be considered to be a natural or expected consequence of the experiment.

4. The injury is considered to have arisen as a direct consequence of the actual research activity if there is a major probability that the injury was caused by the experimental procedure.

5. The research subject has no right to compensation for injury caused by:

   5.1. The fact that the research subject has not followed the instructions given by the investigator.

   5.2. Infection of other causes than the use of non-sterile substances of instruments.

6. **Indemnity rules**

   6.1. Compensation is paid if the research subject has been on sick-leave more than one day due to the physical injury or if he/she because of the injury has obtained permanent disability which is not without significance or if he/she has died.

   6.2. Indemnity for physical injury is paid according to the rules of the Swedish tort law if nothing else is stated.

   6.2.1. Compensation for loss of income is given during the time period of acute illness and shall correspond to the actual loss of income by the injury. Compensation is given for the period of time of lack of working capacity which can be confirmed by a doctors certificate.

   6.2.2. In the case of permanent disability the affected person will be given compensation to the estimated loss of income during the rest of his life. If the degree of disability is less than 30% no life annuity is paid but indemnity for
permanent disability is given only. The latter is, however, increased by a sum which corresponds to three times the sum of indemnity for permanent disability given for the corresponding degree of permanent disability according to issue 6:2:4.

6:2:3. The net loss only, whether economical or ideal caused by the injury will be compensated for. Thus compensation is not paid for those shares of compensation which should be obtained from other sources, such as salary from employers, etc.

6:2:4. Indemnity for personal pain and suffering is paid only if the loss of working capacity caused by the injury has lasted for more than 30 days. For remaining symptoms after the period of acute illness compensation will be paid for permanent disability.

6:3. Indemnity for pain and suffering will not be paid if the patient has died before an agreement on the magnitude of compensation has been reached.

6:3:4. If the claim have been made later than four years after the time of injury.

7. Maximal amount of compensation

For all experiments performed during one year is Skandia's responsibility is limited to the payment of a maximal sum of 5 million SwCr. For each injured person is the maximal payment limited to 2 million SwCr.

8. Other conditions

8:1. The insurance should be valid for one year.

8:2. If a notice of termination of the policy is given later than one week before the termination of the contract, the contract will be prolonged for another year.

8:3. Any injury which has occurred should be reported to Skandia as well as incidents which might cause later injury.
**Attachment II**

**Compensation of Subjects in Sweden**

**SKANDIA**

**Questionnaire**

Injury insurance for people engaged in experimental activities without any direct connection to medical treatment.

**Definition:**

The experimental activities are classified into projects. Each project may comprehend one or several experiments. A number of research subjects will participate in each project.

<table>
<thead>
<tr>
<th>Policy holder (head of the institution/head of the clinic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>Address</td>
</tr>
<tr>
<td>Telephone no.</td>
</tr>
<tr>
<td>Investigator</td>
</tr>
</tbody>
</table>

The insurance shall cover:

- All projects that the policy holder:
  - Will carry out during the insurance year.
  - Only a special project.

The insurance covers the following projects (each a description of projects):

- Specify different experiments indicated in each project (consecutive numbers):

<table>
<thead>
<tr>
<th>Research subjects (state number of research subjects in each experiment)</th>
</tr>
</thead>
</table>

Precautionary measures:

Specify the measures that have been taken to prevent possible adverse effects.

<table>
<thead>
<tr>
<th>Is the project approved by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethical committee</td>
</tr>
</tbody>
</table>

The location of the experiment premises:

<table>
<thead>
<tr>
<th>Institution/hospital</th>
</tr>
</thead>
</table>

Signature

Place and date

The policy holder's signature
### Compensating for Research Injuries: Appendix K

#### Attachment III

<table>
<thead>
<tr>
<th>Application no.</th>
<th>____________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKANDIA</strong></td>
<td>____________________________</td>
</tr>
<tr>
<td><strong>STATEMENT</strong></td>
<td>Re. Injury insurance for research subjects participating in medical research without any direct connection to medical treatment.</td>
</tr>
<tr>
<td><strong>Policy holder</strong></td>
<td>Name</td>
</tr>
<tr>
<td><strong>Project</strong></td>
<td>____________________________</td>
</tr>
<tr>
<td><strong>Elements of risk</strong></td>
<td>____________________________</td>
</tr>
<tr>
<td><strong>Risk assessment according to code:</strong></td>
<td>1</td>
</tr>
<tr>
<td>The insurance is approved:</td>
<td>1</td>
</tr>
<tr>
<td>Sanction refused:</td>
<td>1</td>
</tr>
<tr>
<td>Uppsala</td>
<td>198</td>
</tr>
</tbody>
</table>

Harry Bostrom
Professor
Materials Concerning Compensation of Subjects Injured in Research: University of Leiden, The Netherlands

E. L. Noach, M.D.*

Introduction

We are pleased to provide you with information concerning the insurance-based compensation scheme which is in operation at the University Hospital and Faculty of Medicine of the University of Leiden, The Netherlands. This has to be regarded against the background of the functions of the local Committee on Medical Ethics (C.M.E.) and the system of largely socialized health care in this country.

In brief, our insurance-based scheme is functioning on the strength of arrangements between hospital and faculty boards on the one hand, and a local insurance broker on the other. (The latter, representing a private insurance company, takes care of virtually all insurance matters of hospital and university.) For each investigation requiring the advice of the C.M.E., a decision is made as to whether it should be covered either by liability or by accident insurance. In the former case the existing hospital/university liability insurance is considered to be sufficient, the more so since all extra medical treatment owing to "investigational mishaps" will be provided free of charge.

The premium for accident insurance is settled per investigation by consultation between the C.M.E. and the insurance broker. If an investigator pursues an investigation which has not been accepted by the C.M.E., he remains personally liable; in such cases even the hospital liability insurance is not supposed to be applicable. This prospect is usually sufficiently discouraging for too eager investigators.

*Chairman, Committee on Medical Ethics, University Hospital and Faculty of Medicine, University of Leiden, The Netherlands.

August 1980
Insurance

The Leiden University Hospital carries a liability insurance for its staff and employees. If, due to erroneous treatment or negligence by a staff member or employee, the health of an individual is affected adversely or if bodily harm is inflicted, whether or not resulting in death, such a person (or his/her legal heirs) is considered eligible to receive indemnification. The insurance covers both legal and contractual liability. With respect to scientific research involving patients or healthy subjects, it has been agreed with the insurers that the above-mentioned liability insurance or that of the University of Leiden is only applicable if the research project in question has been found acceptable by the directors of the Leiden University Hospital or the Board of the Medical Faculty on the basis of a positive opinion of the Committee on Medical Ethics. Which of these two liability policies is in effect depends on the place where the investigation is performed, i.e. within a department of the hospital or an institute of the university.

However, matters are different when there is no question of a demonstrable error or of negligence on the part of a staff member or employee of the Leiden University Hospital or Leiden University and the injury to a subject must be ascribed in the final instance to unpredictable circumstances which can occur in scientific research. For such cases a reasonable coverage of risk is desirable. This can be obtained in the form of accident insurance. With respect to this, the insurance companies in the Netherlands have acquired too little experience to make any more than a rough estimate of the risk associated with unforeseen circumstances and the appropriate premium. For the Leiden situation use was therefore made of the excellent personal relations between the Committee on Medical Ethics and the insurer of the university and the hospital, in which situation mutual trust plays a large part. When the afore-mentioned committee, usually after consultation with the investigator, is convinced that accident insurance is desirable, the duration of the policy and the risk to be covered are set by the insurer on the basis of recommendations made by the committee. The premium is levied starting from the basic rate of 44 Dutch florins (i.e. $22) per test subject not older than 65, which is adequate for most cases, or at a few multiples thereof in case of greater risks. The cost of the accident insurance forms part of the research expenses and is therefore to be paid from the research budget or the funds of the group under whose scientific responsibility the investigation is performed.

Since the institution of the Committee on Medical Ethics, in 1976, an accident insurance was considered necessary in only 4 out of 125 research projects. Up till now no patients or healthy subjects participating in an approved research project have put in any claim on basis of liability insurance or accident insurance.
If the health of a patient or employee is injuriously affected by erroneous treatment or negligence of a staff member or employee of the Leiden University Hospital such that he or she is unable to work for a short or long period, he or she can apply for financial compensation by virtue of social legislation. In this connection the following laws are relevant: The Ziektewet (ZW), the Wet op de Arbeidsongeschiktheidsverzekeringen (WAO) and the Algemeen Arbeidsongeschiktheidswet (AAV). The ZW and WAO are only applicable for employed individuals. The AAV is a national insurance and applies to all inhabitants of the Netherlands, whether they are employed or not.

If an employee's disability to work lasts less than 52 weeks, he/she receives a sickness benefit according to the ZW. If the disability to work lasts longer than 52 weeks, the WAO must be resorted to. Under these conditions the WAO benefits supplement the allowance under the AAV.

Relationship between the liability insurance of the Leiden University Hospital or Leiden University and payments made under the above-mentioned laws.

When a subject makes a claim on the liability insurance of either the Leiden University Hospital or the Leiden University in connection with injury sustained during participation in a scientific study, the amount to be paid will be determined in relation to the benefits he or she will receive via the above-mentioned legislation. However, the body responsible for the application of this legislation has the right to recover this amount from the insurance company with which the hospital or the university arranged its liability insurance.
Attachment I

Guidelines for the Committee on Medical Ethics of the Academic Staff of the Leiden University Hospital and the Medical Faculty of the University of Leiden

(1.) Objectives and functions
The Committee on Medical Ethics, to be called here the committee gives advice, on request, concerning the medical ethical aspects of:

(1.1.) Patient care in general, i.e.:
(1.1.1.) Daily care of the patient.
(1.1.2.) The confidential relationship between the physician, nurses, and auxiliary staff on the one hand and the patient on the other.
(1.1.3.) Frequently recurring medical problems with unusual ethical aspects.
(1.1.4.) Incidental problems involving medical ethics.

(1.2.) Scientific research involving human subjects and performed by members of the Medical Faculty of Leiden University, to be called here the Faculty, and of the Leiden University Hospital (LUH) within the hospital or an institute of the university. Advice may be requested by any member of the staff of the LUH or the faculty or appropriate officials of these bodies, and requests may be made directly to the committee.

(2.) Implementation of the objectives and function of the committee:

(2.1.) Patient care in general,
(2.1.1.) Problems related to daily patient care.
(2.1.1.1.) These problems will often concern patients' complaints about the care they receive. These complaints should be reported to the managing board of the hospital. They should be handled according to the guidelines of the Committee on Errors, Accidents, Near-Accidents, and Complaints. In cases where medical ethical problems are at issue, advice may be requested from the committee.
(2.1.1.2.) The committee may provide advice concerning the ethical acceptability of diagnostic and therapeutic procedures which in the light of new advances may be considered out of date.

(2.1.2.) Confidential relationship between physician or nursing or auxiliary staff and the patient.
In this area the task of the committee consists in promoting the formulation and, if requested, the evaluation of guidelines and observance of such provisions intended for the protection of medical secrecy, to ensure the confidential nature of the relationship between the physician or nursing or auxiliary staff and the patient.

(2.1.3.) Frequently recurring problems concerning medical ethics.

(2.1.3.1.) One of the tasks of the committee is to promote, via the academic staff, the effectuation of rational forms of consultation within the departments of the LUH to facilitate decisions concerning recurrent problems involving medical ethics.

(2.1.3.2.) If rational consultation does not yield a generally acceptable solution for a frequently recurring medical ethical problem, the committee will accede to a request to study this problem.

(2.1.4.) Incidental problems involving medical ethics.

In general, this category will only concern cases in which a physician or a member of the nursing or auxiliary staff is confronted with a matter of conscience. No general rules can be given for such cases. The committee will be available for consultation and may provide advice.

(2.2.) Scientific research involving human subjects.

(2.2.1.) Under scientific research submissible to the evaluation procedure of the committee is understood: all investigations of patients or healthy volunteers that are not, or not exclusively, related directly to diagnosis and/or therapy for the individuals in question. Under investigator or requestor of advice is understood a member of the academic staff of the LUH and/or the faculty who is responsible for the research project.

(2.2.2.) In principle, a preliminary condition for the ethical admissibility of scientific research in human subjects is scientific acceptability. Evaluation of this point demands specific expertise which the committee cannot be expected to dispose of completely.

Therefore, the committee will only undertake evaluation of the ethical aspects of a research proposal submitted to it after receipt of positive advice from the research committee (or an equivalent scientific body) of the relevant clinical or preclinical department, or from an equivalent scientific body of the relevant field of investigation. If the committee cannot endorse this opinion, they should discuss it with this committee or body.

(2.2.3.) If the investigator requesting advice is participating in research that is being coordinated outside the LUH or the Faculty, the committee is to find out whether
both the scientific and ethical admissibility of this research have been explicitly and seriously weighed on the basis of sound argumentation. If this proves to be the case, the committee is held to seriously consider subscribing to the opinion reached on this basis.

[2.2.4.] All scientific studies in the sense of art. 2.2.1. and 1.2., wherever performed (LUH or institutes of the University of Leiden), must be reported to the directors of the LUH or the Faculty Board. In connection with, among other things, the liability aspect, the above-mentioned bodies must submit a research project of this kind to the committee for their opinion on its medical ethical aspects.

[2.2.5.] Scientific research performed under the auspices of one of the departments of the LUH but for which material or data must be collected outside the hospital, falls under the conditions stipulated in art. 2.2.4.

[2.2.6.] The agreement of the directors of the hospital or the Faculty Board to the performance of a research project means that this research falls under the liability insurance of the LUH or the university, and makes obligatory the observance of the conditions stipulated in the policy. Nevertheless, in certain cases the committee is obligated to point out that supplementary accident insurance is necessary for the subjects, and in particular for healthy volunteers.

[2.2.7.] Research in the sense of art. 2.2.1. performed entirely outside the hospital or university institutes should be reported by the investigator as defined in art. 2.2.1., wherever employed, to the directors of the hospital or the Faculty Board. If requested, the committee will give advice on the medical ethical aspects of this research. Once the agreement of the directors or the faculty has been obtained, the liability insurance mentioned under art. 2.2.6. covers this research.

[2.2.8.] Applicants for evaluation belonging to the LUH or the faculty can appeal against the committee's advice concerning their planned research. This appeal must be made within a month and be addressed to the board of the academic staff or the Faculty.

(3.) Composition of the Committee.

(3.1.) The committee is a permanent committee of the academic staff, established by art. 13 sub 3 of their statutes. The committee will also serve as the faculty's committee on ethics.

(3.2.) The committee will have minimally five and maximally seven members. The members are appointed by the academic staff, after consultation with the faculty for a term of four years, and may not serve more than two terms in
succession. The sequence of retirement from the committee is determined by the committee itself, the need to ensure continuity of its work being taken into account.

(3.3.) The committee has a chairman and a vice-chairman, both of whom will be elected from among and by members for a period of one year and will be eligible for re-election. The committee will have the disposal of a secretary ex officio, preferably holding a law degree.

(4.) Rules

(4.1.) The meetings of the committee have a private character. Minutes are kept. Decisions may only be taken at a meeting if at least four members (if the total number is five) or five members (if the total number is seven) are present.

(4.2.) If dealing with a matter on which advice has been requested the committee may invite the applicant and/or one or more experts to attend the meeting and take part in the proceedings. Such persons are expected to respect the confidential nature of the meetings as defined in art. 4.9. The committee is also empowered to take any other steps it considers proper to reach well-founded recommendations.

(4.3.) When the committee has received a request for advice one of the committee members may serve as reviewer and provide the committee with provisional recommendations concerning the project in question. This reviewer should contact the applicant as soon as possible after his assignment as reviewer.

(4.4.) The committee is to make its recommendations promptly. To this end, it will be handled in the order in which they are received. Recommendations will preferably be made according to the unanimous opinion of the number of members mentioned under point 4.1. A committee member has the right to convey his minority view via the minutes. The committee's recommendations in no way abrogate the specific responsibility of the attending physician (or of paramedics under his direction and/or the investigator).

(4.5.) The committee keeps a register of the recommendations it has made. In principle, the committee's recommendations are confidential. If the advice on a research project is negative, this will be reported, together with the arguments to the applicant and without argumentation to the directors of the hospital or to the Faculty Board. When the opinion is positive, the report will be made to both the applicant and the directors or Faculty Board where appropriate together with other information requested by either of the latter. In special cases (according to the nature of the research) the committee may stipulate that it will be regularly informed about the progress of the project.
(4.6.) Applications as indicated in art. 1 should be addressed to the secretary ex officio of the committee. The secretary will without delay inform the members of the committee concerning such applications.

(4.7.) On request or as often as it considers necessary, the committee provides information, via the academic staff or the faculty, concerning the norms it applies in reaching its opinions.

(4.8.) It is incumbent on the committee, in cases in which a situation involving ethical problems in the area of patient care comes to its attention, to discuss this confidentially with the head of the department in question and the directors of the LUH. If necessary, the committee will make recommendations on such cases to the board of the academic staff and inform those involved concerning its opinion.

(4.9.) All information concerning applications for advice placed at the disposal of the committee members in connection with their membership is to be considered confidential. Resigning members will return such material to the secretary ex officio of the committee.

(5.) Further stipulations.

(5.1.) These guidelines, which replace the tentative guidelines approved in March, 1977, by the academic staff and by the Faculty council on May 30th, 1978, will go into effect after they have received the full approval of the above-mentioned organs.

(5.2.) Proposals for the modification of the present guidelines can be made either by the committee or by the board of the academic staff or Faculty council. Such proposals require the approval of these bodies.

(5.3.) In cases not covered by these guidelines, the committee will reach an arrangement in consultation with the boards of the academic staff and the faculty.

Attachment II

Sample Consent Form
Committee on Medical Ethics

The undersigned hereby declares that he/she has been fully informed by the investigator, Dr. ____________, as to the form, nature, and purpose of the investigation designated as "__________", in which he/she has been asked to participate as a volunteer subject. Detailed information has also been provided concerning any discomfort and possible risks for the subject that might ensue from this investigation.
He/she has been informed that any unforeseen financial damage he/she might incur due to the investigation will be covered by insurance (of the Leiden University Hospital or the University of Leiden).

He/she has been given sufficient opportunity to ask any questions about the above-mentioned investigation, and these questions have been satisfactorily answered by the investigator.

Furthermore, it has been clearly intimated that he/she may withdraw from the investigation at any time and that such withdrawal will have no negative influence on his/her further treatment and/or care.

On the basis of the foregoing, the undersigned agrees to participate in the investigation designated as "__________"

__________________________
signature
(for minors, the legal representative)
Attachment III
Sample Form for Notification of Patients or Healthy Volunteers in Research Subjects
Committee on Medical Ethics

General Information
(1.) Title of the project:
(2.) Name of the investigator (scientific leader of the project):
(3.) If the investigator is not the same person as the physician responsible for the well-being of the patient or subject, please state the physician's name:
(4.) If the study is to be done in healthy subjects, will these individuals be medically or psychologically examined beforehand? (If so, please state who will perform this examination):
(5.) If the study is to be done in patients, will it concern the disease from which they suffer? (If not, please indicate why patients are to be used and how they are to be selected):
(6.) Does the study require any treatment you consider to involve a risk of injury or discomfort for the patient or subject? (If so, please give details, if necessary referring to the protocol: see under point 7):

Project Protocol
(7.) If the protocol you have submitted to the Committee on Medical Ethics does not include the following information, please supply it as follows:
(7.1.) When do you expect to start the investigation?
(7.2.) How long do you expect the investigation to take?
(7.3.) How many subjects do you estimate the investigation will require?
(7.4.) Will the investigation be performed in collaboration with other departments of the Leiden University Hospital or Medical Faculty, or with other hospitals or institutions? If so, which?
(7.5.) If collaboration of this kind is planned, whose will be the coordinator of the entire investigation?

General Regulations
(8.) Can you provide the Committee on Medical Ethics with a statement indicating that the scientific committee (or other relevant body) of your group or department agrees that this investigation be performed?
(9.) Have the directors of the Leiden University Hospital or the Board of the Medical Faculty been notified about this project?
[10.] Have steps been taken to obtain supplementary accident insurance for the subjects to cover possible injury due to unforeseen circumstances?

(That is, in addition to the existing Liability insurance of the Leiden University Hospital or of the University of Leiden.) If you do not consider such supplementary insurance necessary, please state why:

[11.] Please describe briefly how you inform the subjects about the investigation and how you obtain informed consent. In this respect we attach importance to the following points:

1. how the patients or subjects are informed about the nature, purpose and possible risks of the investigation;
2. whether they are assured that they can withdraw at any time, "without grudge";
3. whether their agreement, if not requested in writing, is noted in the protocol or files of the investigation.

Attestation

The undersigned (physician in charge and investigator, see points 2 and 3) hereby declare that the investigation in question will be performed under the following conditions:

(a) any unexpected complication occurring in the subjects during the investigation will be reported to the Committee on Errors, Accidents and Near-Accidents;
(b) any important changes in the protocol of the project will be submitted to the Committee on Medical Ethics;
(c) termination of the investigation, whether because it has been completed or for other reasons, will be reported to the Committee on Medical Ethics.

Leiden: ____________ (date)

(physician in charge)                            (investigator)
Possible Compensation Mechanisms
Existing Federal Programs as Models for Compensation of Human Subjects

Stanley B. Jones*

Purpose

The purpose of this paper is to review the relevant experience of Social Security Disability, Medicare, Veterans’ Benefits, Federal Employee Compensation and Black Lung and Workers Compensation programs to determine what they teach regarding the problems and possibilities of implementing a compensation program for injured research subjects such as that proposed by the HEW Secretary’s Task Force in January 1977. Specifically, the paper will look at these programs with regard to:

(1.) Defining injury and determining eligibility for compensation.
(2.) Defining types and determining levels of compensation.
(3.) Administrative issues—including relation to other compensation programs, and
(4.) Cost experience and factors.

Wherever the experience of federal programs suggests it, the paper will offer recommendations for a compensation program for research subjects and/or factors to be considered in designing such a program.

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"Injury" as used throughout this paper also includes disease conditions.

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The Characteristics of the Compensation Program for Research Subjects Proposed by the 1977 HEW Secretary's Task Force

Before examining existing federal programs, it will be helpful to describe the criteria (characteristics) from an insurance standpoint, of the program proposed by the 1977 Task Force.

Proposed criteria for defining injury and determining eligibility for compensation of research subjects:

The individual must be a human subject in Public Health Service-conducted or supported research (page II-2), whether therapeutic or non-therapeutic.

The individual must suffer physical, psychological, or social injury in the course of the research, which:
1. "is proximately caused by the research."
2. "on balance exceeds that reasonably associated with 'any' illness from which the subject may be suffering as well as with treatment usually associated with such illness at the time the subject began participating in the research." (page II-2). "On balance" implying subject is worse off compared to patients treated in the usual way—including consideration of:
   (a.) the types and frequency of benefits and harmful side effects that the usual treatment might have had for the individual,
   (b.) the actual benefits and harmful side effects of the research treatment (VI-10, example 4) on the individual and third parties who are injured as a result of the research,

except that the individual will not be compensated for such injury if the experimental treatment proves to be superior treatment in terms of the types and frequency of benefits and harmful side-effects experienced by all subjects participating in the research (VI-II, ex. 9).

Defining Types and Determining Levels of Research Subjects Compensation to be paid. The Task Force proposed "the compensation be equal that provided injured federal employees under the Federal Employees Compensation Act" (II-2), i.e.:
(a.) payment for all medical care required by "the injury" and for conditions (including pre-existing conditions) that must be treated in conjunction with the injury—with no limits on cost or duration of care,
(b.) regular annuity payments to partially replace lost wages or earning power during the period of disability caused by the injury:

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including both total and partial disability, including both temporary and permanent disability, and payments for "attendants" for those permanently and totally disabled who require it.

(c.) annuity payments, over and above any earned wages for specified numbers of months for specified injuries, such as loss of limbs, loss of hearing, etc.,

(d.) monthly survivor benefits to spouses and/or dependent children of deceased injured subjects who die as a result of "the injury," calculated at 50-75% (depending on number of dependents) of the employee's pay at the time of the injury.

The Task Force proposed that the amount of each type of compensation should be limited to the "excess" injury due to the research, i.e., to the injury or extent of injury which "exceeds that reasonably associated with the illness from which the subject may be suffering as well as treatment usually associated with such illness at the time the subject began participation in the research" [page VI-9]; one would assume this implies:

(a.) only the cost of additional medical care required by the injury over and above what costs otherwise would have been incurred should be compensated,

(b.) only those lost wages should be compensated that are due to the disabling effects of the injury (or illness) over and above what would otherwise have resulted from the injury from which the patient was suffering,

(c.) cash payments should be only for the portion of extent of certain injuries such as loss of hearing or limbs that is over and above what would otherwise have been suffered,

(d.) annuities should be paid to spouses and/or dependents only for the extent to which death caused excess loss of wages by occurring earlier due to the injury than it otherwise would have occurred.

Administrative issues. A group of "competent individuals" should review each case and determine "whether and to what extent compensation should be given" before compensable injury criteria above are applied, since application of the injury criteria will be so difficult in some cases "that reasonable persons may not agree." [VI-9].

Subjects participating in PHS-conducted research should be "included" in the FECA, which is administered by the Department of Labor, with actual costs of the awarded compensation "charged back" to the federal agency by which the individual was employed—which in this case would be the NIH or another agency of the Public Health Service.

Subjects in PHS grant and contract-sponsored research should be assured compensation equal to FECA's by the institution conducting the research, which would require PHS grants and contractors to purchase private health insurance or self-
Compensating for Research Injuries: Appendix M

insure, in either case, paying the costs of any awards either as premiums or as direct payments.

The Task Force did not address the question of the relationship of this program to other means of compensating injuries.

Relevant Experience of Existing Federal Programs

The following notes do not attempt to exhaustively describe these programs. They note only those features of the program that raise problems or suggest possibilities for implementing the kind of compensation programs for research subjects proposed by the Task Force, and described above.

Federal Employees Compensation Act

Defining Injury And Determining Eligibility For Compensation

FECA is designed around the concept of employment and the specific workplace environment. This concept is not always satisfactory for groups now covered by FECA. When Job Corps volunteers were included under the program by law, they had to be regarded as employed 24 hours per day and the workplace environment as almost unlimited. A compensation program for research subjects on this model would also have to cover the subject for 24 hours a day and extend to all aspects of the research subject's life, as well as the actual experimental setting and interventions. For example, an auto accident injury to an outpatient research subject might be attributable to dizziness, disorientation, or even anxiety resulting from the research, and might be compensable under FECA.

FECA has an arbitrary time limit of 3 years on filing a claim, but the Employees Compensation Board has construed the law to mean 3 years from the time the individual knew or should have known he was injured, opening the possibility of claims for injuries or diseases of long latency, or associations between diseases and workplace factors discovered years after the injury.

FECA, by law, adjudicates claims through its own review mechanisms and Appeals Board based on the body of workman compensation law; no appeal can be made to courts. The Board has ruled that pre-existing conditions do not affect eligibility for compensation. That is when an employer employs an individual he is taking him "as is," and if the workplace environment aggravates, accelerates or precipitates such a condition, the worker is eligible for compensation for medical care, lost wages and survivor benefits compensation just as if he had no such condition. If the employee's condition would have likely resulted in death in the near future anyway, and the workplace condition simply hastened it—nevertheless, the workplace would be regarded
under the law as causing the death, and pay benefits as if the individual were originally unimpaired. This raises a difficult issue regarding the cancer patient who is "employed" as a research subject and whose disease is aggravated or accelerated by the experimental treatment. Under FECA, the "employed" eligibility for compensation for medical care, any lost wages, and survivors' benefits would be determined as though the "entire" cancer were work-related, and not just the "excess injury" resulting from the aggravation."

FECA, guided again by principles of workers compensation law, does not weigh or assign percentages to the several contributing "causes" of an injury or illness. To be eligible for compensation, it need only be established that one cause or contributing factor is work-related. Under FECA therefore, any injury or disease to a research subject to which a circumstance of the experimental treatment or situation is a contributing factor makes the subject fully eligible. For example, a subsequent psychiatric problem might arguably be related to the research setting. The FECA Board has ruled that "Although compensation awards must be based on evidence and not on mere speculation, surmise or conjecture, the evidence required is only that necessary to convince the adjudicator that the conclusion drawn is rational, sound, and logical." 3 and "It is not necessary that the evidence be so conclusive as to suggest causal connection beyond all possible doubt in the mind of the medical scientists." 3

If FECA procedures were used for research subjects, especially if by regarding them as 24 hr./day employees, it would be difficult to single out for compensation only those injuries primarily caused by the research, or in excess of what would have occurred anyway.

Defining Types And Determining Levels of Compensation

Medical care. FECA compensates a far wider range of health and health related services than Medicare and most private health insurance programs, including drugs, devices and appliances, and even custodial care by an attendant when needed by the permanently and totally disabled. Most seriously ill or injured individuals, as well as their physician or hospital, would be better off financially if they were eligible for FECA coverage. One can argue this would create an incentive to qualify very ill research subjects for the program.

FECA attempts not to pay for medical care for chronic or other conditions unrelated to the workplace-caused condition, but often finds the care cannot be separated, and pays for other care.

In cases where a pre-existing condition is aggravated or an acute occurrence is precipitated, FECA covers the entire cost of the medical care for the condition until the individual is recovered from the episode. This model would lead to paying the entire cost of subsequent care to a research subject with cancer—or arthritis—if his condition were aggravated by the research or something in the research environment, and not just the "excess" share of the costs are attributable to the aggravation.

In cases where the workplace is only one of several contributing factors to the condition, the FECA program nevertheless pays for all of the costs of medical care for the condition—not just a percentage, or those in excess of what might have been incurred anyway as suggested by the Task Force for research subjects.

Compensation for lost wages or earning power. FECA makes payments to the disabled based on their monthly pay in the job in which they were employed when injured. The basic rate is 66⅔% for total disability (75% if the worker has dependents) and 66⅔% of the difference between earning capacity and monthly pay for partial disability. Since previous or current earnings with other employers, and future earning potential are not considered, this model would pay the injured research subject based only on their monthly pay, if any, as a research subject. For some groups that have been added by law to the FECA program, such as Job Corps Volunteers, the monthly pay is presumed to be at the GS-2 level, yielding a payment for total disability of approximately $402/month. Such a presumption of monthly pay for their services at the GS-2 or a higher level, could be made for all research subjects in the FECA model. This approach, however, would not allow consideration of earnings of research subjects before any current illness, nor of their earnings from a job they had at the same time they are participating in the experiment, nor of the future earnings they might have had—but for the injury.

Because of the principles of workers' compensation law, FECA compensates totally and partially disabled employees for their lost wages as if the work related "cause" was solely responsible for their disability, regardless of other "causes" outside the work environment or pre-existing conditions that made the injury more likely. Following this precedent for research subjects would seem to mean the program would compensate for all of the work loss due to disability of a research subject whose cancer or arthritis was aggravated by a research project—and not just the "excess" injury as proposed by the HEW Task Force.

FECA pays for work loss due to "partial disability" by estimating for each individual case of injury the earning power that the disabled individual still possesses. The difference between this estimate and the monthly pay when last employed is the basis to which the 66⅔% rate is applied. The estimate of earning power is based on medical judgments concerning extent of func-
tional impairment and remaining functional capacity, judgments by the claims reviewer of what jobs might be filled by the individual based on their remaining functional capacity, education and other factors, and current payment levels of these jobs. Because of the degree of subjectivity of these judgments approximately 50% are appeals to the Board. One would expect the appeals rate to be even higher in this area if attempted to isolate the "excess" disability attributable to the injury.

Once begun, compensation for wage loss under FECA continues until the patient recovers from the disability or dies. Permanent disability may be reduced to partial disability whenever partial function is recovered. The compensation level is automatically increased in increments in the cost of living.

Cash payments over and above earnings for specified injuries. FECA pays specified amounts for certain injuries (such as loss of a hand) even though the individual returns to work at the same job. Like wage-loss compensation, these amounts are computed on the basis of the employee’s wage when the injury occurred, but are payable for a specified number of weeks according to the injury (loss of hand gives 244 weeks of such payments). These compensation amounts appear to have no clear rationale. They are what politics supports and the comparable private insurance market place generally provides. Schedules of this sort are widely used in private insurance and other public programs (such as VA Benefits). While relatively few injuries (mostly loss of extremities or organs) are covered, the same principle might conceivably be used for research subjects to cover kinds and ranges of research injury, or even injuries in "excess" of the subjects’ existing illness or injury. The list would be long, however, and rational quantitative judgments of degree of excess would often be difficult. Moreover, rules do not presently exist for determining the amount of compensation to be provided for many types of impairments.

As with other compensation, these payments are made by FECA as though the entire injury were due to the workplace "cause" even though other "causes" or pre-existing conditions are involved. If compensation for a list of compensable injuries were used in place of or in addition to wage loss, it might create disincentives to conduct some types of research on subjects who are likely to suffer an "expensive" listed injury (e.g., diabetics who might lose their eyesight) because the research might be judged a contributing cause, and the research budget obligated to pay for the entire injury.

Annuities to spouses and dependent children. If an employee dies as a result of a workplace injury the work-loss payment calculated as above is made to the surviving spouse until they die or remarry and to dependent children until they are age 18 (or 23 if in college).
As with other compensation, FECA pays this annuity as though the entire injury were caused by the workplace condition, even though there were other causes or pre-existing conditions. Since these annuity payments can be very costly to the program over time, incentives would exist in a research subject program under FECA to avoid subjects with dependents whose death might arguably be contributed to or hastened by the experiment—since in these cases the death would be judged for compensation purposes to have been wholly caused by the experiment, and the research budget would be assessed for the long term costs. Such selectivity might even bias the research results.

In general, the methods under FECA and workers' compensation law for determining levels of all types of compensation seem to create incentives for the patient—and perhaps the researcher—to implicate the research in the injury or death. Since the program would compensate for the full injury, not just the "excess" injury, and since it would do this by considering the research only a contributing factor and not necessarily the major factor, there may often be an enormous amount for the subject and his survivors to gain and relatively little for the individual researcher to lose by doing everything possible to qualify the subject for compensation. Given the history of awards under FECA and workers' compensation to date, one could envision a situation where some types of patients (e.g. terminal cancer patients) would be almost routinely awarded compensation if the research was at all invasive. This could raise concerns in PHS grant institutions about the budgetary impact of research on human subjects, especially forms of research that result in numerous and large claims.

Administrative Issues—Including Relation to Other Programs
FECA and workers' compensation programs generally do not "coordinate benefits" with any other programs of compensation except for social security disability. That is to say, an injured worker may collect from any private disability insurance he may own in addition to FECA. If he is eligible for Social Security, the social security disability payment will be reduced by the amount of his compensation from FECA, however.

FECA permits no appeal of agency decisions to the courts. Appeals are made within the agency to an Employee's Compensation Appeals Board. This Board is directed by the Act, however, to base its findings on the body of workers' compensation law in the country, and is ultimately affected by the findings of courts on compensation cases. If different criteria were to be used for research subjects, they would have to be spelled out in the law. It is not clear whether the existing Board could be charged with ruling in these very different cases.

FECA determines whether compensation should be given by applying criteria for compensable injury. There is no initial
screening of claims to determine "whether and to what extent compensation should be given" by a group of "competent individuals" as recommended by the Secretary's Task Force' (page VI-9).

FECA has been amended to include a number of groups who are not federal employees in the usual sense, including:

- Individuals rendering service to the United States in a capacity similar to that of a civil officer or employee of the United States, whether paid or unpaid, are eligible for coverage, provided that the service rendered, travel or other expenses, are authorized by statute.
- Individuals other than independent contractors and their employees, who are employed on the Menominee Indian Reservation (Wisconsin) in a capacity relating to tribal timber and logging operations.
- Individuals (other than those stipulated above) employed by the government of the District of Columbia.
- Individuals appointed to the office staffs of former Presidents in accordance with the provisions of section 1(b) of the Act of August 1938 (75 Stat. 838).
- Members of the Reserve Office Training Corps.
- Civil Air Patrol volunteers.
- Peace Corps volunteers, and those volunteer leaders and volunteers with one or more minor children as specified and defined in section 2504 of title 22 of the U.S. Code.
- Job Corps enrollees.
- Youth Conservation Corps enrollees.
- Members of the National Teachers Corps.
- Members of the Neighborhood Youth Corps.
- Student employees of the U.S. Government (as specified and defined in title 5, section 5351 of the U.S. Code).
- Employees of the Panama Canal Zone.
- Employees of the Alaska Railroad.
- Non-federal law enforcement officers who are killed or injured under certain circumstances involving a crime against the United States.
- Other persons performing services for the United States within the purview of the Act, and all its amendments, substitutions, and extensions.4

FECA requires that the employee's supervisor be notified of the injury or illness within 30 days of the occurrence or that a

Compensating for Research Injuries: Appendix M

claim be filed within 3 years of the time the employee became aware of the problem. The supervisors' roles can be important in establishing that something did happen in the workplace that could be a factor in the injury. With regard to injuries to research subjects, the principal investigator may also be the supervisor in the FECA model and may find himself with conflicting incentives—the first to deny the relevance of the workplace factor for fear of its costs or other threat to his project but the second, to support it in deference to the tragic needs of the patient/research subject. Some administrative device may be necessary to protect both the P.I. and the subject in this situation.

FECA's costs are covered by charging back to each federal or other agency under the program the costs of compensation for their previous employees for the prior year. Most agencies include a separate "line-item" in their appropriations request to Congress to cover these costs. This would mean that NIH and others would simply request these additional funds from Congress. It is conceivable that total agency appropriations might not keep up with these rising compensation costs and that they could eat into program dollars. In a program for research subjects, these budget pressures could raise concern about the number of experiments of a type which experience indicates produce many claims. It would be possible, of course, for NIH to levy these costs in the form of a premium against all grantee institutions in which human subjects are used—in order to create disincentives (for fear of higher premiums) to "abusing" the system. This might, however, also discourage legitimate claims.

Cost Experience and Factors
The FECA program's benefit costs rose from $132 million in FY 1970 to $477 million in 1976, of which $287 million was for permanent disability. They are projected to exceed $1 billion in 1980. Their average rate of increase for the period 1970-1976 exceeded 23% per year. Costs for permanent disability rose from $54 million in 1970 to $277 million in 1976.

Claims increased from 1970 to 1976 by 127% to 40,324 from 17,795.

Factors often cited as contributing to rising FECA costs include:

a. Benefit payment levels have greatly increased due to amendments to the original act increasing the maximum level of benefits, and building in benefit increases to keep pace with the cost of living. Benefits can now be paid up to 75% of the highest wage step of a GS-15,

b. Greater awareness by employees of the compensability of diseases and injuries,

c. "More subtle and increasingly liberal determinations of work-related injuries",

d. Growing awareness of relation of occupational factors to disease,
e. Acceptance of workplace factors as a "contributing cause rather than the specific cause as justification for awarding benefits."

f. Tax incentives favorable to receiving workers' compensation as opposed to Civil Service Commission disability benefits or returning to work.

A compensation program for research subjects consistent with the recommendations of the Secretary's Task Force would seem to involve all of these suggested cost contributing factors even more than FECA. Based on the FECA experience, it is clearly important to find ways to define eligibility and compensation levels more narrowly for research subjects. The concept of "excess" injury is relevant to this.

Black Lung Program

Defining Injury and Determining Eligibility for Compensation (as of the 1977 Amendments)

Any person is eligible for benefits if:
- they have been employed in or around a coal mine or its environs,
- they have or are presumed to have any chronic dust disease of the lung that arises out of coal mine employment,
- the disease in their case arises out of coal mine employment, and
- they are totally disabled or have died from the disease, i.e., "partial" disability is not covered.

A person who has been employed for 15 years or more in a coal mine and is totally disabled or has died from a chronic dust disease, is presumed eligible for the benefits; for those with less than 15 years employment a combination of X-rays, tissue biopsy, autopsy and opinions of examining physicians ("when based on clinical findings and supported by a medical rationale", p. 28) are the bases for deciding eligibility.

A person with an advanced stage of the disease is presumed to be totally disabled, even though he may be currently employed.

Because the black lung program focuses very specifically on a poorly defined family of diseases, legislation and regulations have focused in great detail on tests and symptoms that indicate the disease is present and whether it is employment-caused. For example, the law specifies technical or other conditions under which X-rays and pulmonary function studies can establish the disease is present. In every case, these diagnostic tests cannot be used to disprove presence of the disease if other evidence sug-

gests it exists and considerable weight is given to the opinion of examining physicians—whom the individual is free to choose. A compensation program for research subjects where experimental procedures are being used for often poorly understood diseases might also run into similar legislative and regulatory efforts to rely on quantitative tests or measures of injury if they are positive but hesitancy to trust them as conclusive when they are negative. It might also allow the individual to choose his own examining physician. The variety of diseases or injuries dealt with in research subjects and the unfamiliarity of most examining physicians other than researchers with the treatment would make quantitative standards very complex and limit the value of the average family physician's option.

By a process of amendments to the law, all limitations on when claims must be filed relative to the date of last employment or death have been removed. A survivor may now file a claim no matter how long ago a miner died, for example, and the judgment will be made solely on the basis of affidavits and whatever medical records may still exist when no direct medical or other evidence can be obtained.

Since the enactment of the black lung program it has been continually broadened to include more and more injured workers and their dependents associated with mining, and in many respects appears to represent a Congressional effort to provide assistance to those individuals regardless of whether cause and effect can be established. Might Congress react to political pressure by using a program of compensation for research subjects to provide relief to cancer patients, for example, who agree to treatment that is in any way experimental?

Defining Types and Determining Levels of Compensation
The program provides compensation for medical care for black lung disease, lost wages and survivor benefits only for total disability and death. Lost wages and survivor benefits are calculated at ¾ of the amount paid under FECA to a federal employee in the first step of a GS-2 level, and increased for dependents up to the full FECA rate for a GS-2. The benefit is increased to reflect increases in the cost of living. A program for research subjects might adopt this approach of establishing a specific GS level on the basis of which benefits would be computed in lieu of any current employment pay rate.

Administrative Issues
The federal government is responsible for reviewing claims and establishing eligibility for benefits—and also what mine operator is liable for the injury. Initial decisions by claims examiners based on medical and other evidence can be appealed to the Benefits Review Board and to the U.S. Court of Appeals by either the individual or the mine operator.
Mine operators are liable for the cost of benefits awarded to former employees, and may either self-insure, or insure these costs with private insurance companies or the State Workers' Compensation funds. All mine operators who have sought such insurance have been able to obtain it either with an individual insurer or an insurance pool established by some 300 companies for this purpose. A research subject program might deal with research institutions on this same basis, with government determining eligibility for benefits but institutions insuring their own liability either privately or through State Workers' Compensation funds.

Responsible mine operators have been identified in 36% of the cases, but as of 1976 all had been appealed to higher courts, except 3.1%. Clearly the acceptance of liability entails potentially very high costs to mine operators either in direct payments or insurance premiums. If the research institutions were similarly assessed, one can presume resistance to accepting liability and dispute of the validity of the claim—and perhaps less enthusiasm for doing research using human subjects.

Cost Experience and Factors

The cost of claims that cannot be assigned to mine operators and administrative costs of the program are paid from a federal trust fund funded by an excise tax on coal producing companies.

The black lung program will expend approximately $900 million in FY 1980, and rise to over $1 billion in FY 1981. There were minimal expenditures under the program until FY 1979 when the effect of the 1977 Amendments was felt.

Social Security Disability Insurance/Medicare
Define Injury and Determining Eligibility for Compensation

Any individual who has worked the requisite number and pattern of calendar “quarters” in covered employment, and who is totally disabled (or expected to be totally disabled) for 12 months or more, is eligible for disability benefits beginning 5 months after the disability began, and for Medicare benefits beginning 2 years after eligibility for disability benefits began. The program has no mechanisms for paying for partial disability—or for determining increases in disability—that might be caused a research subject. The requirements for eligibility for disability benefits are higher than for retirement benefits.

No relation of the disability to the workplace or any particular cause is considered by the program. If the disability is total, and the individual has worked the requisite number of quarters in covered employment, he or she will be paid benefits. The program has no mechanisms for relating the disability to its cause.

Total disability is defined conservatively by the program to mean the individual is not only unable to do their previous work but also cannot engage in any other kind of substantial gainful
work. Thus an individual who is required by an injury to accept a lower paying job would not receive any compensation under the program. This is more conservative than Worker's Compensation and FECA programs, and inconsistent with the Task Force's recommendations.

Younger Americans, including students, are less likely to have established the number of quarters in covered employment necessary for eligibility, or if eligible to have established an earnings record reflective of their future potential. Some older Americans also are ineligible because they have not worked recently in covered employment and no group has ever been added to the Disability Insurance rolls on any basis other than working the required quarters.

As with FECA and workers' compensation programs, determinations of disability are subjective and widely contested with regard to whether or not the particular individual is so disabled that he or she cannot engage in any "substantial gainful work". In a report to the Subcommittee on Social Security of the House Ways and Means Committee in February, 1979*, consulting actuaries suggested the Courts ultimately decide such cases more on the vocational potential of the individual than on his medical condition, at a substantial increase in costs to the program.

Death and survivor benefits are paid under the Social Security Program when the individual has worked the requisite number of quarters, regardless of the cause of death or its work-relatedness.

Defining Types and Determining Levels of Compensation

The program makes payments to the totally disabled and their dependent spouses and children strictly according to his average wage over the period from, generally speaking, age 22 to the date of disability. There is no concept of "excess injury" or adjustments of payments for pre-existing conditions, etc. The maximum benefit permitted in 1979 was $552 for an individual and $987 for a family. Benefits are indexed to the cost of living once the individual is on the rolls. The average payment is $320 per individual and $639 per family, free of federal taxes.

Death and survivor benefits are similarly computed based on previous earnings and length of service in covered employment, with no adjustment for causes or other factors.

Full Medicare benefits are provided the disabled after two years.

Administrative Issues—including Relation to Other Programs

States make determinations of eligibility, with federal role limited to reversing, when warranted, positive eligibility decisions.

Individuals can appeal state and federal determinations to an Administrative law judge, an appeals council, and as far as the U.S. District Court.

Social Security disability benefits are generally reduced by any amount paid an individual under a workers’ compensation program. There is no such coordination with private or other public (e.g., VA benefits) programs.

The costs of the disability and other Social Security programs are paid through the FICA (payroll) tax.

Cost Experience and Factors

The cost of the Disability Insurance program in terms of benefits paid rose from $2.8 billion in 1970 to $13.6 billion in 1979; while the number of disabled workers grew from 1.3 million in 1969 to 2.9 million in 1979.

The long-range cost of the program in terms of percent of payroll was estimated at 0.42% in 1956, when the benefits were substantially narrower, and is currently estimated at 1.92%.

Since 1975 there has been a decrease in the rate of awards made per 100 insured workers (7.1 in 1975 and 5.2 in 1978) and in the number of applications received.

Factors cited by actuaries as contributing to the increase in costs of the disability program include:

- Rise in benefit payments to the point where some individuals receive more than their previous take-home pay.  
- High unemployment rate in early 1970’s making disability more attractive than available work.  
- Changes in attitude toward work, and in social pressures to remain productive.  
- Multi-step appeals process to levels where subjective factors (rather than medical) prevail in determination.  
- Attempts to expedite processing of claims during early years at expense of careful review.  
- “The difficulty of maintaining proper balance between sympathy for the claimant and respect for the trust funds in a large public system.”  
- Progressively healthier individuals have been granted benefits and/or allowed to stay on the rolls.

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The decrease in awards and applications since 1975 is the basis for a reduced projection of long-range costs of the SSA, but actuaries are still uncertain of their long-term significance.

The Amendments to the disability program recently sent to the President by Congress respond to some of these factors by changes in the incentives of the program, such as extending the "trial period" during which an individual may return to work without losing his benefits, and eliminating the 2nd 2-year waiting period for Medicare if an individual must return to disability status after a period of work.

Veterans Service-Connected Disability and Dependency and Indemnity Compensation (DIC) Programs

Of the several VA disability/retirement programs, the service-connected disability and DIC programs seem of most relevance to the compensation of injured research subjects.

Defining Injury and Determining Eligibility for Compensation

To qualify for total or partial disability and health care benefits in this program, an individual must have an injury or disease that is connected with his or her service in the military. There is no precedent to date for this, but if participation in research experiments were deemed by law to be equivalent to service in the military, research subjects might be covered by the program.

In most cases, "connected with," is interpreted as incurred in, or contributed to, or aggravated by the service—not necessarily "caused" by the service. For example, an individual who is disabled by a heart attack while in the service need not show it was "caused" by service—but only that it occurred while he was in the service, and/or that service factors were in any way contributory or aggravating. In cases where there is reasonable doubt about service connection or contributing factors, the VA as a matter of law is on the side of the beneficiary in consideration of the service to the nation rendered by military. This may arguably be an appropriate instance for participants in some research experiments. However, for many research subjects, who were already ill before the experiment and where reasonable doubt might often exist on whether the experiment worsened the condition, this might result in frequent and expensive benefits.

The VA eligibility determination apparently operates very much like the FECA operates in those special cases, such as the Job Corps, where the employee is considered to be employed 24 hours a day. This approach seems consistent with the risks taken by research subjects who may be affected by the experiment while off the site of the research.

VA service connected disability benefits, unlike workers' compensation or social security disability benefits, do not end if the individual returns to work.
The VA also compensates individuals for injuries or diseases or death as a result of their treatment in a VA medical facility, or in the course of treatment authorized by the VA just as though the injury or death were service connected. For example, a disabled veteran whose injury or illness is made worse during treatment may receive an increased disability benefit. The coverage does not extend, however, to the untoward results of normal treatments properly administered. Research subjects participating in VA experiments are currently compensated under this provision (Subchapter VI, Sec. 351 of Title 38 of the U.S. Code). The law covers any injury or death under this provision on a "no fault" basis, and are reduced by the amount of any award made to the individual in a civil suit. The size of the benefit would be determined according to the standard VA procedures described below.

This legal precedent would seem important for protection of other human subjects, and the actual experience of the program in awards to research subjects—if it can be described—might be helpful to the Panel in costing out a compensation program. The provision might also seem useful in attempting to define "excess injury" with respect to compensation for lost wages and medical care given the limits indicated below. No attempt is made to pro-rate death benefits for "early death" as a result of these injuries.

Defining and Determining Levels of Compensation
Compensation for Lost Wages (Disability Benefits). The VA compensates for lost earning capacity based on an exhaustive schedule of injuries and diseases—and varying severity of the same disease or injury. Each disease, or level of severity of the disease in the schedule is assigned a percentage of disability that this condition would cause in the "average man" (person). The schedule is expressed in quantifiable terms wherever possible—for example, loss of X° in arm flexion = S Y% disability.

To determine the level of compensation this percentage of disability is multiplied by the earnings of the "average man" (person) in the nation.

The "average man" concept averages out the differing disabling effects of the same injury on people of different professions. Similarly, the "average man" concept averages out the differing income potential of people in different professions. Consequently, for example, a former violinist, college student and bank president would all receive the same payment for loss of a hand.

Historically, this "average man" concept was resorted to (and a rank and service based payment abandoned) because so many of the military are young people with no substantial employment history, who would otherwise receive very low payments for the rest of their lives. The concept assumes all of these young people have the potential for attaining the income of the
"average man". The payment for total disability is currently $889/month, tax free. This "averaging" concept might be useful in resolving the question of how to compensate a young or student research subject.

The payment levels are adjusted yearly by Congress to respond to cost-of-living increases.

The work loss compensation as calculated above can be reduced if it can be documented or convincingly argued that the individual was already disabled before entering the service in a way definable in the schedule for rating injuries and diseases. If so, only the additional is compensable. This concept might be useful in determining "excess injury" as conceived by the Task Force, and the rating schedule perhaps warrants study by medical staff. However, the VA apparently applies this concept at present only for clearly documented physical injuries—such as where an individual was already missing several fingers and subsequently lost part of his hand. Moreover, in cases where total disability results from an injury, the VA does not even try to deduct earlier levels of disability. If the individual's suspected or known earlier condition cannot be defined in terms of the schedule, it is not deducted. While the schedule seems exhaustive to a layman, it seems unlikely that it distinguishes, for example, various degrees of severity of various types of cancer in sufficient detail to fix clearly the level of payment appropriate to the degree of "excess" injury.

Medical care. Individuals are offered medical care and rehabilitation for service-connected injuries or diseases for the duration of the injury or disease that is more comprehensive than Medicare.

Whenever possible, care is provided only for the service-connected injury or disease and not other conditions. In cases where a pre-existing condition is aggravated, the care is provided only for the "episode" whenever it can be defined. The program does not attempt to pro-rate costs of care in diseases where "episodes" cannot be meaningfully defined. The "episode" concept might be copied for a research subject, or broadened to cover only the "spell-of-illness" or the "hospitalization" clearly associated with the research.

Death benefits. Death benefits, since 1957, have been paid under the Dependancy and Indemnity Compensation (DIC) Program of the VA.

Under this program, widows, widowers, and unmarried children under age 18 of veterans are paid dependency benefits in the case of death due to service-connected injuries or disease, or a disability that is service connected.

Under this program, the monthly rate varies according to the in-service pay grade of the veteran from $326/month to $935/month, with additional payments for children, and is not
based on the “average man” concept. There are also special allowances for “aid and attendance” for patients in nursing homes, who are helpless or blind, or who are housebound.

**Administration—Relation to Other Programs**

VA service-connected disability benefits are payable even if the individual returns to full-time employment, and they are not reduced by any private disability, life or health insurance or workers’ compensation that the individual may have.

The VA does reduce benefits for injuries sustained in obtaining medical care for a service-connected injury by the amount of any damages awarded under a civil suit.

Individual cases are never closed; a veteran may present new or clarifying evidence at any time and obtain reconsideration of his application.

Individuals may appeal VA decisions to the Board of Veterans Appeals, but not to the courts. Most appeals are made of decisions concerning the extent of disability (e.g., 30% vs. 40%) and of the service-connectedness of the injury of disease. Of three million appealable decisions each year, 27% or 60,000, are questioned by the claimant. Of these 60,000, only 35,000 result in appeals.

The set schedules of disability benefits and the fixed benefit levels given the “average man” concept simplify administration of the program and, no doubt, account for the low appeals rate. Most appeals seem to be related to injuries and diseases where it is difficult to measure levels of disability precisely, and to the issue of service-connectedness.

**Cost Experience and Factors**

The program is paid for by an annual appropriation from general revenues.

Size of expenditures fluctuate on an annual basis relative to the number of active-duty military personnel and involvement of the military in combat. These total numbers, therefore, do not clearly exhibit the influence (or lack of influence) of the social and other factors that seem to be pushing up the costs of the FECA and workers’ compensation programs.

One aspect of the VA service-connected disability program would seem to provoke higher costs, although administration is greatly simplified. Namely, once an individual is judged to have suffered a service-connected injury that is permanent (e.g., loss of a hand) he will be paid the specified percent of disability for the rest of his life even if he returns to full employment.

To determine whether the VA or FECA compensation programs would be more or less costly for research subjects, an analysis of awarded benefits by types of injury over several years would be required.
Workers' Compensation Programs
Defining Injury and Determining Eligibility

Workers' compensation programs are legislated and administered at the state level, and eligibility varies from state to state. Many states (14) exempt employers with fewer than a minimum 3 to 6 employees and exclude many agricultural, domestic, part-time and other specific types of employees. In addition, for many (12% in 1975) who should be covered according to state laws, employers have not obtained coverage. In several states the coverage is elective for employers. To assure coverage of all research subjects under these programs, each state would have to review and amend their laws to require the research institution to include them in such coverage.

State programs also vary greatly in the types of injury or disease considered compensable, the meaning of "causation", the period during which a claim may be filed and other matters. Some, for example, are written in terms of "accidents". Others exclude "ordinary diseases of life". Others require the working condition to be responsible independent of any other cause. While court cases seem to be moving toward common interpretations of many of these variations, to cover the situation of research subjects each law would need to be studied and appropriately clarified.

Defining and Determining Levels of Compensation

The level of compensation for work loss varies greatly among states. For example, maximum weekly payments for permanent total disability range from $98.00 in Arkansas to $426.40 in the District of Columbia. (The FECA program maximum is $722.78.)

State programs also use arbitrary schedules of payments for some specific injuries (such as loss of a hand), but vary in the number of weeks of work loss paid for each injury.

Most states cover medical care for the injury without time or monetary limitations. Seven states, however, have maximum limits on total costs (ranging from $100-$20,000), or types of diseases (Ohio excludes silicosis and pneumoconiosis), or on specific services (such as artificial appliances).

Death or survivor benefits vary from a maximum weekly payment of $98.00 in Mississippi to $353.19 in Illinois—and no limit in the District of Columbia. Some states limit duration of benefit, total lifetime amounts that can be paid and other features. (The FECA program maximum is $722.78.)

To adjust these varying programs to the FECA levels suggested by the HEW Task Force would require amendment of virtually every state law. At a minimum, the Panel might want to consider extents of variation among states that might be permissible in a program for federal research subjects and seek state accommodation to resulting minimum changes.

Administrative Issues—Relation to Other Programs

Employers obtain coverage in compliance with the state law by either self-insuring or purchasing qualifying insurance from private insurers. In some states, the state government operates a state insurance program competitive with private insurers, or in place of all private insurers.

By accepting compensation under state laws individuals surrender their right to bring suit against the employer.

Individuals who qualify for both workers' compensation payments and Social Security disability payments will generally have their Social Security payments reduced.

The federal role in workers' compensation programs is primarily one of technical assistance to the states and national reporting. There are no federal standards for eligibility, benefits, or other elements of the program—although there is periodic debate in the Congress on the need for such standards. Any changes in the programs must be made by each state legislature at its initiative.

Cost Experience and Factors

Costs of state programs are currently borne primarily by the employer premium payments, with only a share of the administrative costs of the state program coming from state revenues. There is debate between the advantages of "internalizing" all the costs of occupational injury in the employer premium to encourage efforts at workplace safety, and the need for tax subsidies when the courts or law, for example, expand coverage into areas where risks are high and hard to determine. This tension would seem to be especially strong with regard to research subjects.

Actual costs of the program, as reflected in insurance premiums, between 1969 and 1979, have increased by a factor of 2 or more in most states, and by a factor of as much as 5 in Pennsylvania and the District of Columbia.19

A major portion of the increases in premium rates is attributable to expansions of the law. Factoring out the cost of such changes, Pennsylvania's growth factor was 2 and the District of Columbia's 3.

Premium costs in a state do not reflect the costs to individual employers, since most employers' premiums are "experience rated" and "retrospectively rated"—that is the premium reflects

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the level of past claims by the employer or the experience of similar employers under insurance. Smaller employers are often offered premiums that reflect the claims for all small employers—insured in the area—and are typically higher. Thus some employers have experienced a far higher rate of increase than the figures cited above, and are sensitive to any changes in the law that would further increase their costs. Given the range in size of "employers" of research subjects, considerable variation in premium impact might be expected if states mandated this coverage.

Fifty percent of the benefit payments under state programs are for disability and death, even though they are responsible for only 5% of the cases. "Excessive litigation" is often cited as a contributing factor to these costs, along with other factors that cannot be predicted by actuaries, and similar to those suggested for the increases in FECA costs.

FECA, in most respects, can be characterized as an exceptionally generous workers' compensation program for federal employees. Because it bases its claims review and adjudication on the body of workers' compensation law, it reflects the experience of the states—and the cost factors at work in the states.

Suggestions for a Compensation Program for Research Subjects

Based on the problems and possibilities noted above in using existing federal compensation program models to cover research subjects, we can offer the following suggestions for the design of a program for research subjects. These design suggestions, for the most part, should be considered for both a program administered directly by the federal government for research subjects in direct PHS conducted research, and programs provided by private insurers to PHS contractors and grantees. In our view, if private insurers find it difficult to market or administer a program that is responsive to suggestions such as these, then a program administered by the federal government should be made available to all PHS research subjects, whether involved in PHS directly or grant/contract funded research projects. Federal coverage can best be provided, in our view, by either amendment of the Federal Employees' Compensation Act or the veterans benefits authorities.

The suggestions that follow are meant more to indicate types of steps needed to implement the Task Force's suggestions than to precisely specify changes in existing laws. After review and discussion of these suggestions by the Commission, precise specifications for changes in law will need to be drawn.

Defining Injury and Determining Eligibility for Compensation

Suggestion #1

Existing federal programs for injured persons determine eligibility for benefits by first, establishing that the injured person
is covered by the program, and second, establishing that the injury is covered. FECA, for example, covers persons who are employed and the coverage is provided only during their employed hours. The VA covers persons who are or have been in military service. The Social Security disability and Medicare programs cover anyone who has worked for covered employers the requisite number of quarters. Of these various approaches, research subjects are most like military employees or veterans, and also some of the added populations under FECA such as Peace Corps and Job Corps. Research subjects, even ambulatory subjects, will in all likelihood need to be covered 24 hours per day (like military) while they are participating in the experiment. This seems clearly true for hospitalized subjects, but also is true of outpatient subjects who are taking drugs or are involved in some other intervention. Any injury or disease in their daily experience (an auto accident injury, for example) might be contributed to the experimental procedure. Therefore we suggest that:

#1 Research subjects be covered 24 hours per day during their participation in an experiment or, the basis solely of the service they render the country by agreeing to participate.

Suggestions #2, #3, and #4

Establishing that an injury is covered for FECA, VA and other government programs means establishing that a workplace or service factor contributed to the injury or illness, whether it is a very severe or relatively minor injury. For Social Security and black lung, such an injury is eligible only if it results in total disability or death. The HEW Task Force would go a step further than existing programs in the disability measurement process, and require "excess" injury to be identified to establish eligibility. No public program has succeeded in implementing such an "excess injury" concept. In most cases, FECA, workers' compensation programs generally, and the VA do not reduce benefits to reflect pre-existing conditions, "early death", or injuries for which there are multiple causes, most of which are unconnected with service or employment. This raises important problems for those research subjects who are actually selected because they have pre-existing conditions (and who are sometimes terminally ill), and subjected to procedures whose results are not fully known. From an insurance standpoint, this is selecting for coverage persons who have the greatest potential for making large claims knowing at the outset that their conditions are serious and it will be difficult to show the experiment has no connection with their death or worsened condition. This suggests that for research subjects there needs to be some tightening of procedures for determining whether the injury is service- or workplace-connected, and other narrowing of eligibility of benefits. We therefore suggest that:
#2 Research subjects who are classified critically or terminally ill should be offered a narrower and standard benefit (as described under benefits below) if the event their conditions are worsened or they die earlier as a result of the experiment, and the extent and prognosis given accepted clinical care for their condition be spelled out and documented prior to the experiment to provide a basis for judging the consequences. (This suggestion presumes an effort should be made to define "excess" injury but it will prove impossible often to determine [or defend in court] how much earlier death occurred or how badly a condition was aggravated in the critically or terminally ill, and that concern with costs and fairness argue for standard amounts made known and agreed to in advance by the subject [for example, "we are giving you an insurance policy for death and disability covering wage losses of up to $1,000—and all medical care for injury from the experiment for up to 1 month."])

#3 Research subjects selected for pre-existing conditions, but who are not critical or "terminal", should be offered standard VA or FECA benefits in the event they are killed or injured to the degree that their pre-existing condition is worsened as a result of the experiment. The extent and prognosis for their condition given accepted clinical care would be spelled out and documented clinically prior to the experiment as a base for measuring the worsening effect. (This presumes an effort should be made to define and compensate only "excess" injury in those with pre-existing conditions and that the clinical documentation will help—but that in many cases this effort will not succeed, and then these individuals should be treated like those under VA or FECA who had pre-existing conditions. A less risky and more fiscally conservative position would be to offer these individuals a coverage more limited than FECA and VA but more generous than that offered the critically or terminally ill [for example, life insurance of $100,000 and disability coverage for up to $100,000 depending on seriousness and duration, and medical treatment until the end of the "episode" of illness or 6 months maximum]. In fact, several levels of coverage might be developed to limit the government's liability proportionate to the seriousness of various pre-existing conditions with the more generous benefits for those whose pre-existing conditions are least likely to be disabling or terminal.)

#4 Research subjects who are "normal" should be covered under standard FECA or VA procedures for eligibility.
Suggestion #5
The HEW Task Force adds a third condition of eligibility—namely that the research subject treated for an illness through an experimental procedure is not eligible for compensation if the new procedure is found to be a medically preferable procedure overall—even if the results for the specific individual in question were worse than might result from existing procedures. No existing federal program contains such a condition. It would seem to suggest both delay and serious cause for litigation given the evolutionary way that new procedures are accepted into medical practice. Moreover, the public will never understand this requirement. We therefore suggest that:

#5 The exception for injuries resulting from experimental procedures that were found to be medically preferable procedures be dropped as unadministerable.

Suggestion #6
One unavoidable lesson of the black lung program is that Congress can use occupational injury programs as a means of offering needed relief to a special population to the point where issues of workplace or service connectedness are made secondary to the needs of that population. Given Congressional interest in cancer and heart disease and in catastrophic health insurance, it is not difficult to imagine a compensation program for research subjects becoming a program of medical care and compensation for terminally ill cancer and heart patients and their families. A politician might argue for a broadening of the definition of what constitutes an experimental treatment and urge the benefits be available to anyone who participates even in the least risky of "experiments". One might argue for merging compensation for research subjects into another program with minimal change so they are not so visible and separate a target for such expansion. If this were done, the VA service-connected disability program would be the best, since FECA and workers' compensation decisions are appealable to the courts, which have shown a tendency to liberalize compensation for research subjects in the same way as Congress. We suggest alternatively that:

#6 The program specify fixed benefits payable to terminally or critically ill patients and patients with pre-existing conditions, as suggested above (thereby laying the issue clearly before Congress in a way that does not ultimately influence compensation for all research subjects, including "normal" volunteers).

Defining and Determining Levels of Compensation
Suggestion #7
In all government compensation programs, broad medical care is provided without regard to the level of earnings of the injured party. Once eligibility is established for the person and the injury, the medical services covered are very broad. An at-
tempt is mad: to differentiate medical care for the injury from care for other conditions the individual may suffer, and to differentiate between the specific “episode” of a chronic illness that may have been workplace or service connected and subsequent “episodes” that are not. This is not always possible, and depends on the specific condition and circumstances. Generally, it is difficult to define the costs of treating the “excess” injury only. We therefore suggest that:

#7 Non-critically ill research subjects should be offered comprehensive medical care for injury exactly as under the FECA and VA programs. Critically or terminally ill patients who are injured should be offered all care associated with their original illness or injury, or any new injuries for a fixed period, for example, 6 months or until their death.

Suggestion #8
Compensation for lost wages and survivor benefits under most government programs is related to earnings of the individual in his employment prior to the injury, and in most cases are calculated as a percentage of such earnings. The VA has a different concept with regard to service-connected disability compensation for lost wages to pay a percentage of the earnings of the “average man” (person) in the nation—rather than the prior earnings of the particular person injured. This difference was made to take account of the fact that many military personnel are young, have little history of earnings, and what they have does not reflect their lifelong potential. The “average man” approach seems fairer, and is more easily understandable and less litigious than attempting to estimate the potential earnings of young people—or even old people for that matter. Indeed, under both FECA and VA among the most often litigated cases are those dealing with such non-medical factors as employability or earnings potential of the injured employee. Such litigation is costly, it delays benefits, and it is cited as causing over-liberalizations and rising costs of the programs. We therefore suggest that:

#8 Injured research subjects should be compensated for lost wages and survivor benefits based on the “average man” (person) concept used by VA. The specific “average” wages specified in VA law and regulations—which are updated regularly to reflect wages in the nation—should be used as a base for injured research subjects.

Suggestions #9, #10, and #11
The percentages applied to an earnings base to calculate compensation for lost wages in FECA workers’ compensation, and VA programs reflect the extent of disability caused by the injury. No government program defines “excess” injury over and above a pre-existing condition; instead they pay for aggravated or accelerated conditions as if they were wholly caused by the in-
jury. The only possible exception to this is the VA practice of compensating for additional injury caused by an already compensated patient during the course of treatment. On this situation, however, the individual is already being compensated by VA for a service-connected injury, and the percentage of disability is simply increased to reflect the additional injury. This is a different situation than would exist in research settings when the individual’s pre-existing injury or illness is not being compensated. It would be worth additional research into VA awards to (if there are any) research subjects (under Sec. 351 of the law) whose pre-existing injury was not being compensated—as a means of refining provisions for covering research subjects. However, it seems likely that “excess” injury to research subjects will often be impossible to define for purposes of compensation for lost wages in existing programs, and likely that some fixed limits must be placed on levels in addition to excess injury determination for reasons of both fairness and economic factors.

Existing government programs also differ in how they determine these percentages of disability. Under FECA, cases seem to be reviewed on a more individual basis than does VA, considering both medical factors and the education, personality, and employability of the individual. This type of review results in an approximately 50% rate of appeal on these decisions. The VA weighs medical factors more heavily, and averages their disabling impact on individuals by extending their “average man” (person) concept into this area as well. The VA is able, because of this approach to follow an extensive schedule of medical injuries and illnesses with a percentage of disability associated with each. Since a wide range of percentage of disability is often associated with the same disease depending on its level of severity, and since it is sometimes difficult to cite quantifiable measures of the level of severity—with regard to emotional disorders, for example—there can be appeals here also. The “average man” approach also should be questioned regarding its “fairness” to the young, those employed in physical jobs, and others for whom most injuries might prove more serious with regard to wage loss than for older employees or employees with sedentary tasks. We therefore suggest that:

#9 Injured research subjects who are critically or “terminally” ill should be awarded compensation for work loss of a fixed number of months (for example, 1 month) with the benefit amount based on the VA “Schedule for Rating Disabilities,” with the percentage of disability reduced to reflect pre-existing disabilities. (The percentage would be applied to the “average man” (person) earnings as recommended above.)

#10 Injured research subjects who are selected for pre-existing conditions, but who are not critical or terminal should be awarded compensation for work loss based on the VA “Schedule for Rating Disabilities,” with no fixed
limit on the number of months, with the percentage of
disability reduced whenever possible to reflect pre-
existing disabilities. (A less risky and more fiscally con-
servative alternative, as mentioned above, would be to
offer these individuals a fixed level of coverage that
limits the government's liability proportionate to the
seriousness of the pre-existing condition.)

#11 Injured research subjects who are selected as
"normal" be compensated for work lost based solely on
the VA "Schedule for Rating Disabilities".

Suggestions #12, #13, and #14
Survivor benefits should be similarly structured. No pro-
gram can distinguish "early death" to the end of paying only for
excess injury. However, attempts to reduce the number of
months to the level of the prognosis prior to the experiment may
be warranted if the fixed benefit is set higher than six months.
We therefore suggest that:

#12 Injured research subjects who are critically or
"terminally" ill should be awarded survivor benefits, if
at all, for a fixed number of months (for example, 1
month) using the FECA percentages and regulations,
but using the "average man" (person) earnings as rec-
ommended above as a wage base.

#13 Injured research subjects who are selected for pre-
exisiting conditions but who are not terminal should be
awarded survivor benefits using the FECA percentages
and regulations, but using the "average man" (person)
earnings as the wage base. In cases where the pre-
exisiting condition clearly indicated a reduced life ex-
pectancy, the payments should be limited to the number
of months or years indicated as the life-expectancy of
the patient prior to the experiment.

#14 Injured research subjects selected as "normal"
should be awarded survivor benefits using the FECA
percentages and regulations, but using the "average
man" (person) earnings as the wage base.

Administrative Issues—Relation to
Other Programs

Suggestion #15
The administrative structures in place for the various gov-
ernment programs are extensive, and each has evolved a body of
regulations and precedents for adjudicating claims. It would ap-
pear to be unnecessarily expensive to duplicate these or-
ganizations to handle the relatively small numbers of research
subjects. Of these federal programs, the FECA or VA programs
seem best suited to incorporating this population in terms of their
current eligibility, benefit, and administrative structures. Either
could administer their basic program with the modifications sug-
gested above for research subjects. The choice should be made, once the panel has decided on the relevant issues of eligibility and benefits, on the basis of a) administrative similarity of the final proposed program to the two existing programs, b) the relative cost of the program under the two alternatives, and c) the political ramifications of the two approaches. We therefore suggest that:

#15 A compensation program for research subjects involved in directly conducted federal research at NIH or other PHS organizations should be administered under the existing FECA or VA programs with appropriate changes for this new population. If the Panel decides on federally provided coverage, also for research subjects under PHS grants and contracts, the coverage should be similarly provided.

**Suggestion #16**

The decision as to whether to provide a compensation program to research subjects under grants and contract through a federal program or through private insurers is primarily an issue of administrative practicality and politics. Whichever way the program is implemented, the Panel will have to establish standards for the coverage to be provided by government or by private insurers, and decide such issues as how much of the cost burden to place on the grantee/contractor institution by how it handles the costs in its calculation of the grant or contract.

Administratively, the issue is whether the grantee/contractor institution can obtain private insurance that meets the Panel's standards if mandated to do so. Politically, the issue is whether the federal government and federal budget should bear the burden of the administration and costs of the program. Given the complexity of the programs, the uneven record of the federal government in the area, and the politics of the day, we believe the best course is to use the private sector to the greatest extent possible. Moreover, by establishing a program under FECA or VA for research subjects in direct federal research at NIH, the commission and NIH will gain experience and sophistication needed for reviewing the situation of grantees and contractors again in a few years if the private insurance approach proves problematic. In addition, since obtaining changes in all the state workers' compensation laws would be cumbersome, the law should assure coverage of PHS research subjects by requiring grantee/contractors to provide the specified coverage as a condition of grants or contracts:

#16 Mandate PHS grantee/contractor institutions to provide compensation coverage for research subjects through private insurers as a condition for receiving a grant or contract.

**Suggestion #17**

The HEW Task Force recommended that a special panel of competent individuals review claims prior to their review and
Compensating for Research Injuries: Appendix M

adjudication within a compensation program. No existing government program uses such a mechanism. Panels are used for appeal and adjudication purposes, and medical examiners, on-the-job supervisors and others involved in the case are asked to provide evidence for the claims review or adjudication. It is not clear what purpose the Task Force intended for this special panel, but 2 purposes might be conceived. First due to the state-of-the-arts nature of much research using human subjects, it might be necessary to resort to a small group of clinician/researchers familiar with the field of the research in a particular case to determine whether an injury is in “excess” of what would have happened in the usual treatment. Second, because the researcher in any given case is frequently also the physician, “employer”, and “supervisor”, of the individual, he is in a situation filled with conflict of interest, and a Panel of people familiar with these diverse interests, and the interests of the patient, may be needed to do an initial review of claims for basic credibility, and to establish the needed full and accurate information. To be thorough, however, such a panel could reduce the danger of a researcher making decisions or offering patient advice from a conflicted situation. Third, given the state-of-the-arts nature of the research, such a panel might be given authority to render final unappealable judgments on “experiment connectedness” of the injury and degree of “excess”.

Of these roles, the second seems clearly desirable; the first might best be handled on an ad hoc case-by-case basis and, based on the heavy litigation in other compensation programs, the third is apt to result in grievances and court challenge to the law itself. We therefore suggest that:

#17 A special panel of competent individuals review the possible injuries to research subjects (to relieve the researcher of this responsibility) to identify those which merit a claim being filed and reviewed within the program.

Suggestion #18

The means of financing a compensation program for human subjects can change the costs of research differentially among areas of research, and create incentives for behavior during the course of research that should perhaps be reviewed by the Commission. The “charge-back” approach used by FECA, whereby federal agencies are charged after the fact for any claims awarded their employees, would seem to create greater safety consciousness in the employer. The black lung approach of assigning liability for awarded cases to the mine operator whenever possible is aimed at exactly this goal. It also seems likely that such a “charge-back” to the specific institution creates an incentive for the institution to discourage the filing of claims.

Moreover, in a research setting, if costly claims proved to be frequently awarded to some types of research subjects (for exam-
ple, terminal cancer patients), whether because of real injuries or the inability of the process to establish causation or "excess", this charge-back could make these types of research more expensive to the government and/or grantee/contractor institution, and increase the difficulty of financing the research. Conversely the VA system, which obtains a separate appropriation solely for its programs without "charge-back" to the military service or unit where the injury occurred, would seem to create no incentives for safety or carefulness, and may even establish incentives to encourage individuals to make claims wherever there is a chance of award. The VA approach could be implemented best in federally provided insurance (as opposed to private insurance) but the incentives under even a private insurance system can be affected by how much of the costs of the private insurance are paid by government in grants and contracts, and how much is required of the institution. This critical set of issues was not resolved by the HEW Task Force, but is a key cost factor, since cost of a research subject's compensation programs would seem highly influencable by such incentives. We suggest that:

#18 The costs of the program be borne by the federal government under a separate appropriation (or the VA model) and other mechanisms be used to assure adequate care and safety in experiments.

Suggestion #19

Government programs present several models for reviewing and adjudicating claims. Under FECA and VA the claims are reviewed and awards are paid by the federal government. Under Social Security, claims are reviewed and awarded by state governments (with federal reversal possible) and paid by the federal government. Under the black lung program, claims are reviewed and awarded by the federal government, but paid ultimately by mine operators or their private insurers, and finally, under workers' compensation, claims are reviewed, awarded and paid by private insurers (or state insurance funds). The HEW Task Force selected the FECA model for research subjects in direct federal research, but did not indicate for grantee/contractor subjects whether claims review and award should be done by government or insurers. For the sake of consistency, and to minimize the role of the courts and its potential cost consequences, the FECA program or VA might review and award all claims, with insurers making payments for subjects in PHS grantee and contractor experiments. If insurers are unwilling to surrender this degree of control, they might be given the claims review and award functions with the possibility of the FECA or VA later assuming both this function and direct payment of awards if FECA or VA experience on direct federal research subjects is favorable. We therefore suggest that:

#19 The FECA or VA should review and adjudicate all claims, including those made against private insurers for research subjects of PHS grantees and contractors.
Compensating for Research Injuries: Appendix M

Suggestion #20

The VA program requires no coordination of benefits with Social Security or other programs, based presumably on the idea that the injury is the result of government service, and compensation by government should be unrelated to the benefits which the individual is due from other programs whether private or social security. The VA does, however, offset against benefits it awards to the individual made as a result of a civil suit against the government. We suggest that:

#20 The compensation program for research subjects follow the VA model, and not coordinate benefits with other programs, and offset any civil awards against benefits.

Discussion of Costs and Cost Factors

The costs of compensation programs are clearly rising, whether measured in terms of premiums for private workers’ compensation insurance or federal costs for FECA. It is also clear that actuaries are hard pressed to quantify the factors that are contributing to this increase. The table below compares actuarial projections for the Social Security Disability Insurance Program made in the past with current projections for the same years.

Growth in Estimated Cost of DI Program

<table>
<thead>
<tr>
<th>Year of estimate</th>
<th>Long-range (as percent of payroll)</th>
<th>Short-range † (millions)</th>
<th>1980 projection (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1956.</td>
<td>0.42</td>
<td>$379</td>
<td>(†)</td>
</tr>
<tr>
<td>1957.</td>
<td>0.49</td>
<td>492</td>
<td>$1,380</td>
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<tr>
<td>1958.</td>
<td>0.56</td>
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<td>1963.</td>
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<tr>
<td>1965.</td>
<td>0.95</td>
<td>2,068</td>
<td>3,351</td>
</tr>
<tr>
<td>1966.</td>
<td>1.54</td>
<td>6,295</td>
<td>N/A</td>
</tr>
<tr>
<td>1967.</td>
<td>2.97</td>
<td>9,640</td>
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</tr>
<tr>
<td>1969.</td>
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<td>16,197</td>
</tr>
<tr>
<td>1971.</td>
<td>3.68</td>
<td>14,822</td>
<td>16,817</td>
</tr>
<tr>
<td>1972.</td>
<td>2.26</td>
<td>16,532</td>
<td>16,532</td>
</tr>
<tr>
<td>1974.</td>
<td>1.92</td>
<td>17,212</td>
<td>15,600</td>
</tr>
</tbody>
</table>

† Short-range represents intermediate estimate of cost for second year after the year of estimate.
† No 1980 projection made; 1975 costs were projected to be $949,000,000. NA—not available.

Source: Estimates prepared by the Office of the Actuary of the Social Security Administration in connection with legislation (1956-67) or as a part of annual trustees’ reports (1973-79). Short-range costs shown in this table are benefit payments only.
In every case until 1979, the older projection markedly underestimated the growing cost of the program. The decrease in claims experience and costs since 1975 in the program are also unexplained at present—and their long range significance is unclear.

Similarly with FECA and State workers' compensation programs, actuaries and GAO studies can only suggest factors contributing to the rise.

Much of the speculation concerning causes of the increases relates to a few critical factors however:

- the awareness of the availability of the benefits to possible beneficiaries,
- the attractiveness of compensation benefits to individuals, especially as compared to the benefit of returning to work, and especially in hard economic times in the nation,
- the medical difficulty of establishing "causation" in workplace or service connected cases, and the increasingly liberal interpretation of "contributing factors" as grounds for awarding benefits,
- the principle of workers' compensation law that "pre-existing" conditions aggravated or accelerated by an injury be treated as though wholly caused by the injury, and the medical difficulty of quantifying the "aggravation" in any case,
- the subjectivity of judgments regarding percent of disability associated with various injuries and their effect on specific individuals,
- the role of the courts in liberalizing interpretation of the law, "in favor" of the "beneficiary", and
- the tendency for Congress to liberalize such programs as means of insuring assistance to needy populations.

These factors are clearly troublesome when considering the likely costs of compensation to research subjects. Such subjects will surely be made explicitly aware of the availability of the benefits as part of an informed consent procedure. The benefits would clearly be attractive, especially to terminally ill patients who may not be able to return to work at all and are surely concerned about their survivors' welfare. They may also seem attractive to the researcher and clinical facility because of broader coverage of medical care and assistance to a patient with whom they empathize.

- In experimental procedures it may in many cases by very difficult medically to establish "causation" or that the intervention was not a "contributing" factor.
- For patients who are selected because they are already ill with a disease, there will be a higher percentage than in the general workforce for whom "excess" injury cannot be quantified, but the total impairment will be very severe.
- Because many research subjects are young, the real effect of an injury on their long range potential is very speculative.
- The possibility that Congress would liberalize the program on behalf of cancer or other patients whose illnesses are undergoing research seems higher than with many other beneficiaries.

Given the lack of actuarial certainty on cost factors and the seemingly high "score" of a program for research subjects with regard to hypothesized factors, the Commission can only guard against high costs by incorporating provisions designed to lower the program's "scores" on these factors. Many of the recommendations already made are consistent with this objective.

(1) By requiring documentation of pre-existing conditions and their prognosis and an effort to pay only for "excess" injury, the program may succeed in making smaller awards than are currently made. Experiments are conducted after all, in medical settings where personnel are capable of rigor in documenting both the pre-existing condition and its aggravation; this allows for a far greater opportunity to distinguish "excess" injury than is possible based on an induction examination or pre-employment physical, for example.

(2) By setting an upper limit on the number of months benefits would be payable to high-risk or "terminally ill" subjects, a ceiling is established for actuarial purposes on this most difficult category. If the commission wanted to further limit costs, as suggested earlier, it might also set upper limits, albeit somewhat higher, on benefits to all research subjects who are selected because of a pre-existing condition. Please note that the subject need not be classified as "terminal", but only that he/she is in a higher than normal risk category—and therefore the government is willing to accept less liability. In any case, the subject could be informed of his precise coverage and its limits before agreeing to the experiment.

(3) By using the VA's "average man" (person) concept, the problem of estimating the long-range impact of an injury on a young person's earning potential is eliminated by "averaging" it out. Likewise, by using the "average man" concept to assess the disabling effect of injury regardless of the individual's vocation, etc., the problem of estimating these specific effects is eliminated. These subjective areas are the source of many of the appeals and court cases in compensation programs.

(4) By using the VA "Schedule for Rating Disabilities" which for each disease or injury and level of severity sets a percentage of disability, we can attenuate a further area for liti-
This schedule may also serve, in some cases, as a means of quantifying both the disability attendant to the pre-existing condition and the injury compensable. In many areas of disease and injury, however, the schedule itself is far too subjective in its distinctions of levels of severity to be much use in this regard.

(5) Lastly, by establishing a panel of individuals to make a preliminary review of the credibility of a subject's claim, the program would lessen any incentive in the research or health care facility to “err on the side of compassion” in encouraging or documenting claims—as well as helping assure that credible claims do get filed.

One last step that the Commission might take to limit cost is to eliminate appeal beyond the FECA or VA programs to the courts. The VA program currently does not permit appeals to the court, and the advisability of this law was recently upheld in the Senate when suggested amendments to permit such appeals were defeated in committee. The FECA program does permit court appeals.
Arbitral Processes for a Program to Compensate Injured Research Subjects

Irving Ladimer, S.J.D.*

Executive Summary
Federal regulations for protection of human research subjects define informed consent to include "an explanation as to whether compensation and medical treatment is available if physical injury occurs" (45 CFR 46.43, FR 51559, Nov. 3, 1973). No system of compensation is proposed. Claims for injury have already been made and paid, and others will doubtless be filed. Thus some review and dispute resolution methods must be considered.

Under any system, or none, differences will arise regarding entitlement to compensation, responsibility and liability. This report is concerned solely with adjudicating such differences. In the absence of an alternative, disputes not informally settled by the parties will generally be litigated under various state laws. Court trials and judgments are often time consuming, costly and inconsistent.

Proposal. Upon review of available possibilities and methods best suited to the research field, this report proposes arbitration, binding or advisory (for public agency sponsors) as the optimum forum for adjudicating disputes. Voluntary, contractual arbitration would be offered by research investigators and sponsors as an option as part of the customary consent agreement. It would be binding as to private parties and advisory for public agencies that cannot cede the right and responsibility of determination to others. Arbitration voluntarily chosen can be employed with or without special authorizing legislation, for resolving differences under any compensation system, whether based on conventional tort or contract causes of action or a no-fault principle with scheduled benefits.

Arbitration Defined. Arbitration is a recognized form of private dispute resolution, generally voluntary, employed to deter-


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mine issues presented to neutrals for adjudication in accordance with the rules and conditions presented by the parties under governing law. Although arbitration is an alternative to litigation, it is also subject to specific law in most jurisdictions or accepted and enforced under common law contract principles. In brief, it is a method generally available for resolving differences or selected issues within the legal system. There are various forms and types of arbitration and, for the most part, all are generally available in most jurisdictions. The classic form of arbitration and the one most widely used is voluntary binding arbitration.

Arbitration in some form is available under state and federal jurisdictions, by virtue of general or special state arbitration statutes and the U.S. Arbitration Act. The modern arbitration acts recognize and enforce agreements to arbitrate future as well as existing controversies.

Arbitral Processes. Arbitration is a versatile process based on contract which allows for different formats, modes of administration and methods of adjudication by expert arbitrators or panels determined or selected by the parties. Administration, as recommended in the Proposal, would be through the national network of American Arbitration Association offices which can provide professional service, for fees, to the parties.

Alternatively, administration can be undertaken by a federal agency or on behalf of a federal agency. Such arrangement, however, would be linked to a statutorily established compensation program.

Selection of Arbitration Components. Although the Proposal sets out a particular format deemed suitable for the issues likely to arise in research injury disputes, the report also presents a checklist of options for establishing an appropriate plan. The list includes selection of types of arbitration; contract issues; administrative and operational considerations; composition of arbitration tribunals; financial aspects; awards, recoveries and remedies, use of arbitral data for preventive purposes and improvement of research activity; and relationship of the process to institutional review boards (IRB's) and other committees.

Essentials of the Procedure. The report concludes with the steps in the procedure to implement the Proposal.

1. Formal complaint filed with research organization, after injury, indicating claim and confirmation or rejection of arbitration. Notice by research administrator to AAA or other administering agency of complaint

2. Assuming confirmation, filing of a formal demand for arbitration, effective thirty days after notice, to allow for settlement negotiations

3. Start of process by request for statements of parties by administering agency and offer of arbitrator candidates to parties for panel membership
Arbitral Processes for Compensation

4. Prehearing procedures: discovery, examination, as needed
5. Hearing or review
6. Award, opinion or recommendations delivered
7. Compliance with award and order

Introduction
Under any method for asserting a right or claim, differences will arise between the parties, public or private, regarding entitlement, responsibility or liability. In the absence of a specified or accepted alternative, some or all disputed issues which are not informally settled are generally litigated. Requests for redress by subjects of research alleging injury are no exception. The subject or representative will go to court for compensation, other remedies and possibly punitive damages, unless there is another recourse or option.

An alternative preferred by many concerned with appropriate and effective resolution of disputes in the health field is arbitration or a related process. Such a mechanism may be especially suitable for settling controversies in a compensation program for injured research subjects to insure reasonable consistency, economy and speed. This technique can also serve as an integral part of a comprehensive protection program and can be styled to meet the needs of the parties and the enterprise in which they are engaged.

The following discussion describes arbitral processes for a program to compensate injured research subjects under special statute, with exclusive or voluntary application; by contractual agreement, or both.

Federal Regulatory Requirement
The Code of Federal Regulations (45 CFR 46), relating to protection of human subjects, specifies that appropriate informed consent underlies the performance and participation in human research. Informed consent is defined to include several basic elements such as a fair explanation of the project, a description of attending discomforts and risks, a statement of expectable benefits, and disclosure of alternative procedures. The definition (Section 46.103(7), amended in 1978), concludes with the requirement that subjects be advised of possible compensation in the event of injury:

With respect to biomedical or behavioral research which may result in physical injury, an explanation as to whether compensation and medical treatment is available if physical injury occurs and, if so, what it consists of or where further information may be obtained. This subparagraph will apply to research conducted abroad in collaboration with foreign governments or international organizations.
absent the explicit nonconcurrence of those governments or organizations.*

As of August 1980, no further detail has been provided by regulation regarding the nature or type of compensation appropriate for this purpose or conditions for receipt. Thus, there is no suggested method for considering or adjudicating disagreements or disputes initially or on appeal.

Purpose of Report
This report proposes to offer recommendations regarding the management of unsettled disputes in the spirit of this requirement, applicable to any compensation system which may be formulated, whether based on conventional negligence, some type of no-fault principle, or special statute.

Issues Requiring Determination in a Compensation Program
Coverage: Eligibility, Scope, Parties

The regulation stipulates that an explanation must be given as to whether “compensation and medical treatment is available if physical injury occurs”. This specification cannot limit the demand of a subject or representative, in the event of a claimed injury to “physical” injury. Unless an exclusive statutory program and remedy is enacted for this class of research activity, based on a cognizable federal or other public interest, there would seem to be no basis for any advance restriction on the type of claim to be presented or remedy requested under customary standards of personal injury law. Accordingly, the coverage of any resolution mechanism would have to extend to disputes arising from the widest range of claims and amount of compensation including medical service, rehabilitation, cash payments for incurred and anticipated expense, perhaps punitive damages and other possible redress. Before such considerations, there will be questions regarding the breadth and limits of the compensation program and those eligible to assert claims.

Threshold Questions. Any special compensation program will inevitably generate threshold questions of the following types:

(a) applicability or scope of program, i.e., if the program is exclusive, such as the Federal Employees Compensation Act, some parties may assert coverage, if the program offers easier payment or better benefits.

(b) eligibility or standing of parties, i.e., certain classes of relatives or representatives of injured subjects, and third parties claiming injury, loss or damage, because of actions of investigators or subjects, may not be entitled to sue or claim unless specifically named as included. Similarly, certain defendants or respondents may or may not be covered depending on the purpose, scope and reach of a program, i.e., drug and device manufacturers, distributors and those responsible for the facilities or environment in which the research takes place.

(c) basis of claim, i.e., must it be grounded on tort liability such as negligence or does it extend to any relationship through contract or guarantee? Would injury to property as well as person be included? Would alleged social harms, such as invasion of privacy, libel and slander, false imprisonment be recognized?

Thus, questions of jurisdiction, access and application will have to be considered as well as claims for damage due to injury.

Applicable Liability

Liability may be based on (a) legal grounds (b) medical* or (c) both.

Legal: The validity or adequacy of the consent provisions, or failure to warn, may be a primary issue in cases under this program. Injury may well be alleged for lack of proper information or satisfactory understanding. Whether there would be liability solely because of a touching or battery, without physical injury would be a critical question in the research area. (Many states have enacted laws requiring proof of physical injury to maintain “informed consent” actions.) Such claims may also raise questions of waiver or assumption of risk for a particular act and the possibility of an exculpatory clause as part of consent or permission in research investigations. In addition, consent on behalf of others, such as a parent for child or guardian for ward, may be an entering legal question before liability can be considered.

Medical: The chief medical issues will relate to cause-effect relationships within the context of participating, i.e., whether the injury complained of is related, directly or indirectly, to the particular research or to circumstances or incidents associated with it. Absent a special statute, liability will obtain only if there is dereliction such as negligence, substandard practice, or improper conduct, in addition to a recognized relationship. This ties—duty, dereliction, direct relationship and damage—is the customary medical and professional requirement to support a cause of malpractice. But, if a compensation program establishes liability or entitlement to a benefit, without regard to fault, then only the occurrence of injury within the research relationship would have

* Medical is broadly used to cover biomedical and behavioral research as well as clinical studies.
to be demonstrated. This accords generally with worker compensation principles allowing compensation if injury has occurred in the course of duty within an employer-employee relationship.

Both: Generally, both legal and medical issues will have to be considered. Recovery would usually be predicated on showing of a legal duty based on stated or presumed relationship between the subject and investigator and a demonstrable medical injury or effect flowing from that relationship. Where these are in dispute, adjudication is required; where not in dispute, differences may arise regarding remedy, recovery and relative responsibility for payment.

Nature and Severity of Injury
The occurrence or existence of an injury requires consideration of the basis as well as its seriousness. If the injury is admittedly directly and proximately caused by participation in research and was an anticipated adverse effect, a simple allegation of tort liability founded on fault or no-fault, as the case may be, would be sufficient. On the other hand, if the injury appears to be unrelated to the research activity but was discovered within the context, time or recognized aftermath of the research, there may be some question as to the applicability of the program or the basis for recompense. This question would be particularly pertinent if the claimant is a person other than the subject who charges injury or damage of some association with the research activity.

The most difficult problem, however, relates to distinguishing research-induced injury from that resulting from the expected course of the condition under study. Obviously, this is not an issue in research on normal subjects but it is the most common problem in the great majority of medical investigations on chronically ill parties whose disease may produce the same ill effects as, say, drug reactions or response to certain procedures.

Second, the severity of the injury, from slight discomfort to death, and possible impact on others, will have to be evaluated if the compensation plan includes a schedule of benefits or range of payments as under worker compensation laws. Otherwise, under customary tort liability, the nature of the injury and its severity, income loss, age, occupation, health condition and medical expense and other special factors will determine the amount and type of recovery for the subjects and for others who may be entitled by virtue of relationship or dependency.

Defenses
In defense of claims asserted under common law or special statute, the following are likely:
Assumption of risk—whether the consent to participate precludes all or some recovery for injury or detriment stated or reasonably to be anticipated. This central question has not been
litigated in either treatment or research cases since reported suits have been based on failure to inform or negligent practice, thereby obviating this defense. Could this defense be successfully asserted if there were no claim of malpractice?

**Timeliness**—whether the claim was filed within the appropriate statute of limitation, including allowance for a recognition or discovery of the injury following participation in research.

**Action by patient/subject**—whether contributory negligence or failure to follow orders may have contributed to the occurrence or severity of the injury. Although all research protocols permit the subject to discontinue or withdraw at will, the circumstance or condition for such discontinuance may be considered as contrary to professional judgment or orders and resultant injury might be attributable to the subject not the investigator. On the other hand, an abandonment or, in some circumstances, involuntary detention or false imprisonment.

**Defendants or respondents named**—some of those specifically named may deny liability under a special statute or, under general state law, claim that they were not wholly responsible, but only contributors (if at all) to the injury, or that others be added or ordered to contribute proportionately toward payment or recovery.

**Damages and Remedy**

Final issues in a case in which injury and liability have been established relate to the appropriate remedy and the method of payment or performance and possible enforcement. As indicated, the amount will be determined under standard malpractice rules or, under a special statute or use of state worker compensation law, by formula or schedule specified by law and regulation. Recovery may include cash compensation, in lump sum or installments, medical service, rehabilitation, after-care and surveillance. These could serve not alone for the benefit of the injured person, but also as guidance for conducting research in the future. There may be differences not only as to amount between the claimant and respondent as well as the insurer, but also form of payment to arrive at the optimum remedy.

In determining the amount due, collateral source may be raised, since many subjects of medical research are entitled to health insurance or disability payments from public or private sources.

Rights to punitive damages may also be considered. Are they allowable in instances of gross negligence or deliberate tort action, in the research context? Generally, under compensation plans, payments related to emotional distress or social disadvantage are not authorized. However, these are not ruled out in customary malpractice cases.

Subrogation and possible off-set through suit or recovery from a third party, such as the manufacturer of the drug or device
involved in the project or against the institution, are also available issues. With increasing frequency, malpractice and product liability or other claims are filed based on the same incident.

Limits based on the type and coverage of the insurance policy applicable to the individual research subject or the entire research project or program, may also come into contention. Such limits may also be set by statute under provisions of recently enacted medical malpractice statutes. There may also be restrictions with respect to legal fees and other expenses under such laws.

Finally, hospital or medical fees owed by the patient-subject where the research is considered part of a treatment covered under a health program or initiated by the patient may be cited to reduce damages claimed.

In sum, remedies and recoveries are likely to vary considerably throughout the country even for apparently similar injuries in similar contexts because of jurisdictional differences, case law regarding general and special damages, rules regarding contribution of defendants and potentials for collection. Net recoveries and enforcement of court orders add to the possible variations or inconsistencies. For example, laws and practices differ in respect to gross amounts or percentages allowed to attorneys paid by contingency fee. Payments from public agencies, including the Federal Government, are subject to tort claims acts. And courts differ markedly from state to state in insuring that payments are made promptly and in accordance with orders.

These differences exist at present for medical malpractice cases and other personal injury cases and are justified on the theory of local need, interest and policy as expressed by legislature and court. On the other hand, the Federal Government has, in selected areas, established consistent and uniform systems for social security beneficiaries, veterans, and victims of certain conditions (black lung, kidney disease) among others. Whether a compensation system for research injuries and recoveries should be locally responsive or nationally consistent, of course, must be determined on major policy considerations of general control of the subject, equity, administration, cost and needs of the participants.

Adjudication and Appeal

The issues illustrated and described above may arise independently or in various combinations and will generally be settled informally by agreement of the parties. In this domain, it has been customary for the research institution, investigator or sponsor to volunteer compensation or reimbursement, mainly through providing medical and related service, without charge and be covering out-of-pocket expenses from general funds or under a general or special insurance policy.
Often, claims are not submitted to the insurer in order to maintain the premium rate and to avoid the possibility of rate review. If such offers are not accepted, the issue must be adjudicated on the basis of a claim in the form of a court suit or a demand under the contractual agreement or other plan which may be available for this purpose.

Adjudication of any or all of these issues will be undertaken through (a) litigation (b) an administrative process of a public agency. Federal or state or (c) private contractual agreement, generally arbitration.

Litigation employs the State or Federal courts, depending on the program, issue and jurisdictional elements involved. It contemplates trial by jury or judge and permits the widest scope of appeal to review procedural or factual error. Causes of action will be based on tort doctrine—negligence, professional malpractice, assault and battery, among others—contract, including product liability (warranty and degrees of liability).

Administrative procedures would be employed if a Federal or state agency were, by new statute or extension of existing authority, empowered to adjudicate such issues. Generally, such jurisdiction would be exclusive, that is, the special benefit law (like that for veterans or civil service employees) would apply and no other forum would be available except by limited appeal from agency action. Claims against the Federal Government, in the absence of legislation placing these claims under FECA or other program would have to proceed under the Federal Tort Claims Act, under which there is administrative review by the Department of Justice and cognizant agency, with right of appeal on specified grounds to the Federal district court.

Contract arrangements under compensation plans by investigators or sponsors could prescribe a complaint or grievance mechanism to be followed by some arbitral process as appellate forum. In effect, this would follow the industrial model of arbitration as the final step in a grievance procedure under a collective bargaining contract or, more appropriately, arbitration as the end stage of a consumer or subscriber complaint mechanism in a prepaid health plan. Arbitration awards under these patterns, unlike administrative determinations, are binding. Court review would be limited to structural or procedural flaws.

Selection of Issues for Arbitration or Other Processes

A major question in planning a special compensation program will be whether the processes for dispute resolution should

*Quincy Research Center's injuries to subjects have been covered under the Missouri Worker Compensation Law, on application by the Center. For this purpose, the subjects are deemed employees and their service is considered employment under the law. Premiums are paid to an insurer to cover benefits prescribed by the law.*
be [(a)] mandated as a condition of participation or [(b)] optional at the request of either party or both, or [(c)] a variant, such as presumed accepted, unless rejected by either or both parties.

In large part, the determination of a "compulsory" versus "voluntary" resolution process relates to what issues should be subject to this process. To avoid jurisdictional problems, questions of coverage and a variety of administrative judgements, it is generally deemed preferable that all issues be subject to the process, thereby equally entitled to all steps in proceedings, hearings and awards. This avoids distinctions and differential treatment. On the other hand, it may be considered appropriate, at least at the outset, to place in arbitration only issues of compensation and remedy following a determination of liability, on the ground that public courts are best able to decide major questions of policy and issues of first impression. (It should be noted, however, that in this country, a contractual arbitration has been employed effectively for a wide range of issues as well as cases with substantial claims and complexity which parties may wish to refer to this forum. All types of civil questions have been so considered, but criminal cases and matters requiring public or state determination have generally not been arbitrated.) On balance, therefore, if arbitration or a related process is selected for dispute resolution, it should be available for all disputes.

Arbitral Processes and Formats Available
Arbitration is a recognized form of private dispute resolution, generally voluntary, employed to determine issues presented to neutrals for adjudication in accordance with the rules and conditions presented by the parties in accordance with governing law. Although arbitration is an alternative to litigation, it is also subject to specific law in most jurisdictions or accepted and enforced under common law contract principles. In brief, it is a method generally available for resolving differences or selected issues within the legal system. There are various forms and types of arbitration and, for the most part, all are generally available in most jurisdictions.*

Format
Voluntary Binding Arbitration. The classic form of arbitration and the one most widely used is voluntary binding arbitration. Briefly, it is a process subject to law whereby parties may submit specified present or future controversies to a neutral party for final determination. When cases are conducted according to terms of the arbitration agreement and legal requisites, the determination of the arbitrator or panel, known as the award, is enforceable by entry of judgment on the same basis as a court order.

Essentially, arbitration is characterized by the design of the process to suit the problem and requirements of the parties; relative informality and privacy; and, if properly administered, economy, speed and finality. The award is not subject to judicial review, except on narrow technical grounds, including fraud, duress and procedural flaw. Arbitration awards ordinarily cannot be appealed on merit and even determinations as to what may be arbitrable are often considered within the authority of the arbitrator. Awards do not constitute precedents but, in some fields such as labor and medical malpractice, opinions accompany awards and are available (with the parties' permission) for study and analysis.

Arbitration must be specifically agreed to or accepted by the parties, unless imposed by statute. Therefore, provision for arbitration often appears in a contract or set of conditions applying to a program, such as a collective bargaining agreement or in prepaid health plan. In these contexts, it is often the capstone of an integral or continuum system of dispute prevention, adjustment and resolution procedures, leading to final and binding determination of issues and disputes.

Binding arbitration in one form or another has been applied in this country for resolving disputes and controversies in labor and industrial relations, in commerce, business and industry, including international trade; in insurance and product liability; and, most recently, in consumer cases, personal injury and other tort-founded cases.

The particular applicability of arbitration to compensation for injuries incurred by research subjects derives from the use of arbitration in the health and technical fields for controversies founded in contract or tort, such as medical malpractice and other professional malpractice. Since binding arbitration is often considered in relation to conventional litigation, a simple comparison between the court and arbitration systems is presented in the following table.

**Comparison Between the Court and Arbitration Systems**

<table>
<thead>
<tr>
<th>Court</th>
<th>Arbitration</th>
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</thead>
<tbody>
<tr>
<td>Formal pleadings</td>
<td>Statement of nature of dispute and possible answering statement</td>
</tr>
<tr>
<td>Pretrial procedures by motions, discovery, and examinations before trial</td>
<td>Ordinarily no pretrial procedures (discovery usually available in medical malpractice cases)</td>
</tr>
<tr>
<td>Trial by judge or jury</td>
<td>Hearing by party-selected panel, usually having expertise in the subject matter of the dispute</td>
</tr>
<tr>
<td>Rules of evidence followed at the trial</td>
<td>Arbitrator judges relevance and materiality, conformity to legal rules of evidence not necessary</td>
</tr>
<tr>
<td>Decision according to law</td>
<td>Award deemed equitable (presumably, but not necessarily, the same as if litigated)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------------------------------------</td>
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<tr>
<td>Right to appeal; possible reversal</td>
<td>Award final and binding</td>
</tr>
<tr>
<td>Public proceedings: decision and proceedings reported</td>
<td>Private hearings; announcement of decision only to parties</td>
</tr>
</tbody>
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Voluntary Non-binding (Screening, Fact-finding) Process.
The term arbitration is also occasionally applied to a voluntary, but non-binding, process for resolving controversies essentially on a recommendatory or advisory basis. This form is most commonly found in the medical malpractice statutes recently adopted by several states which permit (most states require, see below) review by an impartial panel which issues an opinion for acceptance by the parties. These are in effect screening, fact-finding or mediating processes intended to assist the parties in arriving at a mutually satisfactory conclusion, but have only the force of persuasion rather than contract or law. Thus, the parties are not bound and either may request a court trial, generally de novo, with or without reference to the determination and opinion of the panel, depending on the local statute.

The generally stated purpose of these processes is to discourage baseless claims, to get the benefit of unbiased expert advice at an early stage, to provide a better exchange for neutral settlement and to sharpen the issues if the case proceeds to court. Non-binding arbitration is often deemed the only available type where one of the parties, such as a government agency or public corporation, considers that it cannot be legally bound by an outside tribunal other than the court. However, both federal and state statutes and regulations have provided for binding arbitration with respect to certain activities or controversies.**

Mandatory Binding Arbitration (Statute, Non-statute). Mandatory binding arbitration is rare. Generally, arbitration is considered a process which the parties choose on the basis of suitability to special problems, convenience and appropriateness of procedure, such as impartiality and expertise. This is especially true in arbitration provisions developed through collective bargaining. Labor relations in this country have in consequence been largely governed by arbitration awards interpreting the provisions of contracts applicable to working conditions, hire and fire, entitlements and benefits, and determinations of relative prerogative of management, unions and individuals. However, binding arbitration may be required in some labor relations acts or emergency law where, after protracted negotiation, settlement has not been achieved by the parties. Such arbitration is imposed to determine significant issues involving the public interest.

A form of mandatory binding arbitration applicable to individuals occurs in some health contracts or policies for prepayment plans. The best example is the provision in the Kaiser-Permanente contracts negotiated with groups including public agencies under which enrollees on admission or by use of the services accept arbitration as the exclusive means of deciding controversies arising under the health program. (A limited, mandatory, binding arbitration is provided under the Puerto Rico medical malpractice statute, discussed below.)

Mandatory Non-binding (Screening, Fact-finding) Process. Mandatory, non-binding arbitration is a favored form for resolving medical malpractice claims provided by statutes enacted as part of the recent reform movement. *Essentially, these establish exclusive systems for medical and health claim resolution through determination by panels, usually consisting of a physician, lawyer and lay person, with authority to encourage party resolution or recommend settlement either upon determination of liability or recovery or both. (The success of these systems is generally judged by the number of cases which are resolved within the system or by the panelists compared with the number which proceed to court.) To limit the number of court reviews, statutes often provide that determinations are final, unless rejected within a limited time, or specify that determinations of the panels are admissible in de novo court trials.

It should be noted that only the voluntary binding approach, as first described in this section, may properly be defined as arbitration. The term has been flexibly and variously applied to other systems, but general arbitration acts, federal and state, which will be later discussed, define arbitration as binding, with only limited judicial review.

*There are over twenty jurisdictions with such statutes, some of which have been declared unconstitutional in whole or in part. See discussion below.*
An adaptation of the voluntary, binding arbitration concept may be found in the 1977 Michigan medical malpractice law (Mich. Comp. Laws, Sec. 600.5040 of Chapter 50A). Under this law, arbitration must be offered by specified health providers as a condition of insurability and may be accepted by the patient on hospital or clinic admission. If accepted, arbitration is then mandatory on both parties and the award is final and binding, not subject to appeal by either party accept on procedural grounds: In short, this represents a type of executory contract which becomes complete upon the acceptance of the offer.

**Pre-claim and Post-claim Systems.** All types of arbitration are available under either a pre-claim or post-claim system. Two principal patterns have been used in medical malpractice, most applicable for resolution of research injuries, based on the type of agreement:

1. **Pre-claim**—agreements prior to claim that a controversy which may arise in the future will be submitted to arbitration.
2. **Post-claim**—agreements after claim to submit disputed issues to arbitration.

Within the pre-claim category, there are four types:

1. **Exclusive**—imposed by law (only Puerto Rico; the medical malpractice statute specifies arbitration as sole method).
2. **Mandatory**—arbitration specified for resolving designated disputes under terms of a health plan (e.g., Kaiser plan—California statute permits such provisions by adequate notice to subscribers).
3. **Prescribed**—offer of arbitration required by specific providers, enforceable by voluntary agreement of patient (e.g., Michigan medical malpractice arbitration statute).
4. **Contractual**—based on voluntary acceptance by both parties (e.g., California hospital project; New York contractual arbitration plan).

Within the post-claim category, there are two types:

1. **Plan**—conducted under terms or rules of a plan available to the parties (e.g., Suffolk County [N.Y.] plan).
2. **Ad hoc**—conducted under agreement by the parties under general or malpractice arbitration law of jurisdiction (usually based on prior acceptance of arbitration for the particular case or category by an insurer).

**Other Processes—Conciliation, Mediation, Advisory Systems.** Although arbitration has been stressed because it is the final or determinative stage, that is, resolution by a third party, processes in which the parties themselves achieve agreement also deserve emphasis. In some areas, this effort is likely to be more productive since it comes earlier in negotiations, and directly offers the views of the parties.
When parties cannot themselves achieve resolution, however, mediation or fact-finding is often invoked. Mediation embraces the advantages of direct and continuing negotiation by the parties and the expertise of a third person.

Eva Robins, a skilled, professional arbitrator and mediator chiefly in the labor arena, explains:

Mediation means a neutral person’s effort to help the parties reach their own agreement; if it seems probable that the parties will be able to do so themselves, the mediator may take less than a dominant role in the talks. But whether exerting a major influence in the negotiations or taking a softer, less visible role, whether present before an impasse develops or when real differences have crystallized, the mediator’s purpose is the same: to help the parties develop for themselves contract terms under which they can live.

Mediation should be distinguished from two other dispute settlement processes, arbitration and fact-finding. In mediation the neutral is not a decision-maker: in arbitration and fact-finding he is. The mediator is a catalyst who tries to help the parties come to their own agreement. Fact-finders investigate disputes, make findings of fact, and usually issue formal, advisory recommendations on terms of settlement. While mediation is an extension or continuation of the direct collective bargaining between the parties, in fact-finding and, to a much greater extent in arbitration, the parties hand over decision-making to a third party.*

Although mediation is excellent for advancing negotiations between parties of equal bargaining power, for easing community tensions and even in certain one-to-one differences such as family disputes, it has less purpose and value in achieving a settlement after denial of a claim or benefit. Generally, there has been some interaction between the claimant and respondent or insurer through their representatives toward settling a claim, as in auto accidents, whether under a no-fault or conventional arrangement; introducing a neutral mediator in such circumstances would generally not be helpful.

Administration

Just as the formats or plans for arbitration and related processes may be designed by the parties to meet particular needs, management or administration may also be structured to meet the objective and purposes of the program. Generally, existing mechanisms are accepted, such as the rules and processes of the

American Arbitration Association or specified by statute, as in medical malpractice arbitration plans, or set forth in the agreement between the parties before or after the controversy.

Public Administration. The major form of public administration, best represented by federal and state benefit systems for worker compensation or social security or other benefits, establishes as part of the program a panel for administrative adjudication, after rejection of the original determination and settlement offer. Generally, panelists or referees are employees or consultants selected by the agency to consider and hear individual or class disputes. Administrative judges in the Federal government and in many states serve this role. Under such systems there is often a higher level, for appeal, and an administrator or executive responsible for final decisions. The adjudicative and appellate bodies technically provide recommendations but, in fact, effectively make conclusive determinations since the basis or reason for later appeal may be limited in terms of issues or time. Also, as often noted, the second review in the same program or agency, even though separate and independent structurally, tends to support initial judgments.

This is the common administrative proceeding, subject always to court review, whether or not stated. The review may be limited to whether the process has met agency statutory or constitutional requirements and whether the matter was properly before the body.

Technically, although such a proceeding has some of the elements of an arbitral process, it does not meet the usual requirements of allowing the parties to select or approve the adjudicators; it is not private and, most important, it is not contractually binding.

In a sense public administration is also available through the provision of public employees as adjudicators, hearing officers or administrative judges at the request of the parties or, in some instance, by regulation establishing the availability of such staff. In general, such assistance has been available in labor relations cases at the federal and state levels and now also for certain civil rights and discrimination cases, under programs for the elderly and the handicapped.

An agency often named for this purpose is the Federal Conciliation and Mediation Service. Parties often have the option of engaging a private arbitrator or referring the matter to the American Arbitration Association or a similar body for arbitration under general arbitration laws of the state or federal government or applicable contractual provisions. The non-public administrator is selected because of greater leeway in choice of arbitrators, informality and confidentiality, and greater accommodation to needs of the parties. The public agency may be less costly and may provide access or procedures preferred by the parties.
Private Administration. Without question, the most prevalent form of administration of arbitration and arbitral processes is through private auspices or organizations. The American Arbitration Association offers the most extensive assistance in this respect. The AAA maintains a countrywide network of offices and both national and local rosters of arbitrators and employs standard rules, procedures, forms and notices. Staff is available for technical aid in the initiation and management of a case and enforcement of an award. For this reason, the inclusion in a contract or plan of the sample arbitration clause or provision—

Any controversy or claim arising out of or relating to this contract, or the breach thereof, shall be settled by arbitration in accordance with the Commercial Arbitration Rules of the American Arbitration Association, and judgment upon the award rendered by the Arbitrator(s) may be entered in any Court having jurisdiction thereof*
makes it possible to refer a case to the Association for administration under the provisions submitted by the parties and local arbitration law.

Private administration is also undertaken within certain industries, often through a trade association or special agency established for this purpose. A notable example is the program for inter-company arbitration by permanent panelists within the insurance industry. Many industries or joint management-union boards have regular full or part-time panels, referees or umpires. Occasionally, such systems call on the AAA for particular experts, either fact-finders or arbitrators, or to resolve disagreements within the system.

At this time, the AAA is the only organization that administers cases of all types, including those covered by private agreement. Thus, AAA may be specified or utilized on an ad hoc basis under state or federal statutes, as noted, or national programs or for single disputes. All of these have in common the prior or post selection by the parties of a particular format for arbitration. Many have published or available rules, procedures** and perhaps a body of arbitration awards, opinions or memoranda furnished by the parties or maintained by the administrators.

There is at present no professional or trade association of privately administered arbitration plans but there are professional societies, such as academies of arbitrators, and the Society for Professionals in Dispute Resolution (SPIDR) for arbitrators, mediators and other practitioners. These provide for exchange of information on processes and practices, training and customary.

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**See for example, the brochure for the New York medical malpractice program. California and Michigan have similar materials.
professional presentations. The AAA offers extensive training for arbitrators and those appearing in arbitration proceedings.

Party Administration (non-administered). Unless otherwise specified, such as in medical malpractice arbitration laws or provisions under no-fault and uninsured motorist cases, arbitration may be conducted and managed by the parties themselves in accordance with federal or state arbitration law. These laws authorize and permit voluntary contractual arbitration, selection of the arbitrators and the nature and enforcement of the award. The Kaiser health plans in several states use this form of arbitration and many business and insurance contracts, including those for health and disability coverage, use or intend to use this method. (For example, many legal instruments include a provision that disputes will be resolved by arbitration without specifying the method; thus, the parties generally understand that each will choose representatives who will jointly agree on a neutral.)

Many controversies subject to non-specific arbitration provisions are submitted to the AAA, which applies appropriate rules or those provided by the parties. With the exception of certain well-established programs such as Kaiser's and similar health organizations, the party-administered approach is essentially used for occasional cases.

Party administration, that is, without the benefit of a public or private organization familiar with local arbitration requirements, may be frustrated at the point of compliance or enforcement unless all of the conditions have been fulfilled for court enforcement. These include a valid agreement, usually formal, demonstrated understanding of the parties, due process, compliance with time requirements, and safeguards in the selection of the arbitrator and appropriate formalities in the rendition of the award and adherence to court rules for entry of judgment or motion for enforcement.

Partial Administration. The great majority of cases are handled under the methods described above, but some arbitrations, which may be deemed referred or partial, are conducted for specific purposes and may extend only to certain issues. Generally, this occurs when a court either requires or recommends an arbitral determination of fact issues within a complex case within the jurisdiction of the court. Or the parties may specifically limit the arbitration to certain issues. Also, under certain medical malpractice screening laws, panel determinations are limited to findings on limited or specified issues.

The use of partial or split arbitration is generally not regarded as suitable or effective. It tends to prolong a case and allows for internal conflict or inconsistency. It is appropriately used only where a specific or special issue has to be resolved promptly in order to permit a larger matter to proceed.
Authority for Process

Arbitration is a legal system. Although it is essentially private and avoids the courts, it still depends on a specific authorizing statute or mutual acceptance under common law as a contract obligation.

Contract—Common Law. Historically, various forms of arbitration were regarded as unenforceable on the ground that they usurped the jurisdiction of the public courts and permitted decisions which might not accord with public policy or legal conditions applicable to others. Today, private adjudication, particularly to resolve technical issues or matters common to a business or continuing relationship is highly favored and generally enforced by the courts unless there is some element of adhesion in the formation of the agreement or unfair process in the management of the case. The common law in the United States, however, is rarely invoked for the purpose of determining the contours of an arbitration agreement or the enforceability of a determination, since every state now has some general arbitration law or provisions for certain controversies.

General Arbitration. Most jurisdictions have some version of the Uniform Arbitration Act, a model law drafted by the National Conference of the Commissioner on Uniform State Laws in 1955. It is the basis for authorizing enforcement of arbitration agreements. The distinctive characteristic of the uniform law and modern arbitration statutes, which vary somewhat but include its crucial provisions, is the recognition and enforcement of future as well as existing claims.

This coverage language appears in the opening section:

Section 1. (Validity of Arbitration Agreement.) A written agreement to submit any existing controversy to arbitration or a provision in a written contract to submit to arbitration any controversy thereafter arising between the parties is valid, enforceable and irrevocable, save upon such grounds as exist at law or in equity for the revocation of any contract. This act also applies to arbitration agreements between employers and employees or between their respective representatives (unless otherwise provided in the agreement).*

At present, 42 jurisdictions have "rern" laws and 27 are patterned in large part on the Uniform. The Uniform Arbitration Act recognizes agreements by parties for appointment of arbitrators, and appointment by the court in the event of failure by the parties.

An arbitration award, under the Act, may be vacated by a court if (1) it was procured by corruption, fraud or other illegal means, (2) there was evident partiality by an arbitrator appointed

as a neutral, (3) there was an excess of power by arbitrators, (4) there was a refusal to postpone a hearing on sufficient cause, with prejudice to the parties, or (5) there was absence of a valid arbitration agreement. In effect, the Uniform Act establishes binding arbitration without an appeal on the merits.

Other state arbitration statutes, for example, Alabama, apply to existing controversies only. There is no state today which does not have some arbitration statute, covering either present or future controversies or both, at least for certain types of transactions or activities.

Some statutes exclude particular areas of controversy such as construction, insurance or labor contracts. Only three exclude tort actions: Alaska,* Kansas and South Carolina.* But, even in these jurisdictions, cases involving such a cause of action are effectively arbitrated and generally enforced if the parties have entered into the agreement with knowledge and good faith.

The absence of an arbitration law or an apparent exclusion of tort actions or claims against doctors and lawyers would not automatically preclude arbitration of the types of controversies outlined in respect to injuries to research subjects. If arbitration were incorporated in consent agreements (See Section IV, below) by virtue of a federal statute or regulation under federal law, the U.S. Arbitration Act could apply. In fact, the U.S. Act would apply extend to mandatory or optional arbitration under such a program for compensation, if authorized by federal statute or regulation, regardless of state law.

The U.S. Arbitration Act first enacted in 1925 and amended several times, applies to transaction in interstate commerce or under federal law, by agreement in writing for arbitration, with federal court enforcement. Like the Uniform Act, it covers any "controversy thereafter arising . . . or an agreement in writing to submit to arbitration an existing controversy arising out of such a contract, transaction or refusal to perform."

The various forms of arbitration and methods of administration previously described could be designed and employed under the federal and state arbitration laws. The conditions to meet are relatively simple, essentially restating fairness and due process requisites and the right of court intervention where parties have not carried out obligations of their agreement or there has been some impropriety. Generally, parties are free and encouraged to develop suitable systems and to choose qualified arbitrators.

Medical Malpractice Arbitration Statutes. Claims or complaints arising under research programs would likely fall under four types of state or federal laws:

*Alaska has a special medical malpractice arbitration statute. South Carolina also excludes disputes involving doctors and lawyers.
Arbitral Processes for Compensation

(a) worker compensation, if the subject is considered an employee or is so defined for purposes of the statute*
(b) medical malpractice statutes providing for screening, arbitration or both
(c) product liability laws
(d) general arbitration statutes, applying to present or future controversy.

Of course, there can always be litigation under case law unless specific statutes provide an exclusive route or remedy for claims arising under a stated activity. Only medical malpractice statutes may be so construed but as later discussed, it is arguable that research activity is not medical treatment and thus not a possible source of medical or health malpractice claims.

In the last few years, all jurisdictions passed some type of medical malpractice law or provision for insurance. As of this date, 29 jurisdictions have some form of pre-trial screening, mediation, or informal review by a panel under an executive or court authority. Fourteen provide for arbitration, all on a voluntary basis, except for Puerto Rico which has a mandatory system applicable to certain types of institutions. Some states permit a choice of screening, arbitration or litigation.

No state requires arbitration of the types of claims previously described for compensating injuries to research subjects. Only Michigan, as pointed out, obligates certain providers to offer arbitration to patients, who may accept the option and, under certain circumstances, may revoke it. Voluntary contractual arbitration is available in any jurisdiction, even where there is mandatory screening, since arbitration is an alternative to the courts, whereas screening is generally construed as a first step within the court process. Thus, in New York State which has a mandatory mediation act, there is a voluntary contractual arbitration program, sponsored by the state medical society and hospital association and a local arbitration program in Suffolk County. A description and comparison of medical malpractice arbitration statutes appears in Arbitration: Commercial Disputes, Insurance and Tort Claims.**

Special Programs. The existence of either general or special arbitration statutes, such as for medical malpractice, has not necessarily encouraged voluntary use of arbitration. Instead it has been adopted and used where interested parties have developed plans or programs for arbitration of particular disputes, usually in conjunction with other dispute resolution or grievance processes. In the labor field this is notably true and, in the health field,

*As noted, subjects of the Quincy Research Center are covered under the Missouri Worker compensation law.
medical malpractice arbitration has been reasonably successful where sponsors such as medical or hospital associations, legal groups and insurance organizations have designed or adopted systems or rules for the arbitration forum. However, a statute passed in response to the needs and practices of those concerned, as in California, will effectively encourage extension of arbitration.

The development of a program usually involves a consideration of the advantages of such a system; the method of operation and administration; agreement on the part of all concerned to participate and monitor the system and an acceptable mechanism for service and selection of arbitrators. As previously noted, these systems may be self-administered or cases may be submitted to a professional organization, public or private.

Legal Aspects. A principal consideration, however, relates to the validity and applicability of arbitration. Arbitration in the health field has successfully met tests of state and federal constitutionality. Arbitration is deemed an alternative forum which may be selected by the parties without any loss of due process, without imposing discrimination and without removal of any rights or causes of action available under litigation. Only one challenge, now pending, based on inclusion of a health representative on Michigan's three-member panel, goes to a constitutional point. In general, arbitration is acceptable and enforceable where appropriate contract conditions are met.

On the other hand, so-called "arbitration" under several medical malpractice screening plans has been declared invalid in whole or in part for denial of access to the courts where the conditions for pre-trial review were considered onerous, time-consuming or costly or where the panel was not considered impartial or neutral. In some instances, the form or structure was considered to usurp the functions of the court. Also there has been some question regarding the constitutional justification for distinguishing medical malpractice from other types of tort or negligence cases.

The application of valid arbitration, however, has been subject to a number of interpretative rulings, generally relating to the form or acceptance of the agreement. Arbitration provisions have not been enforced on the motion of the defendant where there was a flawed contract relationship, because of duress or coercion, at entry, where one party possibly had an unfair advantage (adhesion), or where circumstances precluded a fair consideration of the option. Courts have emphasized the need for explaining arbitration, for insuring understanding and for appropriate documentation of the alleged consent. Also, arbitration provisions which implied or included exculpatory clauses have not been enforced. Enforcement has also been denied under pre-claim agreements where the plaintiff parties have not been signatories, for example, representatives of decedents or parties
pressing derivative claims, unless they were clearly included in the arbitration clause or statutory language.

Arbitration, however, has been upheld with respect to injury of a child under a provision signed by the father and has also been applied to a member of a union or employee of a public agency based on an agreement between such organizations and a health plan. Therefore, although the general principles of contract prevail, specific consideration must be given to the types of cases which may arise to insure that the parties intend to come within the arbitration forum and be subject to appropriate enforcement of awards.

In the fourteen jurisdictions which have enacted medical malpractice arbitration laws, arbitration of research injury disputes may have to comply and conform with statutory requirements for notice, form of agreement, type of panel and other detail in order to insure a valid agreement and enforcement. In most of these jurisdictions, agreements by the parties as to such features are authorized and acceptable.

The provisions in the Proposal (see Sec. IV) meet the principles and essentials of all such statutory requirements, but particular requirements may have to be observed if it is determined that research falls under the local malpractice statute.*

On the other hand, if arbitration as proposed is not used, malpractice cases will be subject to litigation, including the recently enacted mandatory medical malpractice pre-trial, screening and mediation laws which present a variety of requirements and limitations. As previously discussed, some of these statutes have been declared unconstitutional in whole or in part, thus presenting further difference and uncertainty.

Reasonably consistent management and adjudication on a national basis for all research activity calls for a federal statute establishing a compensation program. Such a statute could include voluntary arbitration provisions which would supersede all state laws.

Selecting Arbitration: Checklist for Establishing an Appropriate Plan

Arbitration is a method for resolving disputes which can be adopted for final determination of unresolved differences arising

*In the opinion of counsel of the American Arbitration Association, the medical malpractice arbitration statutes, like other malpractice statutes, apply solely to claims arising out of diagnosis, treatment and related health care but not to research, investigation and human studies, especially those involving normal volunteers. For example, the covered providers listed do not include investigators or research centers or pharmaceutical firms nor do they refer to research or clinical studies. Moreover, by avoiding or rejecting arbitration laws (only Puerto Rico is mandatory) research issues can be referred to arbitration under this Proposal.
within any system for claims management and redress. It is therefore possible, and experience has indicated, that arbitration, in one form or another, can suitably be applied following informal negotiation. And, as in the labor relations field, it may serve as the principle method of contract interpretation and even determination of conflicting interests developed in the bargaining process. Arbitration is best understood, therefore, as an alternative to the conventional procedures: as the end stage in a complaint or grievance system; and as a type of administrative adjudication which may be used by public or private agencies.

Selection of Option(s) Available
The versatility of arbitration and its adaptability, as well as ease of amendment, therefore, permits selection or design of optimum format or style, to serve the issues and requirements of the parties. Thus, one must review the various options and determine how these best fit the current and anticipated circumstances, such as new laws and changes in potential liability.

Limitations must also be considered, such as the fact that voluntary arbitration is based on agreement of the parties, therefore requiring appropriate explanation, notice, forms and adherence to statutory requirements. Technical difficulties, such as may arise in reaching all parties in interest, may also be pertinent. As a private system, arbitration fees and expenses for administration and compensation of arbitrators may exceed those in the court system, at least at the outset.

The essential principles of voluntary arbitration are: (1) agreement by the parties to submit unresolved issues in dispute to a neutral body for resolution and (2) acceptance of and compliance with the determination of the arbitrators (award) as final and binding.

The benefits and problems presented for each type of plan, particularly pre-claim versus post-claim agreements, must be weighed in terms of experience; insurance requirements; relationships between patients and providers; and financial considerations for administration and education. For example, pre-claim systems set the ground rules in advance and thus facilitate planning and cost estimates. But, post-claim arrangements can reduce unneeded preparation and administrative expense. There are, however, possible combinations which use the merits of both.

A wide variety of voluntary arbitration plans are possible without statute. If the systems devised prove satisfactory, they will be used and a statute may not be needed. Without it, there is greater flexibility and more opportunity for improvement.

Jurisdiction and Application
First, what types of cases or claims should be submitted to arbitration? Generally, the developers of any plan will have com-
Arbitral Processes for Compensation

plete choice in this respect, but state laws may set certain con-ditions. For example, as noted previously, mandatory or exclusive malpractice pre-court screening statutes will apply to all mal-practice cases, but not others. Arbitration, however, may be used on a private contractual basis, since it legally bypasses the court system. Arbitration may be used within the same program to resolve medical malpractice claims as well as disagreements over health service entitlements or other differences.

**Mandatory Versus Voluntary.** While arbitration cannot be required as a condition for medical or health service under state laws, some jurisdictions (e.g., California) allow a health contract or policy to include a provision that arbitration will be the sole and exclusive method for resolving some or all issues under the agreement. Such mention of arbitration in the subscriber contract assures a definite and known procedure which produces a final determination. This certainty may be advantageous to all interests.

**Present Versus Future Disputes.** Should the agreement to arbitrate be limited to existing disputes, or should it also apply to disputes which arise in the future? Unless limited by statute to present disputes (e.g., Minnesota), most malpractice arbitration provisions apply to both existing and future disputes, thus establishing in advance what system will be used.

**Parties.** Designers should establish or recognize what parties are to be subject to arbitration. The plan or agreement should, accordingly, refer to the types of issues or circumstances covered and, as appropriate, include or exclude survivors, minors, dependents, and third parties-in-interest, to assure that arbitration will apply to all who may be concerned. Some mal-practice arbitration laws now specify whether arbitration applies to such parties.

In the absence of such a provision (which may be included in the consent agreement or noted by reference) applicability of arbitration may be contested, thus delaying and possibly frustrating the process and decision. Of course, when arbitration is selected by the parties after the injury or at time of complaint or claim, it will not likely be questioned later by either side. The problem of coverage arises only when a pre-claim agreement is not observed or deliberately rejected as not valid or current.

**Legal Conditions; Regulations.** Changing laws and regulations dictate systematic review of applicability of arbitration to pertinent disputes. The conditions for malpractice arbitrations have been discussed. At a local level, forms, provisions for notice, records and reports should comply with current legal requirements.

**Acceptance and Agreement**

**Contract Issues.** Arbitration should be specific and understand-able to all parties for whom intended. In the research field,
the concept would have to be explained to Institutional Review Boards, investigators, hospital staff, and, particularly, to insurers and attorneys. Obviously, it will have to be made clear to the subjects and investigators. Since arbitration is enforceable only when based on a valid contract, certain issues should be considered.

Thus, as earlier discussed, care should be taken to avoid circumstances suggesting adhesion or other unfairness or conditions for health service. In addition, arbitration should not be linked to provisions excusing possible negligence or obligations imposed by law or recognized professional practice. The arbitration agreement cannot relieve any one of a fundamental duty. Finally, pertinent elements of informed consent in research, apply to arbitration provisions. These would include, among others, formal agreement, explanatory materials, opportunity for question and discussion, and also for confirmation or cancellation of agreement, if required by law.

Administrative Considerations. Evidence of notice and agreement to arbitration by all concerned parties must be maintained in appropriate files, to be produced as needed.

Agreements to arbitrate by professional staff (investigators, nurses) and by consultants, contractors, affiliates, and associated health facilities (hospitals, laboratory, pharmacy) should be obtained, filed and kept up to date. Initial written agreements and systematic review are essential to avoid questions concerning the applicability of arbitration. For research, as for practice in hospitals that are enrolled in arbitration programs, one general agreement for staff at the outset would suffice. It could reasonably be a condition for the privilege of engaging in research, just as some hospitals request staff physicians to sign up.

Forms; Records; Other Evidence of Coverage. Records identifying individuals who have signed arbitration agreements, and of the effective periods of such agreements, should be maintained to permit easy checking, to facilitate requests for renewal, for statistical purposes, and to meet any insurance or regulatory requirements of the jurisdiction. Where the effective acceptance is by confirmation after an injury, there will be no need for advance arbitration agreements from patients or subjects.

Operation of System

Initiation of Arbitration. Rules should set forth a precise procedure for requesting arbitration, specifying use of appropriate forms, requiring notice to parties, fees and other requirements.

Time Limits. The agency dispute resolution procedures should specify time limits between informal adjustment steps and referral to arbitration and a time limit for arbitration decisions—commonly 30 days after hearing or review. For the types of claims contemplated under a research injury compen-
sation system, there may be no need to consider prior grievance procedures, except perhaps in large institutional settings such as the NIH Clinical Center. Or, as perhaps at Sloan-Kettering or other large hospital-research centers, the procedure for complaints through a patient representative office may equally apply for initial adjustment.

Adjudication. In most cases, adjudication includes one or more hearings before the chosen arbitration panel. Although formalities are dispensed with, arbitrators follow standard rules of fairness for admission of evidence and consideration of statements of parties, their representatives, witnesses and, on occasion, experts requested by the arbitrators. The hearings are held generally at the convenience of the parties and the arbitrators at a site adjudged appropriate by the parties or by the administrative agency in light of the place of injury or other pertinent circumstances.

Rules or the parties may also stipulate that adjudication may be without hearing, solely on documents such as medical records and presentations of the parties. Such arrangements are rare since, in medical malpractice cases which are similar to those expected under research program, counsel wishes to hear and examine the parties. By agreement, the parties may request transcripts or records or make similar arrangements.

Administration

Party Controlled Versus Administered Proceedings. Party-controlled proceedings: In this pattern, generally there is little set procedure. Where specified rules of procedure are not set or adopted, arbitrators must look to applicable state law to guide proceedings.

Administered arbitration: Under administered systems, the administrative authority ordinarily handles all details in accordance with set or submitted rules and maintains a roster of arbitrator candidates. Cost arrangements vary: the sponsor may pay all costs, may share costs with claimants, or costs may be allocated as part of any award, or some combination of these options.

Rules. Development of full, special rules involves difficult problems of technical drafting, interpretation of new language and conformity to approved models and statutes. Under administered systems, standard rules may be adopted. Or, there may be agency developed “ground” rules supplementing general arbitration rules promulgated by statute, administrative code, or private administrative agency.

Prehearing Process: Discovery, Evidence. Rules can provide for an appropriate prehearing process—in conformity with statutes and the desires of parties as to prior informal settlement, discovery procedures, and involvement of all parties in interest.
They may also require that the claimant notify the respondents in advance of a demand for arbitration.*

Representation (Counsel, Pro Se Cases). Use of attorneys or self-representation at various stages should be specified in the rules. In medical arbitration cases, as in such court cases, attorneys are almost always engaged.**

Advisory Committees. Arbitration programs have been enhanced and promoted through the guidance of advisory committees composed of representatives of all interests at the local level. The Michigan statute establishes such a committee of professional and lay representatives with responsibility for explaining arbitration among medical, legal and consumer groups, setting qualifications for the members of arbitration panels and for evaluation of the system. The advisory group for the New York voluntary contractual medical malpractice arbitration program (non-statutory), similarly prepared explanatory and educational materials, provided training and undertook negotiations with insurers and others to insure receptivity throughout the state.

Although an advisory committee is not an essential element of an arbitration program, it serves the important functions of planning, guidance, and promotion. It can also evaluate the program toward improving the quality of the enterprise.

Arbitration Tribunals, Panels

Party-Appointed and Panel Forms. A distinguishing and critical aspect of an arbitration procedure is the method of appointment and determination of types of arbitration tribunal.

Party-appointed: Each side appoints an arbitrator, and the two mutually select a third, “neutral” arbitrator. Each party pays its appointee, and the parties usually share the cost of the “neutral”, but other arrangements are possible. Parties of their representatives (usually attorneys) directly select arbitrators or choose from panelists who meet the prescribed qualifications established by the rules.

Panel Forms: Parties mutually select one, three or more arbitrators from lists offered by an impartial administrative authority (e.g., American Arbitration Association or other named private or public entity). If there are inefficient acceptances, the authority may name the required number.

Number and Type of Panelists (Legal, Health, Public Representation). Usually, malpractice cases call for three (health, law, other) panelists for large cases and one (attorney) for smaller cases. This pattern is subject to change by the parties or may be stipulated by law.

*Such provisions are found in certain state medical malpractice laws and state arbitration laws, e.g., California, Michigan.

**In the few cases in which parties have represented themselves, issues were relatively simple or damage claims were low or nominal.
Panels, Rosters and Candidate Pools: National and Local

Under administered systems, qualified candidates drawn from or representing the discipline or field of interest specified by the parties or the plan are recruited continuously for possible selection as needed. As noted, parties may also agree to certain arbitrators in advance.

Payment of Arbitrators. Arbitrators may serve without compensation, as a public service, for all or part of a proceeding (one or two days), or they may be compensated at a prescribed daily fee. Payment may be made directly by the parties or through the administrative agency. By agreement, patients may share equally or pay less. Compensation may also be assessed as part of the award.

Financial Support of System

Administration: Case Fees, Arbitrator Fees. Initial support will be required for development of a program, rules, notices, and forms whether undertaken by program sponsors or by an independent authority. Often, such planning is covered by consultation contract. Under administered systems, use of available rules and materials may reduce initial support. All systems impose filing and other standard administrative fees on a per case basis. Fees and other costs may be pre-set when a program is designed and developed. Thus, a plan for research disputes, as for malpractice disputes, may prescribe set fees regardless of size of case. But, this arrangement is possible only within a single plan, regional or national, which applies the same rules and procedures to all cases under the plan.

Generally, costs, fees and other expenses are equally shared, or paid for by the party requesting special service, such as a transcript. Parties customarily pay for their own experts, exhibits and demonstrations, just as in court. The arbitration system does not preclude the contingency fee or other arrangements between attorney and client to cover such costs but since, more often than in court, a complainant may represent himself, it may be desirable to have some fund to insure appropriate presentation of the case.

Revolving Fund. Partial support for a system may be possible through establishing a fund supported by contributions from awards. For example, five percent of compensation could automatically be allocated. This fund would be used for fees and expenses that could not be paid by indigent complainants and might also be used for other purposes such as studies for improvement of the system. Such a fund however is not feasible unless there is a substantial body of cases.

Subsidy. A national or local arbitration plan might also have to be subsidized for administrative purposes only. The compensation or cost of other remedy to the complainant would ordinarily be covered by insurance or otherwise if the sponsoring
agency is self-insured. A subsidy would ordinarily not be re-
quired after installation of the system, except perhaps for con-
tinuing education, information materials and for evaluations.

Proportionate Shares. As in all legal proceedings, an arbi-
tration award may determine that more than one defendant in
arbitration is responsible and liable and may allocate compen-
sation shares. The arbitrator will customarily include agreements
by respondents on this point as part of the award order. This may
include a division of cash payable to the complainant or may
assign one party to provide care and rehabilitation and the other
to provide for periodic payment or set up a trust or other method:
these forms may also be proportionately shared.

Recoveries and Recoupments. Where an arbitration does
not determine all the issues or apply to all parties who may be
involved in a case, the award may recognize that the insurer or
other payor may recoup from other sources if there is recovery
based on the same incident or injury. This accords with the
customary principle of subrogation in personal injury cases and
worker compensation laws. The compensation benefit is reduced
by some fraction in the event of third-party contribution. In short,
arbitration follows the same principles and rules applicable to
recovery and recoupment under other systems.

Award and Remedies
Scope of Award. The rules may specify that in assessing
relief, arbitrators may consider degree of fault and resources
otherwise available. The rules for arbitration awards would re-
flect the basis for any cause of action and the issues subject to
arbitration. Thus, awards would relate to scheduled payments
under an exclusive no-fault system or, otherwise, follow local
law with respect to recoverable damages.

Composite Award (Financial, Care, Follow-up). The arbi-
tration award, serving equity and justice, may provide medical
care and rehabilitation as well as compensation and such prin-
ciples may be specified.*

The scope and type of award contemplated under an arbi-
tration plan should be acceptable to and approved in advance by
the insurance carrier. Individual cases would not have to be
subject to prior approval.

Similarly, the insurer and parties should agree in advance to
supervision of any award involving medical care, rehabilitation,
or periodic payment. This is particularly important when care is
provided by another medical or health institution.

* The New York program rules include: "Section 5. Scope of Award: The
award may grant money damages, hospitalization, medical or rehabilita-
tion procedures, any combination thereof, or any relief deemed equita-
ble and just."
Arbitration awards customarily set forth only the determinations on the issues and the remedy, without opinion, explanation or reason. The rules, however, may require opinions or other statement of clarification. Awards, like the entire arbitration proceedings, are confidential to the parties but may be made available to others (published) with permission. The possibility of sharing of arbitration awards and opinions for research and analysis, if not for legal precedent, may suggest some form of statement of reason or basis for judgment.

Report, Opinions and Other Data

Preventive Analysis. The volume of arbitration awards and opinions in this field is likely to be small, not alone because there have been relatively few claims but because most are informally settled. Yet, the disputes which require arbitral disposition may yield insights and other valuable information regarding the operations of a research project. Awards and history of complaints can (and should) be available for analysis which can help remove some causes of dissatisfaction in research management and improve the quality of research as well as reduce the number of disputes.

Statistical Data Base. Use of arbitration by most or all participants in the research community can produce similar data for creating a centralized source or base for purposes of medical, economic and actuarial study which should prove helpful to research administrators and investigators. Such a feedback system should be designed at the outset so that the forms and reports used under any arbitration plan can easily serve as data sources.

Confidentiality and Privacy. Individual research and arbitration records, however, generally are governed by the same principles and authorities relating to confidentiality and privacy of medical records. These may be aggregated without personal identification for statistical purposes. Arbitration awards generated by a private system are, by nature, private and confidential and are ordinarily not available without permission of the parties.

Closed Case Files—Ownership and Use. Files relating to arbitration proceedings as well as the awards belong to the administering agency and are not released without permission of the parties. Portions of a file in the possession of the attorney, the insurer, witnesses or others remain their property. The information, as in the case of medical records, may be legally obtained under appropriate court order for judicial appeal, as claim for medical benefits or care, or for similar purposes.

Relation to Medical Records. For purposes of risk management, quality control and improvement of research operations, it may be possible and appropriate to merge data from complaints and arbitration awards with medical records within a comprehensive statistical system. Combining such data would produce a
relatively simple method of determining where difficulties have arisen and where improvements are indicated. Such a system would begin to produce useful results only where there is a substantial volume of reports from contributing sources such as research centers, pharmaceutical firms, insurers and independent investigators in hospitals or elsewhere under both private and public auspices.

Enforcement and Follow-up

Entry of Judgment and Enforcement by Court. The award of a properly constituted arbitration tribunal and process may be submitted by either party to a court of appropriate jurisdiction for entry of judgment which renders it enforceable on the same basis as a similar court action. A program designed and administered to insure conformity with state and local requirements lessens the possibility of vacation of awards.

Compliance. Rules and instructions may include a process for compliance without resort to court. Systems administered by an independent authority customarily have such provisions and the capacity to request parties to fulfill arbitration award orders.

Supervision of Cases to Assess Effect of Award. A program based on the concept of prevention, as would certainly apply to research injury compensation, appropriately includes concern for the parties after as well as before the arbitration award. The arbitration plan thus should include an evaluation component to assess how well the award achieves its remedial goals.

Enforcement of "Split" Cases. Where the same incident or injury leads to a dispute with issues in arbitration and in court, it may be necessary to consolidate the outcomes to provide a full recovery for the claimant and to share the payments among all defendants. Ideally, the entire case should be considered in one forum, so that all parties may be heard within the same context. The matter would then be resolved as one with due consideration to proportionate responsibility and liability.

Arbitration rules always provide for the invitation and joiner of all parties with a substantial interest and allow participation accordingly. Arbitration can accommodate multiple claims and cross-claims in a single case and can provide a staged or separate award with respect to the parties.

If a party in interest is not pre-committed to arbitration and does not choose to enter, there may be no way to arbitrate with respect to such interests. In some states, the court may, under special statute or rule, determine whether a cause of action will be wholly within arbitration or the courts or separated, depending on the possibility of conflicting outcomes. Where two forums are used, determinations in one are not necessarily binding on the other. It then becomes the responsibility of the parties to reach an appropriate proportional resolution.
Split forum cases are not common. When they do occur, it is usually based on a prior settlement or waiver with respect to one party or one issue which can then be taken into account in the arbitration proceeding. For research injury compensation cases, this problem would not be likely or serious if there is a general pre-commitment to arbitration.

**Evaluation and Modification of Program.** The advantage of an arbitration plan designed and maintained by the parties is that, subject to law, it is capable of modification to meet new conditions. Rules therefore customarily provide for amendment as well as for stipulations by the parties for expedited action. An advisory committee, as noted, associated with the institutional review board, would be able to assess the program and arbitration plan regularly for possible improvement.

**Relationship to Clinical Research Activity.**

**Suitability.** The central question in considering adoption of arbitration for medical and biomedical and behavioral research is its suitability to this activity and its likely effect in improving the quality of such research. No end-stage resolution process can prevent problems leading to disputes since it cannot, by itself, consider the causes of initial complaint or settlement failures. But certain processes may be more appropriate for adjudication of differences and more likely to prove instructive for their avoidance and prevention.

Arbitration, whether intended to yield a final or advisory determination, is not just a generally faster, less expensive and more accessible alternative to litigation. It is best characterized by its relative informality and privacy and, mainly, the use of specialists acceptable to or chosen by the parties qualified to deal with complex and technical issues. It encourages settlement in a non-adversarial climate and factual presentation to knowledgeable fact finders for impartial disposition. Thus evidentiary requirements are relaxed; parties speak relatively informally; time and place for proceedings are set for the convenience of the parties and the arbitrators.

The types of problems and disputes expected in human studies would appear to be best served in a private arbitral forum which would recognize the importance of continuing the research with minimum interference because of a complaint or claim. Arbitration systems can be modified and adapted locally through rule changes or party stipulations, without loss of due process to achieve expeditious and fair determinations. If the arbitral process concludes with a recommendation rather than a final binding award [for example, because the sponsor may be a public agency which cannot cede its adjudicative rights or responsibilities] the same principles and essential processes apply. Generally, under advisory arbitration systems, the agency ac-
cept the recommendation without change, thus preserving the advantages of speed, finality and prompt enforcement.

Risk Management. Since the objective of any program for compensation is to remove or reduce risks which create a basis for possible compensation, as previously noted, arbitration data can be assembled as a resource in a risk management program involving environmental and safety aspects, evaluation of clinical practices, proper staffing and organization among other matters. Arbitration data can be associated, as needed, with pertinent IRB opinions. A coordinated system of this type can easily be designed for a computerized format.

Professional Committees: IRB’s and Related Review. A private arbitral process for dispute resolution can be managed and modified by appropriate committees, as indicated above. It nevertheless retains the essential quality of neutrality, objectivity and expert judgment.

Specifically, for the research community and its constituency, arbitration provides humane adjudication of disputed issues. Relatively few cases will go beyond informal consideration and IRB review to the arbitral stage. If they do, they can be managed with appropriate respect for the parties and the problems in the privacy that will encourage expression of opinion by experts who might decline to appear in open court. With permission of the parties, members of IRB’s may attend.

Arbitration, as described, fits within the IRB framework already established. The arbitral process can be integrated into the compensation system as a final step and also be considered as part of the total research enterprise.

Recommendations

Proposal

It is recommended that voluntary binding arbitration be offered as an option for resolving disputes based on alleged injury related to participation in research in conjunction with any plan for redress or compensation, including conventional litigation.

In the absence of any other provision, all differences between parties which are not earlier settled can be referred to arbitration for final disposition under rules and procedures set by the parties or accepted by them. Where the research sponsor or investigator represents the Federal or a state or local government which cannot by law be bound by a private adjudication, the arbitration award shall be advisory, subject to final determination by the parties.

Provisions

To carry out this recommendation, the following provisions are suggested:
(1) by policy or statute, investigators, sponsors, insurers and others associated with a research program or project who may be responsible or liable in the event of injury to a research subject or other participant, should be required to offer and accept arbitration for determining unsettled differences. Such an agreement or understanding could reasonably be made as a condition for engaging in research or supporting it. Insurers would be required to accept a determination in arbitration.*

(2) Arbitration would be voluntary, not mandated, for research subjects and for representatives, on the basis of initial notice and later confirmation prior to the institution of a submission or demand for arbitration. Upon confirmation, the investigator and other parties, named as respondents, would be obligated to arbitrate. To permit further negotiation toward settlement, arbitration proceedings would be commenced thirty days after a formal complaint made to the respondent, but this period can be shortened or waived on stipulation of the parties.

(3) Assuming a willingness and agreement to arbitrate, it is recommended that for expeditious disposition and reasonable consistency, cases would be submitted to the American Arbitration Association for administration, under appropriate rules or referral, as may be required under state law.**

(4) To encourage participation in arbitration, administrative fees for complainants and other expenses, such as arbitrator compensation, would be covered in whole or in part under a fund established for this purpose or by the respondents, in accordance with the rules covering such cases.

(5) Rules for arbitration of these cases would be the same for each jurisdiction as to (a) issues and parties covered (b) size and composition of panel (c) procedures for notice and conduct of hearings (d) types of awards and opinions but they may allow for local differences in respect to such matters as (a) fees and expenses (b) state laws relating to time allowed for filing suit, discovery or recognition of injury, contributory negligence.

* This provision is adopted from the Michigan medical malpractice arbitration law which specifies that certain providers shall offer arbitration provisions as a condition for obtaining insurance; insurers, in turn, are bound by arbitration awards.

** Under this arrangement, the AAA would either administer the case or refer to the appropriate state agency as required. Referral would be needed only if the case is deemed to come within an exclusive or mandatory medical malpractice arbitration law which specifies administration other than by party agreement. Since most states recognize agreements and/or since research cases may not be considered subject to such laws, referrals are not likely. Since the proposal contemplates submission arbitration following a claim, the requirements for notice and understanding of arbitration in order to insure an understanding of the process in advance of possible injury, would seem to be obviated.
burdens of proof, expert testimony and similar provisions governing research or medical malpractice (c) recovery limits and (d) counsel fees.

Implementation

Basic Assumption. To initiate the proposed arbitration system as soon as possible, existing bases for claim or causes of action would remain unchanged. Thus, although there will be differences among research projects or programs in respect to compensation for injury for policy or jurisdictional reasons, arbitration would stand as the available method for final determination. (At a later date, a national statute might establish a uniform system of compensation as well as arbitration.)

Guidance would be provided by a federal agency such as the Office for Protection from Research Risks of the Department of Health and Human Services through regulation, instruction or recommendation.* Special arbitration rules for such cases or for this program would be designed by representatives of all concerned interests with the technical assistance of the American Arbitration Association.

Guidance. The federal agency would have the responsibility for providing guidance to administrators of research enterprises throughout the country which are subject to the federal statute or regulations and to others managing such research activity. Guidance would include:

(a) explanations of arbitration and recommendations for inclusion of clauses in consent forms presenting arbitration as an optional method for final determination of unresolved differences arising out of claims for an injury to research subjects.
(b) draft language for inclusion in consent provisions, as suggested below (Statement of Arbitration in Consent Agreement)
(c) explanation of the availability and role of the American Arbitration Association as an administering agency and
(d) availability and conditions for arbitration under state law.

The Proposal would specify minimum model requirements for participation including:

(1) pre-commitment by the investigator and sponsor and insurer to arbitration upon acceptance by the complainant.
(2) payment of certain administrative fees for the complainant to encourage use of the system.
(3) distribution of informal and explanatory materials to research subjects and their representatives and

* This language recognizes that not all research in the United States is subject to federal regulation but most research is subject to federal guidance or influence.
(4) responsibility for notifying the American Arbitration Association or other administrative agency upon receipt of a complaint or when arbitration is demanded in order to insure timely commencement of proceedings.

**Rules.** Rules of the American Arbitration Association or any other agency, including a federal office, would include, among other things:

- (a) a statement of fees for administration, compensation of arbitrators and for other purposes which could be uniform for all cases, regardless of size or complexity throughout the country on the basis of
- (b) standard methods for selection of arbitrators from appropriate panels and statement of procedures including hearings, issuance of awards, with opinion, and specifications for notice to the parties at the initiation and conclusion of the cases. An alternative would be a permanent panel of perhaps five or ten experts of various disciplines who would be available on call, for service as single arbitrators or members of a panel of three, depending on the nature of the case or request of the parties.

Such a system under which panelists would travel to the arbitration site, could still be administered by the AAA which would provide all local services through regional offices. The permanent panelists could be government employees or consultants and, in such capacities, might undertake other functions such as education and training in procedure without impairing their neutrality. In general, arbitrators are in best position when not directly associated with the administrative agency.

- (c) referral of the case, as may be required under state law, to appropriate public authorities if state law does not permit administration by the American Arbitration Association;
- (d) adherence to special requirements of state arbitration laws as may be needed, to insure validity of agreement and enforcement of award;
- (e) design and publication of forms and instructions in accordance with the rules, special state requirements and other elements of this program. These would be distributed, at cost or as part of administrative fees, to the research community and explained at education meetings, conferences and in other ways to ensure an understanding of the program, its purposes and methods.
- (f) In addition, the AAA would maintain records for cases under this program for statistical and other analysis.

**Statement of Arbitration in Consent Agreement**

Any consent agreement respecting research, subject to this program, should include the following statement:
Unresolved differences regarding compensation for injury shall be finally determined by arbitration under the appropriate rules of the American Arbitration Association, to be confirmed at the time of complaint.

By this language, investigators and sponsors of research would be pre-committed to use of arbitration, subject to acceptance by the complainant or any representative who would be advised of the provision upon entering the project, but at time of formal complaint, may reject arbitration or confirm it by positive statement. In effect, this action would constitute a submission on the part of both parties to the American Arbitration Association to commence proceedings, and would not be revocable.

To insure an understanding of the process, appropriate informational literature for subjects would be provided at the outset and at any stage during the research, with opportunity to discuss arbitration with trained staff. However, no pre-admission signature would be required, thus avoiding the cost and administrative effort of obtaining pre-claim agreements from the very great majority of individuals who would never have occasion to consider a complaint.

Participating agencies would have current literature and submission forms which could be immediately filed with the American Arbitration Association and, from time to time, would have the benefit of education and instruction regarding arbitration, its procedure and enforcement of awards.

This system or procedure would obviously apply to any compensation program or even a research project or activity for which there is no program since it specifies only that arbitration, if confirmed, is the forum for final resolution. (The language would be modified if the contemplated arbitration is advisory, for final determination by a public agency.)

Although under this procedure it is anticipated that a considered decision to arbitrate will not be withdrawn or revoked, it is possible that a complainant or legal representative may wish to do so. Under rules of the American Arbitration Association, the Association could be obligated to notify the respondent(s) of such a request and, if both parties agree to withdraw, the case will be removed, but certain filing expenses would have to be paid by the parties. If the respondent does not agree to withdraw, it has the right to seek arbitration by an appropriate motion or request to the local court. The AAA takes no position and plays no part in such an action. The Association, however, may provide information to both sides concerning the nature of arbitration, its process and conditions for use including costs and other obligations.

Essentials of Procedure
The proposed procedure contemplates that arbitration will remain as an open or standing offer by the investigator or sponsor
which can be accepted or confirmed at any time by the complaining subject. Arbitration may be unilaterally declined by the subject at any time, except after confirmation following a formal complaint.

The first step in the process, generally following an injury or grievance, would be a formal complaint, filed with the research administrator. The complaint would not only present or summarize the claim or dispute but signify whether arbitration or another method is selected for resolution. If no choice is made or if arbitration is not selected, it would still be available on request, at any time. (This procedure requires a positive request for arbitration at a time related to injury or complaint, but with prior knowledge of the option. It thus avoids issues concerning consent or application of pre-claim agreements.)

The research administrator would be primarily responsible for notifying the administrative agency (AAA or other) that a complaint has been filed.

This formalization would make it possible to prepare for arbitration, to explain the procedures and to insure that, if needed, it will be timely and in place. The notice would not preclude a pre-hearing settlement between the parties (such settlements often occur before or during hearings, just as in court).

The second step would be the filing of a demand for arbitration, effective thirty days after notice (to allow for settlement negotiation) unless parties agreed to commence earlier.

Third the administering agency would request statements and responses and would offer names of available arbitrators from local lists or the permanent panel.

Fourth, pre-hearing procedures of discovery and examination, as needed, would begin, under supervision of the administering agency with time limits set by the rules.

Fifth, hearings (or other review) would begin.

Sixth, award and opinion would be rendered by the arbitrator(s) and delivered to the parties within time limits set by the rules.*

Seventh, parties would comply with arbitration award and order.

* In the event of advisory arbitration, determination and recommendation would be submitted to the sponsor (public agency) for review and approval.

Richard E. Lerner, Associate General Counsel of the American Arbitration Association, provided technical assistance and comprehensive review of this report, proposal and discussion and is available for further consultation. Patricia Brady, Administrative Assistant, American Arbitration Association Research Institute, was responsible for clerical and coordinating aspects. Their aid and support are gratefully acknowledged.
Interim Report on
Private Research Injury Insurance

George K. Bernstein, LL.B.*

I have been retained to assist the Commission in determining whether private insurance can be made available to underwrite the cost of a compensation system for injured research subjects and whether such a private system is preferable to other compensation mechanisms.

The January 1977 report of the HEW Secretary's Task Force on the Compensation of Injured Research Subjects did not resolve the question of what, if any, role private insurance should play in compensating research victims. Both individual insurers and trade associations had cooperated with the Task Force study, but the nature of the insurance coverage desired by the Task Force was not sufficiently defined to permit carriers to make intelligent judgments as to whether they were prepared to make coverage available.

From my experience, in and out of government, with the development of new insurance programs, I have come to the belief that insurers find themselves in a basic dichotomy in such situations. On the one hand, there is an instinctive resistance to letting government write anything resembling an insurance program if such program could conceivably be underwritten privately. On the other hand, there is an equally instinctive reluctance on the part of insurers, as a group, to enter into untried and unproven areas of coverage. This reluctance is manifested most vividly at the company underwriter level. These individuals, responsible for judgments as to which risk should receive what coverage, who are ultimately held responsible for the resultant profit or loss, develop an understandable caution. Ironically, top company officials who are not involved in day to day under-

* Attorney at Law, Washington, D.C.

May 1980

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writing judgments are more likely to take what might appear to be a more statesmanlike stance in urging insurance industry involvement in new and socially affected fields. Not infrequently, these somewhat inconsistent factors combine to send out conflicting signals, as do the statements of similarly situated representatives of insurers with differing underwriting approaches.

The compensation program envisioned by the Task Force is a classic example of these problems. During the Task Force study, insurer opinions on the feasibility of a compensation program varied widely. Some carriers expressed no interest, others stated their interest in principle, but sought specifics which were unavailable, some viewed the question as involving health insurance coverage while others thought that workers' compensation principles were more appropriate. Generally those insurers that expressed any interest indicated that coverage to compensate research victims could not be sold alone, but would be part of an overall package of coverage purchased by the research institutions. This package would include at a minimum the overall general and professional liability coverage of the institution.

Following the issuance of the Task Force report, insurers as well as research institutions, including the Association of American Medical Colleges (AAMC), had discussions with the Department of Health, Education and Welfare. Following the publication on November 3, 1978 of an interim final regulation requiring disclosure of the availability of a compensation program, AAMC conveyed its specific concerns to HEW. This communication raised a basic issue of insurance availability and also asked specific questions on the nature of the Task Force proposed compensation mechanism. The AAMC letter concluded that an insurance program could not develop on the terms contemplated by the Task Force.

Some of the questions and conclusions of the AAMC letter reflected discussions with the insurance industry. Others may represent the particular interest of the AAMC. In any event, I believe that while there is considerable overlap of concerns between research institutions and insurers, each group has its own interests, not all of which are consistent.

During my review I concluded that it would be useful to approach a number of individual insurers to determine whether particular carriers would be interested, in principle, in issuing private insurance coverage to compensate victims of medical research and, equally importantly, whether the insurer could develop a coverage in this area which it believed would be practical and potentially profitable insurance coverage, without committing itself to actually write such risk. To date, I have explored this question at some length with two insurers. One, after reviewing the report, advised me that it had no interest in developing any such program. The other insurer, Aetna Life and Casualty, in response to my inquiry, established its own internal
task force to review the question of whether a private insurance program was feasible. I attach a copy of my February 19, 1980 letter to Aetna, outlining the type of effort which I thought would be productive.*

I hoped that with Aetna's assistance we could develop a specific theoretical insurance coverage. Despite the extensive time and effort contributed by Aetna, such an insurance program has not been developed. Instead, the company underwriters with whom I met discussed whether the type of program discussed by the Task Force was consistent with insurance principles and the reasonable expectations of insurers.

Based on my review of the 1977 report of the HEW Task Force and my discussions with Aetna and with the American Insurance Association [a trade association representing some 150 property and casualty insurers, including Aetna], I believe that there exists a "chicken and egg" threshold. The insurance industry is unable to develop a specific insurance program, unless the scope of the 1977 Task Force recommendations is narrowed. [As much as the Aetna people sought to be of assistance and continue to commit themselves to help the Commission, I do not expect that an actual insurance policy will be developed until such narrowing occurs.] At the same time, it is essential for the Commission to know what insurance coverage might be available under what circumstances before a decision is made to limit the scope of the Task Force recommendations.

This difficulty is not insurmountable and we can at least seek to determine those areas where, from an insurer's point of view, certain limitations in principle would be essential before coverage were issued. My discussions with the American Insurance Association were quite useful in this respect, and those with Aetna were even more fruitful in developing individual insurance company underwriting concerns. It may be useful to discuss the seven specific limitations on the Task Force recommendations which Secretary Harris raised in her October 1979 memorandum to the Chairman of the Ethics Advisory Board. One consideration not in the nature of a limitation is of threshold importance. This involves the Aetna position on overall insurance coverage which, in my opinion, would represent an insurance industry-wide point of view. Aetna would write no insurance to compensate research victims except in conjunction with the general and professional liability coverage on the research institution. At the same time, however, if the full package was written, Aetna would not seek to impose most of the limitations referred to in the Harris memorandum, including certain

* Throughout this report, I refer to positions taken informally by Aetna. This is not because its positions are either final or representative of the insurance industry, but because it is the first company that I have approached that was able to focus on the issues in a comprehensive manner. I will be conducting similar discussions with other insurers.
As indicated in the Task Force Report appendix, page 269, Aetna had insured the University of Washington in connection with injuries to research victims. In the Washington University situation, Aetna agreed to pay research victims compensation which parallels the benefit system under the State of Washington workers' compensation law. Such payments were provided without regard to fault and without the need to show negligence by the university. Unlike workers' compensation, however, Aetna imposed a cap on the medical payments provided, but payments for lost wages were provided subject only to the limitations contained in the Washington workers' compensation law. In the event of permanent partial disability and such occurrences as loss of limb, the same schedule of benefits applied as is found in the Washington workers' compensation law. No benefits would be provided to cover "pain and suffering" or other non-out-of-pocket or non-economic loss. To the extent that an individual sought to be reimbursed for pain and suffering, he could not obtain benefits under the Aetna injury research endorsement. But would have to prove negligence under the liability coverage itself. Similarly, no research claims would be paid under the endorsement unless the injured party waived his right to sue for negligence.

Aetna points out that it was essential to its coverage in the University of Washington situation that it made an underwriting judgment based on its evaluation of the specific research procedures involved, and that while in principle, it would be prepared to insure other such research situations, in fact, each such situation would be evaluated independently and the acceptance or rejection of the risk as well as the specifics of coverage provided and the rates charged, would depend upon the unique circumstances in each case.

Similarly, the ability of the insurer to obtain policy form and premium rate approval in a given State would be an important factor in whether such coverage would be marketed in that State.

One factor that should not be underestimated in the Commission's deliberations is that even if private research injury insurance is developed, only a handful of insurers can be expected to compete for the business—those with related experience.

*Aetna no longer insures the University, but the current status is unrelated to the research victim compensation factor. Despite statements that injury research coverage has been obtained by the Quincy Research Center in Kansas City, Missouri, my inquiries have indicated that no such coverage exists.
Private Insurance for Research Injuries

With respect to the possible limitations on the Task Force report discussed in the Harris memorandum of October 4, 1979, I have drawn the following preliminary conclusions:

(a) Limiting coverage to non-trivial injuries: Aetna did not believe that this was either a necessary or a desirable limitation. It was of the opinion that fast, complete insured medical treatment would benefit both the injured party and the insurer and that it would be short sighted to impose the equivalent of a deductible on what, regardless of whether it was characterized as a casually or health type coverage, was in fact a health benefit.

This view of Aetna (which at least represents the underwriters to whom I spoke) is different from that which other insurers have conveyed to the American Insurance Association (AIA). Those companies seem to believe that a deductible would be beneficial.

(b) Limiting coverage to long-term injuries, e.g., in excess of thirty days: Again, Aetna believes a waiting period would be counter-productive. Other industry members in their discussions with AIA took the contrary position.

(c) Limiting coverage to physical injuries: Aetna's position was that in the context of an overall coverage including general and professional liability, it would expect to cover psychological as well as physical injuries, as it did in the University of Washington case. Such coverage is currently available under workers' compensation and would not be something with which the company had to deal for the first time. With respect to so-called "social" injury which seems to trouble the research institutions, Aetna's position was that despite the difficulty of defining such injuries, they are, in effect, covered today under various insurance coverages and that, therefore, the company would not oppose a program based on the inclusion of such coverage. I believe that many other insurers would be less sanguine about "social" injuries.

(d) Limiting coverage to injuries occurring in non-therapeutic research: Aetna did not deem this to be an insurance concern, but rather a governmental policy question, and it would not limit the availability of coverage based on this decision. However, overall insurance availability might be affected by this decision, as insurance capacity of individual carriers and the industry as a whole could be affected.

(e) Limiting coverage to injuries occurring only in HHS-funded research and only at institutions in the U.S.: Aetna's response was identical to that in (d) above, and my observations about availability would also be applicable.

(f) Limiting coverage to claims filed within a prescribed period after the injury occurs: This is one of the key areas of concern to the insurance industry as a whole and to Aetna. Unless there is a statute of limitations which begins to run not from
the date of the discovery of adverse effects of the research, but from the date on which the research caused the injury, insurers would be extremely reluctant to provide such coverage. They fear similar problems to those encountered in the medical malpractice and product liability insurance where injuries may not surface for ten and even twenty years after the exposure. In such circumstances, insurers are unaware of the scope of their risk for purposes of both reserving and ratemaking. If it were decided that a finite period should be established, a dual statute of limitations could be devised to cover discovery as well as occurrence. Such a statute might incorporate the following principle: no suit may be brought more than two years after discovery of the injury and in no event more than six years after the exposure to the research procedure.

(g) Requiring an offset for benefits received from other sources: An offset operates as a cost reducing factor by avoiding duplication of benefits. Its importance to insurers involves the assurance that the other coverages involved, which are presumed to be those which insurers write on a more regular basis, will continue to be primary.

The foregoing discussion of possible limitations on compensation to victims of medical research touches on only some of the concerns which we can expect from insurers. These and other concerns must be evaluated in determining whether a private insurance program is likely to develop.

Issues of causation and definition of injury can be expected to constitute major difficulties for many insurers. These questions (which did not trouble Aetna in the context of its Washington University policy) are predicated in part on a fear that it will be impossible to predict how courts and others will relate the research procedure to the injury and how broadly the compensable injury will be defined. For example, how much of the "injury" is the result of a pre-existing illness which may have been treated by the experimental process, and how much damage was caused by the treatment, itself.

Some of the concern in this area reflects the experiences of insurers with similar issues in the field of workers' compensation insurance, where both the extent of injuries and their job related nature have been redefined in recent years to increase the losses paid and the cost of coverage. Insurers will probably fear that to the extent this new insurance is viewed as "social" in nature, it will be impossible to predict the nature and amount of claims that will be paid.

Moreover, there is general consensus in the insurance industry that the body of experience involving experimental injury relied on in the 1977 Task Force report is a totally inadequate base on which to establish rates. Each premium rate for a research institute will reflect the particular type of experiment involved, and insurers believe that insufficient statistics exist on
which to make intelligent rating or even underwriting decisions. To the extent that the Aetna attitude with respect to the University of Washington prevails, it is possible that generalized acceptance of the research risk might occur as part of the overall coverage of the institution, and that somewhat subjective rate-making will be exercised by the insurer and permitted by the insurance regulatory authority. It is unlikely, however, that many insurers will be aggressive in seeking to write research injury coverage.

On the other hand, to the extent that the underlying general costs and professional liability business is desirable and an institution requests the research injury coverage, if some large insurers offered it, others would also have to, in order to compete for the good underlying business.

Another subjective insurer concern is the amount of induced costs which would be generated by the new system. Many insurers believe that as soon as insurance coverage becomes available, compensated injuries would increase significantly and that the costs of such increased losses could be massive. Regardless of the cause of increased loss payments and however valid the claim of the victims, insurers would be concerned that even if an actuarially sound premium could be developed, as experience worsened, rates would have to be increased to levels that were politically unacceptable and insurers would not be able to obtain adequate rates for their exposure.

Another insurer concern which I expect to surface, but which may not be voiced as publicly as others is the effect of a governmental requirement that research institutions purchase the new insurances. It is one thing for insurers, on an experimental or tentative basis, to make a new product available—assuming the issues previously discussed can be resolved or accepted. It is quite another thing for enough insurance to be available to meet the requirements of all such institutions.

If coverage is sought on behalf of all governmentally related experiments, availability problems are likely to develop. Particularly to the extent that insurers will make individual underwriting judgments, some institutions will be unable to obtain insurance. Moreover, insurer capacity may be inadequate if coverage for all risks is demanded. By analogy, there are currently lines of insurance where there is no availability problem but where, if coverage were required by law, existing insurer capacity might well prove inadequate.

Thus, if research institutions were required to obtain insurance protection for their subjects, insurers would anticipate that the next step would be a governmental requirement that insurers make their product available. In automobile insurance today, just as government requires that insurance be purchased, it also requires that insurers make it available. The loss experience in
Compensating for Research Injuries: Appendix O

Automobile assigned risk pools offers a troubling pattern for many insurers.

I believe that it is useful to continue to narrow the issues and discuss with additional insurers the possibility of developing a private coverage to meet those needs which the Commission finds to be socially valuable. At the same time, I think that it would be unwise to ignore the possibility that a private insurance program may not be feasible to deal with certain broad, public policy motivated considerations. Not every risk is appropriate to the insurance mechanism and if the government wishes to compensate victims of medical research in a manner which precludes private coverage, it may have to develop a governmental approach to the problem. The solution may entail amendments to FECA or other approaches including those referred to in the Task Force report.

One approach which would certainly be attractive to a number of large insurers would be a governmentally underwritten, privately administered program, involving the fiscal intermediary approach. Of course, financial risk would then be borne entirely by the federal government.

At the same time, the considerations which impel insurers to reject a private insurance mechanism may constitute a warning of high costs which would be equally applicable in a governmentally underwritten program. Questions of definition, causality, coverage limits, statutes of limitation, types of injuries covered, and induced costs should be of concern to the Commission, regardless of whether the program developed is private or governmental.

Attachment
February 19, 1980

Mr. Willard P. Yates
Vice President—Government Relations
Aetna Casualty & Surety
151 Farmington Avenue
Hartford, Connecticut 06115
Dear Bill:

I have conveyed to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research your very generous offer on behalf of Aetna to look into the issue of compensation of injured research subjects, which we discussed in our telephone conversation of February 7.

The possibility of such compensation was the subject of an HEW Task Force, which issued its report in January 1977. The Task Force recommended that physical, psychological or social injuries suffered as a result of HEW conducted or supported
research should be compensated, without regard to fault, and whether or not the research was therapeutic or non-therapeutic. The Task Force also recommended that institutions which received Public Health Service support for research involving human subjects establish comprehensive compensation programs through insurance, self-insurance, state workers' compensation or similar means.

I was originally retained by HEW's Ethics Advisory Board to assist it in following up on the 1977 report. Subsequently, the research compensation responsibilities were assumed by the President's Commission, and I will be working with it on this project.

On the basis of my review of the 1977 HEW report and appendices (copies enclosed), I suggested that we seek to develop a compensation program which private insurers believed could be underwritten by the private sector. It was my opinion, and the Commission agreed, that it would not be useful, at this stage, for the government to develop an insurance mechanism on its own and then to ask one or more insurers to critique it.

We believe it would be most productive for an insurer to develop a realistic insurance coverage that starts with the 1977 Task Force recommendations, deals with the questions raised in Secretary Harris' October 4, 1979, letter (enclosed), and balances the practicalities of causation, proof and cost. We want to know the extent to which certain exposures are definable and coverable by an insurance mechanism, whether first party or otherwise, and what, if any, limits should be placed on the insured exposure from both a private and governmental perspective. The expertise of an company such as yours is indispensable in such an effort.

Although we hope that, with Aetna's assistance, a detailed insurance program can be developed, we seek to benefit from your knowledge and not necessarily from your underwriting resources. Thus, it should be clearly understood that by assisting in this project and by developing even a specific insurance policy, Aetna will not be committing itself to issue such a policy.

In addition to the materials referred to above, I also enclose a copy of a November 14, 1979, report by the Acting Staff Director of the HEW Ethics Advisory Board, and an October 21, 1978, HEW interim final regulation requiring disclosure of the presence or absence of compensation in connection with the research activity.

I advised the President's Commission of your offer to establish an "Aetna Task Force" to analyze the subject and to meet with us in Hartford after you have had a chance to digest the enclosed materials. I will wait to hear from you on when such a meeting between the Task Force and representatives of the President's Commission is appropriate.
In a personal vein, I am rather excited at the prospect of the federal government addressing, from the beginning, with expert insurance company advice, the practical question of whether an insurance program involving socially desirable goals is feasible and susceptible to the private insurance mechanism.

I look forward to working with you, and on behalf of the President's Commission, thank you and the Aetna for your assistance.

Sincerely,

George K. Bernstein

Enclosures
cc: Barbara Mishkin (w/o encl.)
Compensation for Injured Research Subjects: Funding Mechanisms

Thomas S. Chittenden, J.D.*

You have asked me to give my views on the following: (1) whether the Federal Employees Compensation Act (FECA) is a satisfactory vehicle for compensating injured research subjects; and (2) assuming a compensation system which is reasonably defined and bounded, how can the losses which the system will transfer to researchers and research institutions be best funded.

You have received my "Outline of a Compensation System" at our meeting in Washington on June 16th. As you know, the tort law only permits recovery against a researcher or a research institution if a failure of due care can be shown. Thus, if greater responsibilities are to be assumed, they must be spelled out in an agreement between sponsoring institutions and the funding source, all for the benefit of human research subjects. It is imperative that such an agreement spell out all essential terms of a compensation system clearly and in a fashion which will encourage the development of a variety of insurance and self insurance options for participating institutions. The Outline is an attempt to sketch out the matters which must be dealt with in formulating a compensation system. In re-reading the Outline, I would offer the following additional comments:

(1) If the system is drafted so that some exposures are deemed by insurers to be uninsurable, then the Federal government may have to agree to provide compensation on a direct basis. Examples would be injuries discovered many years after the research took place or psychological trauma resulting from research activities.

* Senior Vice President, Marsh and McLennan, Inc., New York, New York.

July 1980
[2] On second thought, the suggestion of the Secretary's Task Force that therapeutic subjects be compensated for injury which on balance exceeds that reasonably associated with any illness or the accepted treatment for such illness may not be a workable standard. There is no guidance as to the degree to which the injury associated with research must exceed that associated with illness or normal treatment, or the certainty with which such excessive injury must be shown. Also, the standard is ambiguous as to whether all expenses are compensable once a research-related injury has been shown, or only those costs which are directly tied to the research-related injury.

FECA: FECA is essentially a workers compensation system for Federal employees. It pays for injuries related to the workplace regardless of fault and often (in practice at least) regardless of any demonstrable causal link between job functions or conditions and the employee's injury. It is a broad, low deductible system with heavy claims frequency and substantial administrative costs. As Stanley Jones rightly points out, it would be particularly troubling to utilize FECA for research subjects in that therapeutic subjects would probably be awarded compensation in escalating numbers and amounts due to the great difficulty in sorting out causal relationships and the FECA rule that compensation is merited when an occupational hazard or other work-related cause played any significant role in the employee's injury.

The questionnaires circulated by the Secretary's Task Force seem to indicate that injuries are quite infrequent and that when they occur, trivial injuries constitute about 80% of the total. Also, relatively speaking, there are many more injuries to therapeutic research subjects than to non-therapeutic subjects. If these findings are valid, they indicate that the real need is for a tightly administered program which can give adequate compensation to a relatively small group of seriously injured persons, while systematically excluding those with minor injuries and those whose injuries are not clearly connected to research activities. The worker's compensation model is not well suited to attaining these objectives.

Funding: In general, risks which are reasonably predictable, or which can be "stopped" by excess and/or aggregate insurance, should be self-insured rather than transferred to insurance markets. Research hospitals, for example, should assume the cost of medical treatment for a reasonable period after an injury which appears research-related. A larger institution may be able to self-insure medical costs for a longer period, as well as some wage loss.

Commercial markets may or may not be willing to write at reasonable prices excess of such self-insurance retentions. If so, it may be necessary to form a research industry insurance company to insure collectively, subject to reinsurance, the exposures
of participating institutions. The main advantages of creating an insurance vehicle of this sort are:

- greater assurance over time that insurance coverage will be available.
- economies in expenses.
- an opportunity to develop superior claims management and loss prevention programs, thus reducing losses.
- access to reinsurance markets, which are often more reasonable in price than direct markets.
- more flexibility in choosing coverages.
- dedication of income on invested capital, surplus and reserves wholly to the needs of the company.

It seems to me that any industry insurance company should be developed as a partnership between the Federal government and participating research institutions. The government is obviously interested, since it will bear the costs of compensating injured research subjects, and the research institutions are important since they are most familiar with the practical issues in carrying out research and since they are essential contributors to controlling losses.

One model would be a “public authority” type insurance company chartered and capitalized by the Federal government, but with private participation in its governance and broad freedom to operate as an insurance company rather than as a government agency. Whether it should be the exclusive source of insurance for injured research subjects would depend on whether the private insurance industry shows significant interest in providing coverage and also on whether the expected premium volume in this area is enough to support participation by a number of insurers. An advantage of exclusivity is that the public company could easily be tied with quality assurance efforts in the research field in such a way that all institutions which met defined standards and were willing to undertake certain precautions imposed by the insurance company would be granted insurance coverage.

Designing an industry insurance vehicle is a complicated task under any circumstances. Here, the task is made even more complicated by the need to design the underlying compensation first and by the desirability of developing an entity which adequately reflects the interests of the Federal government and the research community. Yet, some effort at devising a vehicle for systematic funding of the liabilities proposed seems essential if the conduct of human subject research in the future is not to be heavily and unpredictably impacted by the vagaries of the commercial marketplace.
Outline of a Compensation System for Injured Research Subjects

Compensable Event: Compensation should be available to research subjects who suffer a physical injury proximately resulting from a conduct of HHS supported biomedical or behavioral research; provided that the injury results in death, permanent disability, or temporary disability lasting more than ten days after the termination of the research procedure which caused the injury.

Comment: This definition focuses on direct physical injury resulting from research and thus excludes psychological or emotional harm which eventuates remotely rather than directly from the conduct of the research. The proviso excluding certain temporary disability situations is intended to exclude trivial injuries which are now adequately taken care of by informal means. For injuries to therapeutic subjects, the definition in the HEW Task Force Report on the Compensation of Injured Research Subjects (p. II-2) is adequate.

Recoverable Losses: After offsets for recoveries from collateral sources of compensation, as described under 'Collateral Sources,' injured subjects would recover actual expenses for medical care and a monthly allowance for lost wages during disability, subject to a reasonable minimum and maximum monthly payment. Regulations would permit a modest co-insurance provision for medical expenses. The devisees or next of kin of a deceased research subject would receive a liquidated sum in lieu of all damages to which they would otherwise be entitled.

Comment: Losses would be restricted to actual losses, taking into account entitlements from other sources (e.g., Blue Cross). No recovery would be permitted for "pain and suffering" or for loss of a limb or a natural function per se. As in ordinary disability contracts, the emphasis would be on installment payments and liquidated payment schedules, so as to minimize disputes over damages. Medical care would be covered without limit, and wage loss payments would be structured to compensate for actual wage loss within broad limits.

Collateral Sources: The proposed system would be excess of all payments to which the research subject is entitled because of his illness, employment relationships or otherwise, except for any recovery for injury due to the negligence of the sponsoring institution, its employees or its staff physicians.

Comment: The intent here is to place the proposed system on top of all other benefits payable to an insured subject (e.g., Blue Cross; Medicare; Workers' Compensation) since it is expensive to make loss determinations and there are costs involved in sub-
rotating. Payments under the proposed system, in turn, would be offset against any tort recovery if this is permitted under state law.

**Funding the Payment of Losses:** The payment of compensation as outlined above would be an obligation of the institution or company sponsoring covered research. The obligee would be HHS and the right would inure to the benefit of research subjects. The risk of losses thus passed to the sponsor of the research could be retained (self insured) or transferred to a commercial insurer or an insurance company established by research institutions. Since the program would be mandatory, some form of residual market mechanism must be established (see 'Residual Market Mechanism'). The costs of complying compensation mechanisms would be passed onto HHS as part of an approved research project budget.

**Election of Remedies:** A research subject should not be required to decide before taking part in the research project whether he or she wishes to pursue tort rights or proceed under the proposed compensation system. However, it is appropriate to require an injured subject, after a reasonable period of investigation and counseling, to elect whether to proceed under the tort law or under the compensation system.

Comment: The two rights in question—the right to damages for negligently-caused injury and the right to compensation for medical and wage loss resulting from participation in research—are sufficiently different in scope and effect that it would be unfair to require a research subject to choose between them prior to entering a research program. This might well lead a court to invalidate the compensation program on adhesion contract grounds. After an injury, however, the situation is different, and the subject should be able to determine with reasonable accuracy whether the injury was negligently caused or not. Such a requirement would eliminate time-consuming, expensive arguments about the applicability of remedies.

**Statute of Limitations:** Except for injuries which could not have been discovered, the proposed compensation system should have a two-year limitation on claims running from the termination of the research procedure alleged to have caused the injury. Even where an undiscoverable injury is involved, there should be an absolute cut-off of rights eight years after the research procedure at issue, and a minor should have a right to bring a claim in two years, or until his eighteenth birthday, whichever is later.

Comment: Statute of limitations problems are always difficult, but it is necessary for a new program without statistical support,
to be reasonably defined so that insurers will be encouraged to write the risk.

Dispute Resolution: Determining whether a particular injury was caused by a research procedure is a very difficult process which involves an understanding of medicine. Any method of resolving disputes about coverage or compensation must be inexpensive, quick and fair to all parties. Such a method should not involve a trial and might, for example, consist of an initial determination of eligibility for compensation by the Institutional Review Board, with a right in the aggrieved party thereafter to take his or her case to binding arbitration, under the auspices of the American Arbitration Association.

Residual Market Mechanism: As presently contemplated by HEW, it would be mandatory for the sponsors of supported research to provide a compensation plan for injured research subjects which meets specific minimum standards. Such a requirement breaks new ground, in that compensation has not heretofore been available for injuries resulting from the inherent, non-negligently caused risks of research. This fact, coupled with the changing nature of research, makes it virtually inevitable that some research institutions will be unable to secure adequate insurance coverage. Thus, unless HHS wishes indirectly to affect which institutions can conduct research, it must provide a way for difficult-to-cover institutions to obtain coverage.

Moreover, it may be that the insurance industry (or institutions) will need some relief, beyond what is available in the commercial insurance or reinsurance market, from an aggregation of losses from a single occurrence or a number of related occurrences.

HEW has an obligation, in consultation with the insurance industry and expert risk consultants, to arrange for a capacity pool for risks which cannot reasonably be self insured or transferred to the private market. It is beyond the scope of this outline to recommend how such a pool should be created and funded, except to say that the ultimate burden of pooled losses should be on the U.S. Government rather than the insurance industry.
The American Insurance Association is a trade association composed of 150 property casualty insurers. Our membership provides the majority of general liability coverage in the United States. If private insurance coverage to compensate human subject research volunteers is brought into existence, it is reasonable to anticipate that a majority of that coverage will be written by our membership. Liberty Mutual Insurance Company is not a member of the American Insurance Association. Rather than make individual presentations I will offer some comments to which Mr. Morrow may add, as appropriate. We will both be available to answer any questions from you. We have both served on committees composed of insurers and committees working with research institutions which have dealt with this issue.

I would state as a goal of our Association that we would like to participate with you in seeing that a reasonable compensation program for human subjects is developed. We believe that it is a worthy goal. If initiated with some degree of moderation it can be successful and flourish. It is important to remember, however, that there is a mixture of very complex subject matter: that is to say, experimental research, ethical considerations, societal needs, and an extremely complex profit-oriented industry, the insurance market.

The insurance industry is a highly competitive industry composed of a great number of companies providing both similar and different services. Industry, markets tend to arise to service the needs of the public but they do not arise instantaneously.

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ance companies will risk their assets only after careful study. This enforces a tendency to effectuate change gradually. The program which is under discussion now is one which has no precise analogue in any other coverage, although there are lessons to be learned from programs which are somewhat similar. It is a brand new system. Within our industry, I think that it would be almost axiomatic to state that such a program will not be successful if it is started on an unlimited scale.

The opportunity for the companies to experiment with the kinds of coverage which would be necessary is an important ingredient in developing a program which will survive over the long run. Insurance markets do not spring up instantly. They grow slowly but they do grow. Moderation is appropriate when there has been no program of any significant size in the past; where there is no credible statistical basis on which to draw conclusions and to set rates; and even if there were some collected statistical background, that background would be of dubious value in any case. The very nature of experimental research means that each program is new and different. Each program varies from all past programs to some significant degree. Therefore, past statistical information is of limited value.

If a program is implemented and the insurance companies (our members and other insurers) are expected to participate it should be known that they will be very careful about providing the coverage. They will be involved in gathering information on how the research programs proceed and, to some degree, what sort of experiments are involved. The larger and more respected institutions will obtain coverage more easily. Viewing into the future, it seems entirely likely that some institutions and some research projects will not be able to obtain coverage in the private insurance market. They may be unable to obtain such coverage because their projects are too risky or because it is impossible to assess the degree of risk in the program. This will be particularly troublesome with respect to research in smaller institutions engaged in high risk, even if potentially beneficial, research. This is a problem affecting the conduct of human subject research about which you must be aware. It is entirely possible that in instances where research projects of the high risk category described are undertaken, the coverage for a program such as discussed here may be available but at such an expensive price that it will be unaffordable. Some of these problems may be dealt with by the development of specialty insurance markets but no matter how it is responded to, the ultimate cost will manifest itself in a reduced amount of money available for research and an increased amount of money available for compensation.

We have in the past suggested that continued study, including the development of pilot programs and assessment of experience under those programs, would be the best route to develop an actual program for the compensation of human subjects. We have
also, during the course of our conversations with members of the Commission's staff and academic institutions, arrived at some suggested approaches to a compensation program which would make the program more affordable for institutions and more attractive to insurance companies for their participation. These limitations are ones which we believe would give the program the best chance of success. We believe that they would, in the end, result in the most successful program of human subject compensation. They do not, however, mean an unlimited and open-ended compensation program. There are limitations and outside of those limitations there may well be instances where persons may be viewed as worthy of receiving compensation. Nevertheless, they will not receive it. I put this to you as bluntly as possible because it is important to understand that by striking a proper balance one can minimize those instances and, on the other hand, maximize the amount of compensation which is available through the whole program, and make the program affordable. It does not, in our view, make sense to double the cost of the program in order to compensate a very small number of individuals. What we have tried to bring out in our suggestions is the experience of the insurance industry with other lines of liability, including automobile no-fault, workers' compensation and the tort law system. Our suggestions will keep administrative costs at a minimum and compensation at a maximum.

It is my understanding that the materials which were prepared for your consideration before today included a copy of a letter prepared by Liberty Mutual on July 1, 1980 on this subject and one dated August 11, 1980, also by Liberty Mutual. The first letter was a preliminary attempt to address some of the issues which would have to be resolved if an insurance program were to be developed. The second letter contained some suggested changes in the first letter made as a result of a meeting among various insurance representatives. In this statement, I intend to supersede both of those letters. Those letters may be useful as insight into the development of what the insurance industry believes could be a useful program.

The industry does not recommend that the level of compensation or the program be attached to any federal workers' compensation program at this time. We have some recommendations concerning levels of benefits but, for the moment, benefits are not an area into which a great deal of research has been conducted. As a general principle, we do not believe that the federal programs should be available for use as models or as sources of benefit levels for a new program. We are not yet in a position to make a recommendation for a specific schedule of benefits. That would require a good deal of study and there has not been time to complete it.

The program, because it does not rely on past experience, is best left with a certain degree of flexibility. Insurers may wish to
make policies available in various forms. This should not be interfered with by regulation so long as the basic requirements are met. The program could be treated by companies and their insureds as compensation, liability or even accident and health coverage, or could be treated as a separate coverage. In the past, there has been consideration given to including it as a workers’ compensation coverage but this could not and should not be made mandatory. If it is not made mandatory, more companies may be inclined to sell coverage and there may be a greater degree of flexibility and perhaps experimentation.

The program should be administered in the most expeditious manner. Initial determinations would be made by the individuals involved, including the research subject, the institution and the insurance carrier for the institution. It is important that disputes be resolved in the most inexpensive possible forum. The possibility of arbitration of disputes might be considered. Since the program is one which is selected by the injured party, the selection could include acceptance of binding arbitration.

The program would pay all medical and compensation costs directly related to the treatment for research. There would not be exceptions made in the case of the terminally ill or for those with excess injuries. There would be no deductible or waiting period for payment of medical expenses.

There could be payment for pecuniary losses which are not normally compensated under workers’ compensation programs but for which compensation is occasionally available under other vehicles such as no-fault automobile insurance. For example, a non-wage earner who was unable to perform housekeeping duties and required the services of a housekeeper would be able to receive payment for those services.

There would be available payment for “social and emotional injuries.” Such injuries would have to be directly related to the treatment for research. The injuries would also have to have some relationship to an actual physical injury. We believe that this parallels a sound reluctance on the part of the tort system to provide compensation for purely emotional or psychological injuries in the absence of some related physical harm. It is felt that since emotional injuries are subjective, both in terms of causation and in terms of effect, they are beyond the capability of reasonable compensation under both liability and compensation systems. Accurate determinations are simply impossible to make and are extremely expensive.

The program would not allow awards for pain and suffering. Compensation would be based upon wage loss and related pecuniary losses, as well as medical expenses. It would not be able to include any compensation for pain and suffering such as is awarded in a “tort based liability system.”

There should be an inside time limitation; that is, a limitation running from the time when the injured party discovers or should
have discovered the injury. This period could be two or three years. Such a time is similar to that allowed in state statutes of limitations. We do not favor a change in traditional state statutes of limitations which would allow the inside limitation to run from the date on which a causal connection is discovered between the research and the injury. It is sufficient that the claimant’s right would, for limitation purposes, begin to run from the time when the individual could or should have discovered the injury. This will undoubtedly remove from the system a small number of valid claims. It will, however, remove from the system a large number of invalid and stale claims. It will reduce significantly the administrative difficulty in making the determinations of who ought to receive compensation. One does not wish to spend $10 administering a system in order to produce $1 in benefits to the injured party. The program would also require a time limitation which might be termed an outside limitation. This is a time limitation which would run from the date of last treatment or participation in the experimental procedure. A time of 10 or 12 years, perhaps even 15 years, could be considered. This outside limitation is essential in permitting both insurers and institutions to place some finite limitation on the program. The period is sufficiently long that it will include most compensation instances and yet will allow the use of economic projections which will make the program workable. It will allow those who must provide funds to have some specific and reliable estimate of what the cost might be. The absence of such an outside limitation would leave the program open to unended uncertainty with costs skyrocketing long after events have occurred and long after recoupment of premium is possible. In insurance contracts, the premium is collected now; the loss payout occurs at a later date. If that later date is limited to some reasonable time, the calculation of costs is more accurate.

There should be a reduction for collateral sources. The compensation program provided for research institutions should not be made a primary source of compensation. It would be secondary to all other sums of money which an individual might receive. If the individual receives benefits from other sources, such as accident and health policies, then those sources would bear the costs initially and the program would function above those payments. This is an extremely important method to reduce the costs of the program and thereby leave more money available for research.

There should be a post-injury binding selection by the injured party of either voluntary compensation or such other remedies as the party may choose to select. The selection of the compensation program would, as I indicated above, include agreement to use of an administrative system which would be designed to be fair to all parties. Binding arbitration, as I indicated, is a possibility. The injured person would retain the option to pursue any fault-based remedy which might be available to
that person but would not then be able to claim the benefits of the compen-
sation system. If an individual is harmed through negligence or fault on the part of the institution, then a traditional liability recovery could be sought but compensation could not be selected along with the tort route. It has been the bitter experience of the insurance industry that in instances where both liability and no-fault compensation are available, the no-fault compensation is often used to try to finance the tort coverage. We believe that this runs up the costs of both systems and should be avoided. A difficulty which remains to be resolved is the precise time of election by the party. The election should be at the earliest possible date when an injured party can be said to be in a position to make such a choice. It is extremely important that there be a cutoff early in the procedures as this will substantially reduce administrative and compensation expenses.

The program would include a lump sum payment on the death of a terminally ill patient. The sum would be scheduled and variable depending on factors such as the patient’s age and life expectancy. The choice of amounts would be dealt with later on in the program.

It is recommended that payment to dependents be made parallel to other compensation programs. The program should not include dependency payments to injured third parties. The attempt to provide compensation to individuals such as DES daughters would raise the costs of both compensation and administration of the program more than the benefits which would flow from such an attempt.

As indicated above, all individuals would receive complete medical expenses but payment of loss of earnings and the operation of the program could be improved by the use of certain limits. For non-wage earners, the injured party should receive 50% of the average weekly wage in the state in which that person resides. The use of the state average weekly wage is intended to provide a benefit which is related to the local economic picture, although a waiting period for wage loss for a non-wage earning party should be established at 30 or more days. This is intended to reduce the opportunity and incentive to mangle. The insurers’ concern is that a student participating in a program who receives some injury may have an incentive to prolong the compensation received under a program by not showing evidence of a willingness to return to wage earning capability. The denial of benefits or a waiting period would reduce this tendency, particularly in cases of trivial injury, and would not result in a loss to the concerned individual since that person was not in a wage earning position in the first place. There also is a need for a shorter waiting period for actual wage earners and a period of 7 days has been suggested. It is possible that if the minimum period is exceeded, then there could be reimbursement for that period. As to wage earners, we strongly recommend that the injured individual receive up to two-thirds of lost earnings with a maximum
established at 100% of the average weekly wage in the state, with a maximum time period to be derived from a schedule to be developed for this program.

It is our hope that these suggestions will be helpful to you and that they can at least provide the beginning for realistic consideration of how a program for compensation of injured research subjects might be developed. If you have any questions, we will be glad to respond.
Introduction

The annual conference of the University Risk Management and Insurance Association (URMIA) was held in Chicago September 28–October 1, 1980. At that meeting, a presentation was made by Mr. Alan J. Weisbard, Assistant Director for Legal Studies, President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, regarding the Commission’s study of whether a compensation program for adverse effects resulting from research should be established and, if so, what should be the nature and scope of such a program. Mr. Weisbard invited URMIA to offer comments and suggestions to the President’s Commission on these issues, and the following points were adopted by resolution at the annual URMIA membership meeting on September 30:

1. That URMIA provide the President’s Commission with its position on this issue, to include terms and conditions of a compensation plan if such is to become a reality.

2. That a committee be formed to study this issue, develop a position and report to the President’s Commission in an expeditious manner, on the position of URMIA, and

3. That the membership be provided with the results of the committee’s report and that the committee continue to monitor the issue on behalf of the membership.

This paper is in response to Mr. Weisbard’s invitation and to the above mentioned resolution.

It is important to recognize that the recommendations contained in this paper have been developed through the informal cooperation of individuals from a number of URMIA member institutions. Due to the time limitations inherent in the preparation...
tion of this paper, no direct approval or sanction of the views expressed herein has been obtained from the administrations of the respective institutions represented, and no such approval or sanction should be presumed or implied. Nevertheless, an attempt has been made to incorporate the views of as many institutional administrators as possible, including those of the key human subjects officers at a number of institutions.

Survey Regarding Adverse Effects

As a starting point, a survey regarding adverse effects was sent to some URMI A member institutions, including most of the major research universities in the country (a copy of the survey form is enclosed as Attachment A). Nineteen institutions responded to the survey (a list of responding institutions is enclosed as Attachment B).

To a large extent, the survey results confirmed points which have been previously expressed to the President's Commission. Specifically, it is clear that (1) most institutions do not currently have mechanisms for accurately determining the number of subjects at risk, (2) the rate of reported adverse effects compared to estimated numbers of subjects is extremely low, and (3) the average severity of adverse effects which have been reported is also very low.

While precise identification of the number of subjects at risk at the responding institutions during the period 1976-1980 is impossible, a figure of several hundred thousand per year (e.g., 250,000-400,000) does not appear unrealistic. During that same period, 346 adverse effects were reported; however, 328 of these were from one institution with a large majority of the adverse effects being minor drug-related side effects. That institution reported only one claim, which was based on a drug reaction and resulted in costs to the institution of $1,000 for sick leave used by the subject and $500 for medical expenses.

Of the other 18 reported adverse effects, ten resulted in identified costs to the institutions involved. Seven of these ten have been previously described to the President's Commission in the report submitted by Ms. Diana McCann and Mr. John R. Pettit in August, 1980. The total cost of those seven claims was $454. The remaining three reported adverse effects may be summarized as follows:

(1) Claim 1 (1977)—A drug was alleged by a subject to have caused the subject to become drowsy while driving a car. The car was in a collision resulting in damage only to the subject's car. The subject was paid $1,000 for repairs, although the principal investigator doubted that the drug in question could cause drowsiness.

(2) Claim 2 (1978)—A subject involved in a study of aerobic capacity, body composition, flexibility and strength of a female
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(3) Claim 3 (1979)—The subject sustained a corneal abrasion from an intra-ocular protective lens. The matter was handled by the institution as a professional liability claim and was settled for $4,583.

Given the small number of reported adverse effects, URMIA believes that the need for a mandatory compensation program has not been established. URMIA recognizes that there may be a substantial number of adverse effects that have not been reported, but the absence of any other known complaints or claims by subjects suggests that existing, informal mechanisms (e.g., "compensation" in the form of free follow-up medical care) are effectively dealing with the vast majority of adverse effect situations. Therefore, URMIA strongly urges the President's Commission to carefully consider whether any such need which may be identified is sufficiently great to offset the additional costs inherent in a formalized, mandatory compensation program.

Further grounds for questioning the need for a mandatory compensation program may be found in the views and recommendations presented to the President's Commission by other interested groups. Even groups that would clearly stand to benefit economically from such a program, (i.e., insurance carriers and brokers), as well as groups which might favor a compensation program for reasons of their own (e.g., researchers interested in assuring a stable "supply" of subjects), have expressed considerable concern as to both the feasibility and wisdom of a compensation program. As long ago as 1976, research into the risks faced by subjects in federally funded research suggested that the risk of injury is similar to that faced in everyday life (Source: New England Journal of Medicine, September 16, 1976).

Recognizing that the President's Commission may nevertheless conclude that a mandatory compensation program is warranted, URMIA offer the following thoughts and recommendations on the appropriate nature and scope of such a program. An attempt has been made to convey a consensus viewpoint where this is possible; however, on a number of issues, a spread of opinions or ideas offered by different respondents has been included.

URMIA believes that if a mandatory compensation program is to be instituted, it should be very basic and limited in scope initially, to allow for the development of experience and accurate data as to the magnitude of the actual need for such a program. The program should also be limited in time (e.g., to a period of
three years; at the conclusion of that demonstration period, more accurate data would be available to assist in judging whether the program should be continued and, if so, on what basis.

**Elements of a Compensation Program for Adverse Effects of Human Subjects Research**

**Definitions**

A fundamental element in the development of a manageable compensation program lies in the careful definition of the terms "human subject" and "adverse effect." In the report of the 1977 HEW Secretary's Task Force on the Compensation of Injured Research Subjects, the analogous terms "subject at risk" and "injury" were defined in terms which URMIA believes are much too broad. In both definitions, it is clear that the Task Force intended that compensation would be provided for psychological and social injuries as well as physical ones. In this respect, URMIA believes the 1977 Task Force's report goes beyond what is either appropriate or practical. Measurement of the degree of damage for alleged psychological or social injuries poses severe practical problems, and goes beyond what should be the fundamental purpose of any mandatory compensation program—the avoidance of an unfair economic burden being placed on an individual who has benefitted society by volunteering as a research subject. Other, more subjective, forms of injury can best be handled through an adequate informed consent process and similar protections for research subjects which are already in place. In fact, one major reason for the relatively small number of known adverse effects in recent years may well be the evolution and strengthening of such mechanisms as the Institutional Review Board, which acts as a protector of the rights and welfare of an institution's human subjects.

Another difficulty with the 1977 Task Force's definition of "injury" is its incorporation of the so-called "on balance" test as a means of determining whether compensation is warranted in a particular situation. This test would be tremendously burdensome and difficult to administer in practice as it does not provide the information necessary either to finance the program or to engage in loss control activities; further, it does not adequately take into consideration the presumed self-interest of patient-subjects in therapeutic research, particularly in the case of critically or terminal patient-subjects.

It is URMIA's position that the scope of any mandatory compensation program should be only for research involving a risk of physical injury, and that compensation should be provided only for physical injury, disability or death proximately resulting from participation as a subject in research. In addition,
compensation to patient-subjects should be substantially different from that provided to normal subjects, as discussed in the Limitations on Coverage section, below.

Finally, it is felt that any mandatory compensation program should apply to all research carried out by an institution, not just federally funded research. To do otherwise would result in substantial administrative problems and create the possibility of unjustly disparate treatment among subjects. It is recognized that URMIA's position on this issue may also create substantial problems in terms of the funding on the compensation program. But the ethical considerations underlying any such program are as strong for one group of subjects as for the other. One approach to this issue would be for the federal government to accept funding responsibility for compensation of all subjects irrespective of the funding source for a particular study on the rationale that society benefits as much from non-federally funded research as it does from federally funded research. To the extent that individual institutions would be expected to fund a compensation program, this problem strongly highlights the need for such a program to be limited in scope and cost in order to be feasible. It would be preferable to treat all subjects in similar circumstances similarly and at a lower level of compensation, than to create categories of first class and second class subjects based on a study’s funding source.

Scope of Benefits

The types and levels of benefits which should be provided under a mandatory compensation program are issues on which consensus is very difficult to achieve, other than to agree that the basic categories of benefits which might be provided include medical expenses, wage loss payments, and disability or death benefits.

Medical costs. There appears to be substantial agreement that it would be reasonable for a mandatory compensation program to cover all medical expenses directly associated with an adverse effect, (as narrowly defined, above) although some sort of stated maximum (e.g., $10,000) is felt by some people to be defensible and important from a funding standpoint. Many institutions currently have a policy of stating that only emergency medical care will be provided, but it is generally conceded that considerable free follow-up medical treatment would probably be provided on an informal basis, should it be needed.

Wage Loss Payments. There is considerable difference of opinion as to whether wage loss benefits should be provided and, if so, on what basis. There is particular concern about providing such benefits to unemployed subjects; many individuals believe such payments would be unwarranted in any case, while others feel that such payments could be appropriate but only if it could be shown that the adverse effect has perpetuated the subject’s
unemployment and the period of continued unemployment is substantial.

One possible approach would be to restrict wage loss payments to situations where the adverse effect results in a temporary disability of more than 30 days and to provide benefits only for any period of disability extending beyond the 30 day waiting period. Such a formulation would avoid compensating employed subjects for presumed wage loss in cases where missed work would be already covered by sick leave, and would minimize any incentive for "malingering" in order to receive the benefits.

With respect to wage loss benefit levels, it is felt that the basis of payment should be either a fixed amount (e.g., tied to some federal GS salary level) for all subjects, or else a percentage of the individual subject's salary or wage at the time of disability. Under the latter approach, reference to a GS salary level would still be necessary for any compensation to be provided to unemployed subjects and to establish a "floor" or minimum benefit level. Use of state worker's compensation benefit schedules as a basis for compensation is felt to be inappropriate, given the wide divergence in benefits and other legal provisions among the states. (By way of illustration on this point, the following are the current published minimum and maximum weekly wage loss payments in three states: Tennessee, $15.00-$107.00; Washington, $42.00-$186.87; Illinois, $120.00-$337.00. Source: 1980 Analysis of Worker's Compensation Laws, Chamber of Commerce of the United States.)

Permanent Disability or Death Benefits. In general, it is felt the permanent disability payments should be treated in the same manner as wage loss payments, and should be calculated based on a percentage of actual wage loss. The payments should, of course, be limited to the period of actual disability, and should be subject to a waiting period following the occurrence of the adverse effect. There is some feeling that this benefit (where applicable) should be stated to be primary to any other available benefit, in order to avoid administrative coordination of benefits problems. Alternatively, some respondents feel that all benefits under a mandatory compensation program should be excess to other insurance or benefits available to the subject and that all compensation under such a program should be clearly stated to be excess or secondary to any other available insurance, and not contributory to any such insurance.

Death benefits should be treated as a fixed or lump sum payment, rather than payable as weekly or monthly benefits, in order to minimize the administrative activity required. The maximum benefit should be limited to a reasonably modest amount (e.g., $25,000), and should be payable only to a surviving spouse or legal dependent of the deceased. Other suggestions on such benefits are discussed in the following section.
Limitations on Coverage

Implicit in the preceding discussions is the notion that a mandatory compensation system should operate on a no-fault basis for events which are covered by the program. In consideration of relieving the subject from the burden of having to establish negligence as a prerequisite to being compensated, it is both reasonable and appropriate that certain causes of action otherwise potentially available to the injured subject must become the sole remedy available to the subject and there must be no compensation for the subjective elements of "pain and suffering" or other general injuries or damages. A number of respondents have expressed concern as to whether it is legally possible to make the compensation program a subject's exclusive remedy, and urge the President's Commission to carefully review this legal issue. This concern is based on experience with the erosion of formerly assumed exclusivity in other compensation systems (e.g., worker's compensation), and on the potential for conflict with state laws on these points.

Naturally, the subject would not be expected to waive other available remedies for injuries not covered by the compensation program. Thus, claims for psychological or social injuries could be pursued through the tort system, as is presently the case.

In the event that it is concluded that the compensation system cannot legally be made an exclusive remedy, it is critical that the program be designed to assure that any benefits paid under the system would be offset against any judgment against the institution in a subsequent tort action. Again, some respondents also expressed the view that the compensation program should be clearly established as an excess, or back-up, system to insurance coverage otherwise available to the subject. Under this approach, benefits otherwise payable would be reduced by an amount equal to any payments or benefits received from other sources.

As noted earlier, it is felt that the 1977 HEW Secretary's Task Force report did not sufficiently consider the differing motivations or normal subjects as opposed to patient-subjects. Presumably, most normal subjects volunteer as research subjects for reasons other than that of direct personal benefit, while the vast majority of patient-subjects clearly have, at least, a hope of personal benefit. These differing motivations, plus the additional complications present in the case of critically ill or terminal patient-subjects, lead URMIA to suggest that normal subjects and patient-subjects should be considered separately in terms of the types of compensation to which they should be entitled under a mandatory compensation program. It seems reasonable to cover direct medical expenses resulting from adverse effects for both groups of subjects; however URMIA believes that a patient-subject should not be eligible for wage loss or disability/death benefits if:
(1.) He or she is critically or terminally ill (this proposition obviously requires that there be a clear and reasonable definition of "critically" and "terminally," but the point is that the system should not provide payments in situations where no actual economic loss can be shown, or where the adverse effect has not materially altered the subject's current or long-term economic situation. One proposed definition of "terminal" is a situation where the subject has been diagnosed—presumably by someone other than the principal investigator—as having a life expectancy of less than some stated period, (e.g., six months—one year), or

(2.) The adverse effect results from an anticipated risk (i.e., one which the subject has been advised of in the informed consent form), or is an effect which would also have occurred with conventional treatment.

Under this approach, normal subjects would be eligible for full compensation for anticipated as well as unanticipated adverse effects, whereas patient-subjects in general would receive more limited compensation for anticipated adverse effects, and critically ill or terminal patients would receive compensation only for medical costs incurred as a direct result of the adverse effect.

Another limitation which most respondents feel is necessary in order for a compensation program to be economically viable is some sort of "statute of limitations." It is realized that some adverse effects may not become known immediately, but virtually all existing compensation systems recognize the need for a statute of limitations in order to provide a measure of certainty and finality. One possible formulation of a limitation for claims under the program being discussed would be that claims must be filed within one year of discovery, but in no event more than five years from the date of occurrence. While these periods may appear short, it should be kept in mind that in a number of jurisdictions, the statute of limitations in medical malpractice cases is two years from discovery, but not more than four years from the date of occurrence.

Dispute Resolution

URMIA has no easy answer for the question of how a dispute between a subject and an institution should be resolved. Review and determination by the institution's Institutional Review Board is attractive from the standpoint of cost and promptness, but may be perceived as being biased. Binding arbitration may be the best compromise solution, but raises the issue of where neutral and knowledgeable arbitrators would be found. Litigation is certainly not desirable from many standpoints, but may be preferable to an arbitration system which in practice operates on a "something-for-everyone" basis rather than on the merits of a particular case.
Funding Mechanisms

URMIA believes that it is of fundamental importance that funding of any mandatory compensation program be designed to meet the differing needs and resources of different institutions. The most obvious means of achieving this result is for the federal government to fully reimburse all costs of claims through funding which is over and above current funding for research. Simply put, if the federal government perceives that there is a currently unmet need of sufficient magnitude to justify the adoption of a mandatory compensation program, then the federal government should equally recognize an obligation to properly finance that program, either on a specific reimbursement basis, or through the indirect cost recovery mechanism.

From an institutional standpoint, any compensation program should be designed to allow for flexibility as to the specific method of financing. Ideally, an institution should be able to choose from a number of mechanisms (e.g., commercial insurance, self-insurance, a captive insurance company, pooling with other institutions); however, given the present lack of accurate data regarding the actual nature and number of adverse effects which may have occurred, there is considerable concern as to whether either commercial insurance or a pooling approach would, in fact, be feasible at this time (except, perhaps, at exorbitant cost).

Conclusion

As previously stated, URMIA seriously questions whether there is a demonstrable need for a mandatory compensation program for adverse effects of human subjects research. The number of reported adverse effects—given the number of subjects at risk—has been remarkably small, and the present, largely informal, mechanisms appear to have been adequate in the vast majority of cases.

To the extent that a mandatory compensation program is nevertheless deemed necessary, URMIA strongly urges that the program be conservatively designed to control its potential cost and to minimize the administrative details necessary to operate such a program. One possible approach to this problem would be an interim program as outlined by one respondent:

As of now, we appear to be trying to apply a 'fix' to a problem that has not yet been adequately defined. I have been thinking along the lines of having the granting agency provide a form of no-fault bodily injury coverage similar to that provided by Medicare. That is, there would be no up-front financing but the granting agency would bear the responsibility for the subject during this interim period on a retrospective basis. I think we can recommend a percentage figure to go with the grant to be held by the
Granting agency in the event of claims. One condition could be that each institution attain the capability of reporting all incidents involving human subjects and that this information be collected historically over a period of years. In the meantime, the liability aspect of such injuries would be covered by a comprehensive general liability program at each institution. I am sure that this is an oversimplification of the problem, but it gets the basic idea before you.

Finally, in consideration of the numerous complex issues surrounding this entire subject, it is easy to lose sight of what should be the basic purpose of any compensation program for injured research subjects—to avoid unfairly burdening a volunteer subject with economic loss as a result of his or her participation as a subject. It is equally important that a program not be created which serves to provide windfall gains or multiple compensation for a single event. URMIA urges the President's Commission to keep these principles firmly in mind in its deliberations on the subject, and remains eager to assist the President's Commission and federal agencies in whatever way possible.
ATTACHMENT A

LOSS HISTORY SURVEY
HUMAN SUBJECTS IN RESEARCH
URMIA—OCTOBER 1980

I. INSTRUCTIONS:
A. Please answer all questions, if no data is available please indicate,
B. Please sign the survey form and
C. Return in the enclosed, self addressed envelope.

II. Definition of Adverse Effect: Any injury suffered by a
human subject in the course of research that resulted in
additional medical treatment, extended hospital care, loss of
earnings or ability to earn, and/or death.

III. A. Number of Human Subjects involved in Bio-Medical Re-
search, (Regardless of Source of Grant)

|------|------|------|------|------|------|----------------|

B. Number of “Adverse Effects” reported occurring in these
years.

|------|------|------|------|------|------|----------------|

C. Cost of Adverse Effects by type of payment

<table>
<thead>
<tr>
<th>Year</th>
<th>Medical Treatment</th>
<th>Disability</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976</td>
<td></td>
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<td></td>
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<td>1977</td>
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<td>1978</td>
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<td></td>
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<tr>
<td>1979</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1980 (To date)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D. Please describe nature and extent of injury of each “ad-
verse effect” mentioned in your answers to questions B
and C.

(Attach additional page(s) if necessary)
E. Please provide any other data or information that might be useful to this survey.

Survey completed by ____________________________

Date ____________ Institution ____________________

ATTACHMENT B

LIST OF INSTITUTIONS RESPONDING TO ADVERSE EFFECTS SURVEY

Georgia State University
Loma Linda University
Mayo Foundation
Michigan State University
New York University
Ohio State University
Purdue University
Rutgers University
Stanford University
Temple University
University of Alabama in Birmingham
University of California
University of Illinois
University of Kentucky
University of Minnesota
University of Pennsylvania
University of Southern California
University of Washington
University of Wisconsin
Six distinct options for a non-fault compensation program for subjects injured in research have been explored by the President's Commission. Three of these—a program based on the Social Security Medicare system, the program recommended by the Secretary's Task Force in 1977, and the option of adopting no program at all—were rejected. Using the Social Security Medicare system to reimburse injured research subjects for medical expenses not adequately covered by personal health insurance or other means would closely parallel an existing provision in the Medicare law providing coverage for medical care costs incurred by live kidney donors, regardless of whether the donor would otherwise qualify for Social Security or Medicare benefits.

[Any individual who donates a kidney for transplant surgery shall be entitled to benefits... with respect to such donation. Reimbursement for the reasonable expenses incurred by such an individual with respect to a kidney donation shall be made (without regard to the deductible, premium, and coinsurance provisions of this subchapter)... for all reasonable preparatory, operation, and post-operation recovery expenses associated with such donation... Payments for post-operation recovery expenses shall be limited to the actual period of recovery. 42 U.S.C. §1395rr(d).

Although initially attractive, this model raises more problems than it answers in the context of research injuries. The identification of expenses incurred "with respect to" kidney donation (and any short-term sequelae) is relatively straightforward, and is unlikely to require complex administrative determinations relating to causation or extent of injury, but a similar presumption encompassing the full range of biomedical research cannot be indulged. Further, the creation of an apparatus to resolve disputes would be incompatible with the prevailing...
Compensating for Research Injuries: Appendix S

structure of Medicare administration, thus sacrificing the advantages of merger with an existing program.

In the absence of accurate determinations of causation and extent of injury, this plan, although intended to provide an inexpensive "safety net," could expand to encompass all the health care costs of former research subjects, whether or not those costs arose from participation in research. While this approach might be attractive to people who wish to enhance "horizontal equity" in the health care system generally, it cannot in conscience be advocated as an inexpensive solution to the problem of research injuries. Moreover, the major advantages of this approach can be captured by plans specifically tailored to the problem of research injuries.

The second rejected alternative, the recommendations of the HEW Secretary's Task Force, would put in place an untested program of large scope, considerable complexity and potentially great cost. The objective of the Task Force—to see all research injuries redressed, without consideration of the therapeutic or nontherapeutic nature of the research—is compassionate, for surely the objective needs of those who suffer may be as great in one type of research as in the other. But the analytic device proposed by the Task Force to keep the program within the limits of fairness and solvency seems likely to sink into an administrative quagmire. Determining after-the-fact that an injury "on balance exceeds that reasonably associated with such illness from which the subject may be suffering, as well as with the treatment usually associated with such illness" and then quantifying the amount of the "excess" injury, are tasks that would impose formidable—and perhaps unattainable—demands on Federal bureaucrats or insurance claims adjusters trying to discharge their duties in a prompt and economical fashion.

Furthermore, the "on balance" test has the potential of discriminating against very sick patients who have volunteered for nontherapeutic research unconnected with their own illness. While it seems prudent for any plan to confine the damages paid to the detriment actually suffered by a particular subject, the "on balance" test injects that notion into the definition of injury rather than confining it to the calculation of compensation.

Instead, three other approaches are set forth below as means deserving consideration because they appear to satisfy significant ethical and policy objectives in a fashion that both respects the need for fiscal stringency and is administratively practicable for the government and for other affected parties. Plans I and II apply solely to Federally conducted research and are alternatives to one another. Plan III is a more modest variant of Plan II which would apply solely to research financially supported but not conducted by the Federal government. Thus, Plans II and III in conjunction would encompass both Federally conducted and Federally supported research. Therefore, the plans could be
combined in the following way: Plan I alone, Plan II alone, Plan III alone, or a combination of Plans II and III. The experiment proposed in the Commission's report is designed to permit the central elements of all three plans to be tested. The results of the experiment will be helpful in evaluating the relative need and desirability of each plan (or combinations thereof) as well as the need and desirability of compensation in general.

While the plans vary in administrative structure and in scope and extent of coverage, they share several common objectives and design features:

1. Coverage is limited to biomedical research and specified behavioral research (i.e., only such behavioral research as is affirmatively determined to impose more than minimal risk of bodily injury to research subjects) which is reviewed and approved in accordance with Federal regulations for the protection of human subjects by the Federal government. Research neither conducted nor supported by the Federal government is not encompassed in the plans presented here.

2. Benefits are provided, through an administrative or insurance mechanism, on a non-fault basis to subjects sustaining nontrivial bodily injuries or death as a result of their participation in covered research.

3. Benefits include short-term, emergency medical care, longer-term medical care and related services, death benefits, and economic costs. (More limited benefits would be available to seriously ill subjects participating in covered research.) The scope of benefits varies among several plans.

4. Benefits are paid only to the extent that they are not provided by other sources (e.g., health or disability insurance, liability insurance, social security, court judgments or private settlements). Under Plans II and III, injured subjects have the opportunity to elect whether to participate in the non-fault compensation program or to pursue alternate legal remedies, but may not do both. Under Plan I, subjects may, in some circumstances, be precluded from pursuing alternative legal remedies.

5. Benefits may be reduced or eliminated when injury results from the failure of the subject reasonably to conform to the provisions of the research (e.g., intentional falsification of medical history, failure to comply with investigator's directions regarding ingestion of alcohol, drugs, etc.).

6. The use of expert fact-finding panels and arbitration for the resolution of disputes is encouraged and, in some cases, required. Compensation decisions under the non-fault program are, with minor exceptions, not appealable to the courts.

7. The compensation program is to be funded by the Federal government. Reasonable costs or private, group, or self-insurance incurred by non-Federal research institutions are
recognized as allowable costs under Federal grants and contracts.

Plan I (the "Modified FECA Model") is based on the existing framework for providing compensation to Federal employees for work-related injuries and occupational diseases (the Federal employees Compensation Act, or "FECA," codified at 5 U.S.C. Ch. 81), with certain modifications designed to reflect the special character of biomedical research. Most importantly, eligibility for benefits is limited to research subjects injured in Federally conducted research that is neither intended nor likely to provide immediate therapeutic benefits to the subjects. This significant limitation on coverage should overcome the most salient objections to use of the F.E.C.A. mechanism for compensating injured subjects. Under this approach, the compensation program would be administered by an existing Federal agency pursuant to well established rules and precedents governing most aspects of the program. Administrative burdens and costs would be kept to a minimum.

Plan II (the "Federal Injured Research Subject Trust Fund," or "FIRST Fund") constitutes a flexible framework for compensation specifically tailored to injuries resulting from Federally conducted research. The plan would establish a special revolving fund from which compensation awards could be paid. Administration of both the fund and the compensation program could be vested in an existing agency (e.g., an office within N.I.H.) or, if desired, in a non-governmental public authority. Creation of such a fund would eliminate the curious irony whereby non-Federal research institutions may now use Federal funds to ensure non-fault protection of subjects in Federally supported research, while the Federal government cannot provide similar protection for subjects of Federally conducted research because of a general government-wide policy against the purchase of private insurance by Federal agencies.

The structure of Plan II allows considerable flexibility regarding the scope of coverage. Injuries arising in the course of "therapeutic" research, for example, may be either included or excluded at the option of those conducting the experiment with alternative approaches to compensation. Further, although Plan II itself would apply solely to Federally conducted research, the plan's administrative structure and basic features are compatible with a supplemental plan applicable to research that is supported but not conducted by the Federal government (Plan III). Thus, Plans II and III in conjunction offer a basis for a more unified approach to federally conducted and Federally supported research in the future than would Plan I. Plan I could not readily be extended to cover Federally supported research because of statutory and administrative barriers to treating as Federal employees subjects of research conducted by non-Federally employed scientists at private institutions.
Plan III (the “Institutional Assurance Model”) covers non-therapeutic research supported (but not conducted) by the Federal government. This plan: (1) establishes standards for compensation programs at non-Federal institutions at which Federally supported research is conducted, (2) sets limits on the non-fault liability of such institutions under this program, and (3) provides for Federal payment of reasonably-incurred costs of private, group or self-insurance for research injuries. The plan is designed to encourage participation by the private insurance industry; to provide participating institutions considerable flexibility in choosing among private insurance, self-insurance, and other means of pooling risk; and to permit access to a Federal insurance fund for institutions unable to secure insurance by other means. Further, the plan is structured to be administratively compatible with Plan II, permitting eventual creation of a unified program covering both Federally conducted and Federally supported research if that should prove desirable.

Those who conduct the compensation experiment may wish to test the assumptions underlying the three plans delineated here, as well as the plans themselves. For example, the experiment might go beyond the terms of the three plans described here to test the feasibility of providing compensation to subjects injured in therapeutic research and to subjects who sustain non-physical injuries, as well as the feasibility of different methods of determining causation or the level of benefits to be provided to injured subjects whose current earnings do not accurately reflect their true earnings capacity.
§1. Definitions
For the purposes of this plan:
(a) "Research" means a systematic investigation designed to develop or contribute to generalizable knowledge.
(b) "Biomedical research" means research involving biological study, including but not limited to, medical or surgical procedures, withdrawal or removal of body tissue or fluid, administration of chemical substances or input of energy, deviation from normal diet or hygiene, and manipulation or observation of bodily processes. For purposes of this plan, research satisfying the definitions of both biomedical research and behavioral research is classified as biomedical research.
(c) "Behavioral research" means research involving nonbiomedical alteration or observation of human mental, emotional, or social processes, including but not limited to, data collection or analysis, surveys and questionnaires, tests and measurements, laboratory and field experiments or observations, and innovative environmental designs or psychological or social techniques designed to affect individual or group behavior.
(d) "Subject" means a living individual about whom an investigator conducting research obtains data through intervention or interaction.
(e) "Therapeutic research" means research to evaluate practices or procedures that are intended to provide, or that have some reasonable possibility of providing, therapeutic, diagnostic or preventive health benefits to subjects.
(f) "Nonbeneficial research procedure or intervention" means a research procedure or intervention occurring in either therapeutic or nontherapeutic research that is unnecessary for subjects' own welfare and is performed solely as an aid to the research process.
(g) "Bodily injury" includes wounds, infections, disease, temporary or permanent impairments or loss of bodily functions or bodily parts, or death. For purposes of this plan, bodily injury does not encompass impairment of mental processes (unless demonstrably associated with a physiological cause or change) or emotional distress.
(h) "Non-trivial bodily injuries" include those bodily injuries (i) requiring hospitalization or prolonging hospitalization for persons already hospitalized; (ii) requiring medical intervention beyond first aid and short-term observation; or (iii) encompassing temporary total disability in excess of 24 hours, temporary partial disability in excess of three days, permanent disfigurement, permanent disability or death.
§2. Scope of Covered Research

“Covered research” shall include research involving human subjects which is:

(a) conducted by agencies of the Federal government ("Federally-conducted research");

(b) Federally mandated for review, and in fact reviewed and approved, according to the provisions of 45 C.F.R. Part 46 (or comparable provisions for agencies outside DHHS);

(c) either (i) biomedical research, or (ii) behavioral research which does not fall within the categories eligible for expedited review pursuant to 45 C.F.R. §46.110 (or comparable provisions for agencies outside DHHS); and

(d) "nontherapeutic".

§3. Eligibility for Benefits

The United States shall provide benefits as specified in this plan to research subjects (or their survivors, in the event of the subject’s death) who sustain nontrivial bodily injuries in the course of their participation in research covered by this plan, unless it is more likely than not that such injuries were not the proximate result of the research. Injuries sustained by third parties, not themselves subjects of covered research, shall be excluded from coverage. A child born with an injury caused by the mother’s participation in covered research during the course of her pregnancy shall be eligible for benefits under this plan.

§4. Standards of Conduct

Benefits shall be provided without regard to whether the injury resulted from the fault of the investigator, the research institution, its employees, or the research subject, except in cases where recovery is precluded by existing provisions of FECA. Pursuant to 5 U.S.C. §8102(a), no benefits shall be provided when the death or injury is:

(a) caused by willful misconduct of the [subject];

(b) caused by the [subject]’s intention to bring about the injury or death of himself or of another; or

(c) proximately caused by the intoxication of the [subject].

§5. Time for Making a Claim

The time for making a claim shall be in accordance with existing provisions of FECA.

Section 8122 of FECA provides, in pertinent part, that:

(a) An original claim for compensation for disability or death must be filed within 3 years after the injury or death. . . .

(b) In a case of latent disability, the time for filing a claim does not begin to run until the [subject] has a compensable disability and is aware, or by the exercise of reasonable diligence should have been aware, of the causal relationship of the compensable disability to his [participation in covered research]. In such a case,
the time for giving notice of injury begins to run when the [subject] is aware, or by the exercise of reasonable diligence should have been aware, that his condition is causally related to his [participation in covered research], whether or not there is a compensable disability. . . .

(d) The time limitations in subsections (a) and (b) of this section do not

(1) begin to run against a minor until he reaches 21 years of age or has had a legal representative appointed; or

(2) run against an incompetent individual while he is incompetent and has no duly appointed legal representative; or

(3) run against any individual whose failure to comply is excused by the Secretary on the ground that such notice could not be given because of exceptional circumstances.


Benefits payable to eligible subjects injured in covered research shall be in accordance with the provisions of F.E.C.A., subject to the modifications indicated herein. Such benefits shall include:

(a) medical and rehabilitative benefits;

[For example, F.E.C.A provides:

§ 8103(a): The United States shall furnish to [a subject] who is injured in the course of research, the services, appliances, and supplies prescribed or recommended by a qualified physician, which the Secretary of Labor considers likely to cure, give relief, reduce the degree or the period of disability, or aid in lessening the amount of the monthly compensation. These services, appliances, and supplies shall be furnished—

(1) whether or not disability has arisen; . . .

(3) by or on the order of United States medical officers and hospitals, or, at the employee's option, by or on order of physicians and hospitals designated or approved by the Secretary. The employee may initially select a physician to provide medical services, appliances, and supplies, in accordance with such regulations and instructions as the Secretary considers necessary, and may be furnished necessary and reasonable transportation and expenses incident to the securing of such services, appliances, and supplies . . . .

§ 8103(b): The Secretary, under such limitations or conditions as he considers necessary, may authorize the employing agencies to provide for the initial furnishing of medical and other benefits under this section . . . .

§ 8104(a): The Secretary of Labor may direct a permanently disabled individual whose disability is compensable under this subchapter to undergo vocational rehabilitation. The Secretary shall provide for furnishing the vocational rehabilitation services . . .]
Model Compensation Programs

(b) Death benefits payable to survivors in accordance with 5 U.S.C. §8133, subject to (d) below; and

(c) Financial indemnities, subject to (d) below, for economic losses associated with the injury, including:

1) scheduled benefits for specified permanent disabilities in accordance with 5 U.S.C. §8107; and

2) compensation for lost wages and specified out-of-pocket costs in the event of total or partial disability in accordance with 5 U.S.C. §§8105, 8106, 8108, 8109, 8110, and 8111.

(d) Death benefits and financial indemnities shall be calculated in accordance with the provisions of F.E.C.A., subject to the following modifications and limitations:

1) Benefits with regard to subjects who are critically or terminally ill at the outset of their participation in the research shall not exceed a fixed schedule of benefits. The burden of proof with respect to any such limitation of benefits shall rest on the research sponsor.

2) Benefits with regard to subjects with preexisting conditions of ill-health shall be reduced to the extent that the death or the occurrence, duration or severity of the injury are attributable, in whole or part, to a preexisting condition of which the subject or those giving consent on the subject's behalf were aware at the outset of participation and which was noted on the consent form. The burden of proof with respect to any such reduction in benefits shall rest on the research sponsor.

3) For purposes of determining compensation for death or for disability extending beyond a specified waiting period:

(A) if the subject's actual earnings fairly and reasonably represent wage-earning capacity over the period of the disability, the subject's wage-earning capacity shall be determined by the subject's actual earnings;

(B) if the subject's actual earnings do not fairly and reasonably represent wage-earning capacity (or future earning potential) or if the subject has no actual earnings, wage-earning capacity shall be presumed equal to the minimum rate for GS-5 for those subjects not physically or mentally handicapped in a fashion precluding employment prior to the research injury, or otherwise determined to be unemployable prior to the research injury. On a showing of clear and convincing evidence, this presumed wage-earning capacity may be adjusted upward, as appears reasonable under the circumstances, with regard to:

(i) the nature of the injury;

(ii) the degree of physical impairment;

(iii) the subject's usual employment;

(iv) the subject's age:
Compensating for Research Injuries: Appendix S

(v) the subject's qualifications for other employment; 
(vi) the availability of suitable employment; and 
(vii) other factors or circumstances which may affect the subject's wage-earning capacity in the disabled condition, including the subject's preexisting condition of health; or 

(C) if the subject is determined to have been permanently unemployable prior to the research injury, actual out-of-pocket expenses (other than medical and related costs covered under §6(a)) shall be indemnified, not to exceed benefits payable with respect to the minimum rate for GS-2; and

(4) Benefit levels shall be adjusted to reflect changes in the cost of living in accordance with 5 U.S.C. §8146a.

(e) No benefits shall be payable under this plan for pain and suffering, punitive damages, or legal fees.

§7. Offset for Recoveries from Collateral Sources
Financial compensation for the costs of medical care, other out-of-pocket expenses, and lost wages shall be payable under this plan only in the event, and to the degree, that such costs are actually incurred by the subject (or the subject's family) and are not paid by any other source. Benefits payable under this plan shall be reduced to the extent costs are paid pursuant to the United States Social Security Act; any state or Federal income disability or workers' compensation law; any accident, health, sickness, or disability insurance; any contract or agreement by an, party to provide or to pay for or reimburse such costs; and any court or administrative judgment or legally effective private settlement covering such costs. Proceeds from life insurance shall not, however, result in diminution of death benefits under this plan. Further, nothing in this section shall prevent any person from expressly insuring against, and receiving payments for, damages in excess of those included in the required benefits under this plan.

§8. Relations to Alternative Legal Remedies
The relationship of this remedy to other existing legal remedies shall be in accordance with the provisions of FECA. In general, as against the United States and its employees, this plan shall constitute the sole and exclusive remedy.

§9. Resolution of Disputes
Disputes respecting the resolution of claims arising under this plan shall be resolved in accordance with the provisions of FECA, except that the Secretary of Labor is also authorized to impanel an expert advisory or arbitral panel to assist in the resolution of disputes arising under this plan.

[For example, §8149 of FECA provides for administrative review, and §8128(b) of FECA provides that final administrative action in
allowing or denying a payment is:

(1) final and conclusive for all purposes and with respect to all questions of law and fact; and

(2) not subject to review by another official of the United States or by a court by mandamus or otherwise.)

§10. Financing Mechanisms
Funding of this plan shall be in accordance with existing provisions of FECA, §8147 of which provides for legislative appropriations on the basis of the compensation experience of the employing agency. The Federal agency funding the research resulting in claims for compensation shall be regarded as the employing agency with respect to such claims.
Plan II

§1. Definitions

For the purpose of this plan:

(a) "Research" means a systematic investigation designed to develop or contribute to generalizable knowledge.

(b) "Biomedical research" means research involving biological study, including but not limited to, medical or surgical procedures, withdrawal or removal of body tissue or fluid, administration of chemical substances or input of energy, deviation from normal diet or hygiene, and manipulation or observation of bodily processes. For purposes of this plan, research satisfying the definitions of both biomedical research and behavioral research is classified as biomedical research.

(c) "Behavioral research" means research involving nonbiomedical alteration or observation of human mental, emotional, or social processes, including but not limited to, data collection or analysis, surveys and questionnaires, tests and measurements, laboratory and field experiments or observations, and innovative environmental designs or psychological or social techniques designed to affect individual or group behavior.

(d) "Subject" means a living individual about whom an investigator conducting research obtains data through intervention or interaction.

(e) "Therapeutic research" means research to evaluate practices or procedures that are intended to provide, or that have some reasonable possibility of providing, therapeutic, diagnostic or preventive health benefits to subjects.

(f) "Nonbeneficial research procedure or intervention" means a research procedure or intervention occurring in either therapeutic or nontherapeutic research that is unnecessary for subjects' own welfare and is performed solely as an aid to the research process.

(g) "Bodily injury" includes wounds, infections, disease, temporary or permanent impairments or loss of bodily functions or bodily parts, or death. For purposes of this plan, bodily injury does not encompass impairment of mental processes (unless demonstrably associated with a physiological cause or change) or emotional distress.

(h) "Non-trivial bodily injuries" include those bodily injuries (i) requiring hospitalization or prolonging hospitalization for persons already hospitalized; (ii) requiring medical intervention beyond first aid and short-term observation; or (iii) encompassing temporary total disability in excess of 24 hours, temporary partial disability in excess of three days, permanent disfigurement, permanent disability or death.
§2. Scope of Conducted Research

"Covered research" shall include research involving human subjects which is:

(a) conducted by agencies of the Federal government ("Federally-conducted research");

(b) Federally mandated for review, and in fact reviewed and approved, according to the provisions of 45 C.F.R. Part 46 (or comparable provisions for agencies outside DHHS);

(c) either (i) biomedical research, or (ii) behavioral research which does not fall within the categories eligible for expedited review pursuant to 45 C.F.R. §46.110 (or comparable provisions for agencies outside DHHS); and

(d) either (i) "nontherapeutic," or (ii) "therapeutic" but employing "nonbeneficial research procedures or interventions" that, in themselves, would require IRB review and would not satisfy the criteria for expedited review pursuant to 45 C.F.R. §46.110 (or comparable provisions for agencies outside DHHS).

§3. Eligibility for Benefits

The Fund shall provide benefits as specified in this plan to research subjects (or their survivors, in the event of the subject's death) who sustain non-trivial bodily injuries (a) in the course of their participation in nontherapeutic research covered by this plan, unless it is more likely than not that such injuries were not the proximate result of the research, or (b) as the proximate result of nonbeneficial procedures or interventions employed in therapeutic research covered by this plan. Injuries sustained by third parties, not themselves subjects of covered research, shall be excluded from coverage. A child born with an injury caused by the mother's participation in covered research during the course of her pregnancy shall be eligible for benefits under this plan.

§4. Standards of Conduct

Benefits shall be provided without regard to whether the injury resulted from the fault of the investigator, the research institution, its employees, or the research subject, except where the injury results from failure of the subject reasonably to conform to the provisions of the research. In the event of injury resulting in whole or part from willful misconduct by the subject, the amount of compensation payable shall be eliminated or reduced proportionately, taking into account both the degree to which the subject's conduct contributed to the occurrence and extent of the injury and the degree to which the subject was in fact aware that such conduct might result in injury.

§5. Time for Making a Claim

The subject (or his or her survivors) shall be allowed at least three years within which to file a claim after the subject's discharge or withdrawal from the research project, provided that in the case of a latent injury, said three-year period does not begin until the

Benefits payable to eligible subjects injured in covered research shall include:

(a) medical and rehabilitative benefits, including:
   (1) short-term, emergency medical care, without fee or charge to the subject (to the extent not provided by other sources); and
   (2) longer-term medical care and related health and rehabilitative services necessitated by the injury, or the costs thereof (to the extent not provided by other sources), not to exceed payments allowable under FECA;

(b) death benefits payable to survivors in accordance with §U.S.C. 813 subject to (d) below; and

(c) financial indemnities, subject to (d) below, not to exceed benefits payable under FECA, for economic losses associated with the injury, including:
   (1) scheduled benefits for specified permanent disabilities; and
   (2) compensation for lost wages and specified out-of-pocket costs in the event of total or partial disability following a reasonable waiting period.

(d) Death benefits and financial indemnities shall be calculated in accordance with the provisions of FECA, subject to the following modifications and limitations:

   (1) Benefits with regard to subjects who are critically or terminally ill at the outset of their participation in the research shall not exceed a fixed schedule of benefits. The burden of proof with respect to any such limitation of benefits shall rest on the research sponsor;

   (2) Benefits with regard to subjects with preexisting conditions of ill-health shall be reduced to the extent that the death or the occurrence, duration or severity of the injury are attributable, in whole or part, to a preexisting condition of which the subject or those giving consent on the subject's behalf were aware at the outset of participation and which was noted on the consent form. The burden of proof with respect to any such reduction in benefits shall rest on the research sponsor;

   (3) For purposes of determining compensation for death or for disability extending beyond [a specified waiting period]:

subject (or his or her survivors) are aware or by the exercise of reasonable diligence should have been aware that the subject's injury is causally related to his or her participation as a subject in the research, and provided further that said time limitation does not begin to run against a minor until said minor reaches 18 years of age or has a legal representative judicially appointed, or against a legally incompetent adult while such individual is legally incompetent and has no duly appointed legal representative.
(A) if the subject's actual earnings fairly and reasonably represent wage-earning capacity over the period of the disability, the subject's wage-earning capacity shall be determined by the subject's actual earnings;

(B) if the subject's actual earnings do not fairly and reasonably represent wage-earning capacity (or future earning potential) or if the subject has no actual earnings, wage-earning capacity shall be presumed equal to the minimum rate for GS-5 for those subjects not physically or mentally handicapped in a fashion precluding employment prior to the research injury, or otherwise determined to be unemployable prior to the research injury. On a showing of clear and convincing evidence, this presumed wage-earning capacity may be adjusted upward, as appears reasonable under the circumstances, with due regard to:

(i) the nature of the injury;
(ii) the degree of physical impairment;
(iii) the subject's usual employment;
(iv) the subject's age;
(v) the subject's qualifications for other employment;
(vi) the availability of suitable employment; and
(vii) other factors or circumstances which may affect the subject's wage-earning capacity in the disabled condition, including the subject's preexisting condition of health;

(C) if the subject is determined to have been permanently unemployable prior to the research injury, actual out-of-pocket expenses (other than medical and related costs covered under §6(a)) shall be indemnified, not to exceed benefits payable with respect to the minimum rate for GS-2; and

(4) Benefit levels shall be adjusted to reflect changes in the cost of living in accordance with 5 U.S.C. §8146a.

(e) No benefits shall be payable under this plan for pain and suffering, punitive damages, or legal fees. During the experimental evaluation period no subject shall receive monetary benefits in excess of $100,000 under this plan.

§7. Offset for Recoveries from Collateral Sources

Financial compensation for the costs of medical care, other out-of-pocket expenses, and lost wages shall be payable under this plan only in the event, and to the degree, that such costs are actually incurred by the subject (or the subject's family) and are not paid by any other source. Benefits payable under this plan shall be reduced to the extent costs are paid pursuant to the United States Social Security Act; any state or federal income disability or workers' compensation law; any accident, health, sickness, or disability insurance; any contract or agreement by any party to provide or to pay for or to reimburse such costs; and
any court or administrative judgment or legally effective private settlement covering such costs. Proceeds from life insurance shall not, however, result in diminution of death benefits under this plan. Further, nothing in this section shall prevent any person from expressly insuring against, and receiving payments for, damages in excess of those included in the required benefits under this plan.

§8. Relation to Alternative Legal Remedies

Injured subjects covered by the provisions of this plan shall have the opportunity to elect, at a reasonable time following injury, whether to proceed under this plan or to pursue alternative legal remedies. No subject (or survivor) may receive any payment or be afforded independent arbitration under the plan unless said individual has waived his or her right to any recovery (whether under tort, contract, or property law) based on the subject’s injury, except under the plan and in accordance with its terms and conditions. Any subject (or survivor) who files suit to secure compensation for an injury covered under this plan shall lose any right to recovery pursuant to this plan.

§9. Resolution of Disputes

Disputes arising under this plan shall be resolved pursuant to a review procedure under which a subject (or survivor) has the right to independent arbitration (e.g., through the American Arbitration Association) of his or her entitlement to compensation, with said arbitration final and binding on all parties thereto to the extent permitted under applicable law. Said arbitral decisions shall not be subject to judicial review, except with regard to any determination respecting the voluntariness and legal validity of the injured subject’s election to waive legal redress in favor of participation in the non-fault compensation plan.

§10. Financing Mechanisms

Initial funding of the Federal Injured Research Subject Trust Fund shall be either by direct Congressional appropriation or by a proportional levy, not to exceed one-tenth of one percent, assessed against funding of research covered under the plan. The Fund shall be replenished in similar fashion on an actuarially sound basis as determined by experience.
§1. Definitions

For the purposes of this plan:

(a) “Research” means a systematic investigation designed to develop or contribute to generalizable knowledge.
(b) “Biomedical research” means research involving biological study, including but not limited to, medical or surgical procedures, withdrawal or removal of body tissue or fluid, administration of chemical substances or input of energy, deviation from normal diet or hygiene, and manipulation or observation of bodily processes. For purposes of this plan, research satisfying the definitions of both biomedical research and behavioral research is classified as biomedical research.
(c) “Behavioral research” means research involving non-biomedical alteration or observation of human mental, emotional, or social processes, including but not limited to, data collection or analysis, surveys and questionnaires, tests and measurements, laboratory and field experiments or observations, and innovative environmental designs or psychological or social techniques designed to affect individual or group behavior.
(d) “Subject” means a living individual about whom an investigator conducting research obtains data through intervention or interaction.
(e) “Therapeutic research” means research to evaluate practices or procedures that are intended to provide, or that have some reasonable possibility of providing, therapeutic, diagnostic or preventive health benefits to subjects.
(f) “Nonbeneficial research procedure or intervention” means a research procedure or intervention occurring in either therapeutic or nontherapeutic research that is unnecessary for subjects’ own welfare and is performed solely as an aid to the research process.
(g) “Bodily injury” includes wounds, infections, disease, temporary or permanent impairments or loss of bodily functions or bodily parts, or death. For purposes of this plan, bodily injury does not encompass impairment of mental processes (unless demonstrably associated with a physiological cause or change) or emotional distress.
(h) “Non-trivial bodily injuries” include those bodily injuries (i) requiring hospitalization or prolonging hospitalization for persons already hospitalized; (ii) requiring medical intervention beyond first aid and short-term observation; or (iii) encompassing temporary total disability in excess of 24 hours, temporary partial disability in excess of three days, permanent disfigurement, permanent disability or death.
§2. Scope of Covered Research
“Covered research” shall include research involving human sub-
jects which is:
(a) supported (via grants, contracts, or similar mechanisms), in
whole or in part, by agencies of the federal government, but
which is not conducted directly by Federal agencies (“Federally-
supported research”);
(b) Federally mandated for review, and in fact reviewed and
approved, according to the provisions of 45 C.F.R. Part 46 (or
comparable provisions for agencies outside DHHS);
(c) either (i) biomedical research, or (ii) behavioral research
which does not fall within the categories eligible for expedited
review pursuant to 45 C.F.R. §46.110 (or comparable provisions
for agencies outside DHHS); and
(d) “nontherapeutic”.
§3. Eligibility for Benefits
Participating institutions shall, as part of their general or special
assurances pursuant to 45 C.F.R. Part 46 (or analogous federal
regulations), set forth the basis upon which benefits specified in
this plan shall be provided to research subjects (or their sur-
vivors, in the event of the subject’s death) who sustain non-trivial
bodily injuries in the course of their participation in research
covered by this plan, unless it is more likely than not that such
injuries were not the proximate result of the research. Injuries
sustained by third parties, not themselves subjects of covered
research, shall be excluded from coverage. A child born with an
injury caused by the mother’s participation in covered research
during the course of her pregnancy shall be eligible for benefits
under this plan.
§4. Standards of Conduct
Benefits shall be provided without regard to whether the injury
resulted from the fault of the investigator, the research institu-
tion, its employees, or the research subject, except where the
injury results from failure of the subject reasonably to conform to
the provisions of the research. In the event of injury resulting in
whole or part from willful misconduct by the subject, the amount
of compensation payable shall be eliminated or reduced propor-
tionately, taking into account both the degree to which the sub-
ject’s conduct contributed to the occurrence and extent of the
injury and the degree to which the subject was in fact aware that
such conduct might result in injury.
§5. Time for Making a Claim
The subject (or his or her survivors) shall be allowed at least three
years within which to file a claim after the subject’s discharge or
withdrawal from the research project, provided that in the case of
a latent injury, said three-year period does not begin until the
subject (or his or her survivors) are aware or by the exercise of
reasonable diligence should have been aware that the subject's injury is causally related to his or her participation as a subject in the research, and provided further that said time limitation does not begin to run against a minor until said minor reaches 18 years of age or has a legal representative judicially appointed, or against a legally incompetent adult while such individual is legally incompetent and has no duly appointed legal representative. However, in no case may a claim be filed later than ten years following the subject's discharge or withdrawal from the research project.

Benefits payable to eligible subjects injured in covered research shall include:

(a) medical and rehabilitative benefits, including:
   (1) short-term, emergency medical care, without fee or charge to the subject (to the extent not provided by other sources); and
   (2) longer-term medical care and related health and rehabilitative services necessitated by the injury, or the costs thereof (to the extent not provided by other sources), not to exceed payments allowable under FECA;

(b) death benefits payable to survivors in accordance with 5 U.S.C. §8133, subject to (d) below; and

(c) such additional benefits, subject to (d) below, not to exceed those allowable under FECA, as would meet or exceed the benefits provided under the workers' compensation law of the jurisdiction in which the research is conducted, were the injured subject considered a covered employee and were the injury considered a compensable injury under the terms of local workers' compensation law.

(d) Death benefits and financial indemnities shall be subject to the following modifications and limitations:

(1) Benefits with regard to subjects who are critically or terminally ill at the outset of their participation in the research shall not exceed a fixed schedule of benefits. The burden of proof with respect to any such limitation of benefits shall rest on the research sponsor;

(2) Benefits with regard to subjects with preexisting conditions of ill-health shall be reduced to the extent that the death or the occurrence, duration or severity of the injury are attributable, in whole or part, to a preexisting condition of which the subject or those giving consent on the subject's behalf were aware at the outset of participation and which was noted on the consent form. The burden of proof with respect to any such reduction in benefits shall rest on the research sponsor;

(3) For purposes of determining compensation for death or for disability extending beyond [a specified waiting period];
(A) if the subject's actual earnings fairly and reasonably represent wage-earning capacity over the period of the disability, the subject's wage-earning capacity shall be determined by the subject's actual earnings;

(B) if the subject's actual earnings do not fairly and reasonably represent wage-earning capacity (or future earning potential) or if the subject has no actual earnings, wage-earning capacity shall be presumed equal to the minimum rate for GS-5 for those subjects not physically or mentally handicapped in a fashion precluding employment prior to the research injury, or otherwise determined to be unemployable prior to the research injury. On a showing of clear and convincing evidence, this presumed wage-earning capacity may be adjusted upward, as appears reasonable under the circumstances, with due regard to:

(i) the nature of the injury;
(ii) the degree of physical impairment;
(iii) the subject's usual employment;
(iv) the subject's age;
(v) the subject's qualifications for other employment;
(vi) the availability of suitable employment; and
(vii) other factors or circumstances which may affect the subject's wage-earning capacity in the disabled condition, including the subject's preexisting condition of health;

(C) if the subject is determined to have been permanently unemployable prior to the research injury, actual out-of-pocket expenses (other than medical and related costs covered under (a)) shall be indemnified, not to exceed benefits payable with respect to the minimum rate for GS-2; and

(4) Benefit levels shall be adjusted to reflect changes in the cost of living in accordance with 5 U.S.C. § 8146a.

(e) No benefits shall be payable under this plan for pain and suffering, punitive damages, or legal fees. No subject shall receive monetary benefits in excess of $25,000 under this plan. During the experimental evaluation period no subject shall receive monetary benefits in excess of $10,000 under this plan.

§7. Offset for Recoveries from Collateral Sources
Financial compensation for the costs of medical care, other out-of-pocket expenses, and lost wages shall be payable under this plan only in the event, and to the degree, that such costs are actually incurred by the subject (or the subject's family) and are not paid by any other source. Benefits payable under this plan shall be reduced to the extent costs are paid pursuant to the United States Social Security Act; any state or federal income disability or workers' compensation law; any accident, health,
sickness, or disability insurance; any contract or agreement by
any party to provide or to pay for or reimburse such costs; and
any court or administrative judgment or legally effective private
settlement covering such costs. Proceeds from life insurance
shall not, however, result in diminution of death benefits under
this plan. Further, nothing in this section shall prevent any per-
son from expressly insuring against, and receiving payments for,
damages in excess of those included in the required benefits
under this plan.

§8. Relation to Alternative Legal Remedies
Injured subjects covered by the provisions of this plan shall have
the opportunity to elect, at a reasonable time following injury,
whether to proceed under this plan or to pursue alternative legal
remedies. No subject (or survivor) may receive any payment or
be afforded independent arbitration under the plan unless said
individual has waived his or her right to any recovery (whether
under tort, contract, or property law) based on the subject’s in-
jury, except under the plan and in accordance with its terms and
conditions. Any subject (or survivor) who files suit to secure
compensation for an injury covered under this plan shall lose any
right to recovery pursuant to this plan.

§9. Resolution of Disputes
Disputes arising under this plan shall be resolved pursuant to a
review procedure under which a subject (or survivor) has the
right to independent arbitration (e.g., through the American Arbi-
tration Association) of his or her entitlement to compensation,
with said arbitration final and binding on all parties thereto to the
extent permitted under applicable law. Said arbitral decisions
shall not be subject to judicial review, except with regard to any
determination respecting the voluntariness and legal validity of
the injured subject’s election to waive legal redress in favor of
participation in the non-fault compensation plan.

§10. Financing Mechanisms
Federal agencies supporting covered research shall consider rea-
sonable expenses incurred by investigators or by research institu-
tions in meeting the requirements of this plan as allowable costs
for purposes of determining costs applicable to research grants,
contracts, and similar mechanisms. Reasonable expenses may
include insurance premiums, contributions to self-insurance or
pooled risk sinking funds, or assessments for participation in the
FIRST Fund for institutions choosing to do so. Nothing in this
provision shall preclude an institution from receiving federal
financial support under existing law or policy for compensation
programs exceeding the scope of coverage established by this
plan (e.g., costs of medical care for subjects injured in therapeu-
 tic research).
Testimony and Correspondence Received by the Commission
Written Materials
Submitted to the Commission

1. John C. Ballin, National Council on Drugs
2. Philippe V. Cardon
3. Thomas C. Chalmers, Mount Sinai School of Medicine, New York
5. John R. Durant, Southeastern Cancer Study Group
6. Audrey E. Evans, Division of Oncology, Children’s Cancer Research Center, Philadelphia
7. Emili I. Freireich, American Society of Clinical Oncology
8. Robert C. Hickey, The University of Texas System Cancer Center
10. Jerry P. Lewis, M.D., University of California, Davis, School of Medicine
11. Gerald P. Murphy, Association of American Cancer Institutes
12. James A. Neidhart, The Ohio State University Comprehensive Cancer Center
13. John F. Sherman, Association of American Medical Colleges
14. Bennett Stark, National Committee for Victims of Human Research

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1. John C. Ballin, Ph.D.
   Executive Director
   National Council on Drugs
   January 15, 1980

   The National Council on Drugs is a consortium composed of
14 members representing the public and eight national organi-
zations in the health care field. Its purposes are to promote the
development and proper use of drugs in human beings, and to act
in an advisory capacity to the government, the scientific commu-
nity, and the public on technical and scientific aspects of drug
development and usage.

   The National Council on Drugs takes this opportunity to
comment on the proposal by the Department of Health and Hu-
man Services that would require institutions to provide prospec-
tive participants in clinical trials with written assurance that
compensation would be provided in the event that these persons
were harmed in the course of the clinical trial.

   The Council has seen no evidence to support fears that there
is a significant problem, either in terms of numbers of individuals
or of financial need, that would justify the requirement of a
compensation provision in all human research. On the other
hand, the Council agrees that compensation claims would inevi-
tably proliferate if such a provision became mandatory.

   In wider perspective, the National Council on Drugs be-
lieves that a compensation provision would produce instant esca-
lation of the cost of doing research on human subjects, thus
prolonging and discouraging the development of new drugs and
contributing to the inflationary spiral.

   Furthermore, a compensation provision would constitute a
powerful deterrent to the investigator who wishes to conduct
research involving human subjects and would impose new legal,
as well as financial hazards on his career plans. As a result, it is
feared that the quality and primacy of American-based scientific
research would inevitably suffer. For the foregoing reasons, and
because of the exemplary safety record of human drug testing in
the United States, we urge that this proposal be rejected.

2. Philippe V. Cardon, M.D.
   Wheaton, Maryland
   July 3, 1980

   While serving on the Secretary's Task Force on Compens-
ation, on my own initiative I put together the same material, in
the form of case reports, thinking it might be helpful in that
setting. At the time, Delbert Nye, head of the Normal Volunteer
Office helped me identify the cases. He ran that office for many
years and probably learned about most of the problems.

   As I recall, there were about 9 occurrences I wrote up. About
half of them had to do with serious mental health problems
which came up during or shortly after participation in research. These were complicated problems, as such problems usually are. I don’t think you will miss much if I don’t try to reconstruct them here from imperfect memory. Instead let me say what my experience has led me to think.

The major health dangers to young adults are accidents (automobiles and motorcycles), and mental illness broadly conceived. Therefore onset of health problems in temporal coincidence with research participation will usually mean involvement in an accident or mental health problems. When the research entailed some intervention which was in any way “mind-bending,” one has the seeds of a real injury. The best and most expert opinion will usually rightly conclude that the research procedure caused neither the accident nor the mental illness as the case may be. Whether the disabled volunteer will concur in that judgement is another matter. If not, I may have what I call the harm of regret. The permutations of destructive regrets (by family as well as volunteer) are surely many; I have witnessed a few of them, and some are worse than trivial by any standard. One would certainly not be surprised to learn one day that a member of the research community has been murdered by someone holding him/her responsible for an accidental death or suicide, or chronic derangement—thirteen volumes of expert opinion to the contrary notwithstanding.

Minimizing “actual cause-effect” harm and the harm of regret isn’t as easy as might seem at first. Good screening comes first to mind, but good screeners aren’t easy to come by, and the best will do an imperfect job. To adopt the rule “when in doubt, reject” raises its own problems. Just think for a minute of what the situation often is. Three friends decide to serve for a time as volunteers. One is rejected because a “good screener” thinks that that one faces a higher-than-acceptable probability of becoming mentally ill within the next few months. The possibility that the rejectee is thereby harmed seems to me real and palpable.

The above paragraphs could be spun out with much more speculation, fanciful but not in my opinion unrealistic. I will stop here by saying that I think at least half of the bad things that happen to normal volunteers are psychological bad things, that it is difficult to avoid them, and the prospect of trying to work out an injury-compensation system for psychological harm would make me blanch.

Turning to more tangible injury; I will describe 5 injuries and one “close call.” Ali but one of the injuries occurred among volunteers on the “normal control” patient unit of National Institute of Mental Health at the Clinical Center. Probably an average NIMH census of 15 is about right, so 20 years of experience means the rough order of 4 injuries in 300 volunteer-years. . . . Staying with the every-day life comparison, and anticipating your own estimate of severity to be made from the case records,
this is probably a bit better than the everyday life risk—confirmed by the fact that in those same years word got back to us within the time of recent acquaintance that one NIMH volunteer had died in an automobile and another had nearly lost a leg on a motorcycle. I will give the cases in rough order of permanence and severity of harm.

A young woman fainted shortly after blood was drawn as part of the admission procedure. She fell forward onto the composition-tile floor, breaking off both upper front teeth at the roots. They had been unusually perfect teeth. Very careful restoration work by NIH dentists was almost perfect, but fine junction lines were visible at the gum line when I last saw her. Anyone with experience of hospital injuries will confirm that much worse things could have happened when her head hit that tile.

The paste used to affix a recording electrode overnight burned the skin of a young woman’s forehead near the temple. It was a second-degree burn about the size of a penny which healed very well, but again not perfectly.

A young man bled profusely from a duodenal ulcer the night after a research procedure. He required several transfusions at a time when the risk of transfusion hepatitis was much higher than it is now. More about the circumstances will illustrate how the ingredient of research can enrich the ambiguities of malpractice litigation. He was not a U.S. citizen, but studying Pharmacy on student visa. He was the first person from a particular Moslem country I or the nursing staff had met, and more extraordinarily he was a Christian. My admitting opinion of his health was unreserved, and I noted to myself that he had a much better sense of his identity and personhood than most of us had of it. He agreed to participate in a study of the effects of reserpine on certain hormonal systems. The study design called for single-blind balanced cross-over intravenous infusion of reserpine or salt solution-only. By chance his first infusion (not just first in the protocol, but first ever for him, first moment of truth as communicant in an alien culture, first in biomedicine’s Mecca a quarter of a world away from the original Bethesda he knew as a child)—the first infusion was salt water.

One might prefer to believe that the Angel of the Pool of Bethesda laid a hand, but probably he could just as well have gotten reserpine that day. (No expert would say that an infusion of reserpine didn’t have an causal relation to the bleeding that followed.) The ulcer crater was big and unequivocally there in the emergency x-rays the next morning. There was no sign of it in two weeks. He went back to school in a few more weeks, apparently as healthy as he was apparently healthy when he came to the Clinical Center.

A young woman received a single oral dose of chlorpromazine (200 mg. as I recall) while participating in a tightly designed study of effects of psychoactive drugs on measures of
behavior. The statistically correct number of days later, she lost her appetite. I knew she had experienced a romantic disappointment, and preferred to think that was the reason, until she became as yellow as a grapefruit. She had chlorpromazine jaundice—as close to the textbook description as one can get! except that no one else seems to have seen it after a single dose. After all, how many people have been given just one dose? She recovered completely, by any criterion I know of. But I also know that Liver failure can be like a brush fire in surprisingly young women who are drinking themselves to death. If this woman should feel driven to the bottle, and if she turned yellow again, how would that be sorted out? Pathologists would say that the processes are entirely different histologically, but I suspect a jury would decide that yellow is yellow.

A young woman (not in a NIMH study) received plasma intravenously. At a not-unusual time later she came down with hepatitis. The investigator, whom I asked about it, said there’s no doubt in his mind she got hepatitis from the plasma he gave her. She recovered completely, but refer to the preceding case. For both of these women, a statistically improbable (but given the then state-of-the-art uncontrollable) bad result occurred initially; both were saved by the lack of occurrence of an even more improbable, but equally uncontrollable, fatal outcome.

A Close Call: A volunteer was given epinephrine by means of a mechanical pump of then-best-available design. Speed of pumping is varied by engaging one of six cogs arrayed in line. The intent was to pump at next to slowest—second from left. The infusion started and the investigator noted that the volunteer became very pale. He quickly realized that he was on the other side of the table from the pump and that second from left was now actually next to fastest—about a ten-fold difference in infusion rate. No IRB and no investigator would ever approve that infusion rate of epinephrine. This was before the time of now commonplace cardiac arrest teams and CPR drills. The investigator is one of the best and most conscientious I’ve known. We agreed that he had run that volunteer very close to the edge.

3. Thomas C. Chalmers, Dean
Mt. Sinai Medical School, New York
January 9, 1981

The following presentation is designed to develop with data the concept presented in the letter to the Chairman of the Commission dated October 29, 1980, in which I presented a number of reasons why the compensation of volunteers for therapeutic research would have a deleterious impact on all efforts to improve diagnostic and therapeutic medicine. It was pointed out that we have a long way to go in learning how to diagnose and
treat most illnesses and that the technological revolution is supplying us with new methods that could improve care or could be deleterious, and that we need to expand markedly the comparative investigation of these new methods. Such research, the randomized control trial, is at present greatly hampered by the fact that there is such a broad gulf between the practice of imperfect medicine and the testing of new therapies. This is caused by the elaborate peer review and informed consent that are required for clinical trials and are almost totally absent in the ordinary care of patients. If it came about that patients who volunteer for clinical trials would qualify for compensation if their therapy was shown to be inadequate, the gap would be made much wider. It would no longer be possible to finance those essential trials to the extent that they should be conducted. Physicians would be reluctant to work on them when they might be liable for a bad outcome if the patient were randomized, but not if they treated the patient as if they knew which therapy was best.

The spectrum of professional activities from practice to research presented in Table I illustrates the problem. First, there is what might be called the "pure" practice of established medicine, and there are very few examples of this: penicillin for pneumococcal lobar pneumonia; Vitamin B\textsubscript{12} for pernicious anemia; insulin for diabetic acidosis; and a few others. These are situations in which it is difficult to conceive of any possible improvement in therapy which might be tested against the standard. But they represent a very small percentage of the practice of medicine. Second is what might be called the "impure" practice of medicine: the use of popular but unproven techniques. This constitutes the vast majority of therapeutic procedures applied to man: the treatment of various infections which do not have a universally satisfactory outcome; the operative management of diseases such as peptic ulcer or gallstones, situations for which the timing and type of surgery are not yet certain; the treatment of most cancers and the management of myocardial infarction. Third is what might be called the innovative practice of medicine. In the case of drugs, this is the use of drugs that are on the market but not yet approved for particular purposes, or changes in the standard dose or duration of therapy. Also included in this rubric are the new operations or therapeutic maneuvers that are not covered by the rules and regulations of the Food and Drug Administration. In this situation it remains entirely possible that what is innovative may not be best for the patient, and from the ethical standpoint the patient might very well benefit more from being part of a randomized control trial designed to evaluate the innovation.
TABLE I
A Spectrum of Professional Activities
From Practice to Research
A. Not Now Covered by any Regulations or Peer Review
   I. Pure Practice of Medicine: Application of procedures
      established as safe and efficacious
   II. Impure Medical Practice: Use of popular but unproven
       techniques
   III. Innovative Medicine and Surgery: Uncontrolled trials of
        new ideas
B. Now Covered by NIH Guidelines
   IV. Clinical Research that is Therapeutic or Diagnostic in
       Intent: Protocol guided studies in sick adults, children,
       and mentally ill
   V. Research in Sick Patients that is not Intended Primarily
      to Benefit the Participating Patient: The patient acting as
      a volunteer
   VI. Research in Normal Adult Volunteers
   VIII. Research in Normal Children and Institutionalized Popu-
       lations with Limited Ability to Give Informed Consent

The next group is clinical research that is clearly therapeutic
in intent, and includes all randomized control trials of diagnostic
and therapeutic maneuvers.

A fifth category is mechanistic research in patients who are
sick and in which the patient acts as a volunteer. In this case there
is clearly a need for protection of the patient with regard to the
relative benefit and risk of the research maneuver.

The sixth category, research in normal volunteers, is not
pertinent to my discussion, except that few people would argue
that some kind of compensation should be made available when
an accident occurs; and the seventh, research in normal children
and institutionalized populations with limited ability to give in-
formed consent, falls in the same category as the fifth and sixth
with regard to compensation, in that some form of help after an
unfortunate accident in a research project that has received ade-
quate peer review and informed consent is indicated.

The reason for presenting these categories is to emphasize
that whenever possible doctors hope to be able to explore new
methods of therapy by calling them innovative and thus not hav-
ing to obtain peer review and informed consent for random-
ization, because those two maneuvers are so time consuming,
and could be interpreted as interfering with the rapid and effec-
tive treatment of the patient. So there is now a tendency to place
new therapies in category III whenever possible rather than im-
prove the exploration of new treatments from both the ethical
and scientific standpoint by constructing randomized control tri-
als. If, as advocated by some, there is no distinction made be-
tween therapeutic and non-therapeutic research with regard to
compensation following misfortune, there will be a still greater impulse not to include patients in clinical trials because they are research, but instead to continue to broaden the activities of so-called innovative medicine. In that case bad research would be substituted for good, and bad clinical research is unethical.

In order to illustrate with data the importance of this problem, I should like to discuss the management of acute myocardial infarction. I have chosen that topic not because I am a hepatologist and, therefore, could not be accused of being a mistaken expert, but rather because it is such a beautiful example of how improvements in therapy so small that they require a precise and well conducted research project to demonstrate them would have a broad impact on the health of mankind.

In Table II is presented the number of cases discharged from United States hospitals with acute myocardial infarction in 1978 and the numbers discharged dead, resulting in case fatality rates of 7.4% under age 55, 22.4% over 55, for an average of 19.1. It should be noted that there were 81,000 people discharged dead during that year, and it has been estimated that two to three times as many people die of acute myocardial infarction without ever reaching the hospital. So, there is plenty of room for improvement in both prevention and medical care.

<table>
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<th>TABLE II</th>
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<tr>
<td>Acute Myocardial Infarction</td>
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<td>Case Fatality Rates</td>
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<tr>
<td>U.S.A. 1978</td>
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<td>&lt;55 yrs.</td>
</tr>
<tr>
<td>Total Discharges</td>
</tr>
<tr>
<td>Discharged Dead</td>
</tr>
<tr>
<td>% Death Rate</td>
</tr>
</tbody>
</table>

The financial impact of this situation is presented in Tables III and IV. Discounted foregone earnings due to premature death have been calculated for three age groups for males and females. These are for the normal population in those age groups, and although they include patients with myocardial disease, the survival can be expected to be less, and, therefore, the earnings less, in people who have an acute myocardial infarction. Comparison of survival curves of such a group with the normal population for that age allows a very rough estimate that expected survival and earnings would probably be shortened or lessened by no more than one-third to one-half, but actual figures are not now available for patients with acute myocardial infarction.
TABLE III
Discounted Foregone Earnings Due to Premature Death*  
(× $1,000)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-44</td>
<td>339</td>
<td>280</td>
</tr>
<tr>
<td>45-64</td>
<td>154</td>
<td>123</td>
</tr>
<tr>
<td>65+</td>
<td>16</td>
<td>23</td>
</tr>
</tbody>
</table>

* See text for qualifications.

In Table IV the cost to the economy of a death from myocardial infarction is calculated according to the foregone earnings lost, and although this varies by age and sex, the total comes out to $3.8 billion per year, or corrected for the differences in survival and workability referred to above, somewhere between $2 and $3 billion per year.

TABLE IV
Cost to Economy of a Death from Myocardial Infarction*  
Cost In Millions

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cost per Death</th>
<th># Deaths in 1978</th>
<th>Total Cost</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>25-44</td>
<td>.339 .260</td>
<td>1,000</td>
<td>339</td>
<td>339</td>
</tr>
<tr>
<td>45-64</td>
<td>.217 .175</td>
<td>4,000</td>
<td>868</td>
<td>1,218</td>
</tr>
<tr>
<td>55-64</td>
<td>.091 .062</td>
<td>7,000</td>
<td>637</td>
<td>1,047</td>
</tr>
<tr>
<td>≥65</td>
<td>.016 .023</td>
<td>32,000</td>
<td>512</td>
<td>1,202</td>
</tr>
</tbody>
</table>

Total cost in foregone earnings for all deaths each year $3.8 billion dollars  
* See text for qualifications.

Now we turn to the case fatality rates, and in Table V are presented for various percentage reductions the resulting percent not dying and, therefore, the number of lives saved. It can be seen that a 10% reduction in case fatality rate—in other words, 17 or 18% dying instead of 19 or 20—would mean 8,500 lives saved per year. Before determining the impact of this on the population and on the economy, one needs to consider the data on how many patients would have to be studied to establish with an alpha of 5%, i.e., a chance of a false positive conclusion of 5%, and a beta of less than 10%, i.e., only 10% or less chance that a true 10% or greater reduction was being missed. The number of patients required for such a study would be 20,400 (Table VI).
TABLE V
Estimate of Lives to Be Saved by Reduction of Death Rate—1978

<table>
<thead>
<tr>
<th>% reduction in CFR</th>
<th>% not dying</th>
<th>Number of lives saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>1%</td>
<td>4,250</td>
</tr>
<tr>
<td>10%</td>
<td>2%</td>
<td>8,500</td>
</tr>
<tr>
<td>20%</td>
<td>4%</td>
<td>17,000</td>
</tr>
<tr>
<td>50%</td>
<td>10%</td>
<td>42,500</td>
</tr>
</tbody>
</table>

Total deaths—61,000

TABLE VI
Randomized Control Trials of A.M.I.

Estimates of numbers required to detect efficacy at \( \alpha \leq 0.05 \) and not miss it at \( \beta < 0.10 \). CFR in control group 20%.

<table>
<thead>
<tr>
<th>Reduction in CFR</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% (to 19%)</td>
<td>82,000</td>
</tr>
<tr>
<td>10% (to 18%)</td>
<td>20,400</td>
</tr>
<tr>
<td>20% (to 16%)</td>
<td>5,000</td>
</tr>
<tr>
<td>50% (to 10%)</td>
<td>746</td>
</tr>
</tbody>
</table>

In Table VII is presented the total cost of the study if one uses a maximal figure of cost per patient of $15,000. In actual fact it should be possible to do pretty good studies of the treatment of acute myocardial infarction for around $1,000 per patient, and the $5,000 figure comes primarily from prevention studies carried out over several years. At any rate, such a study revealing a 10% reduction in death rate would save $400 million in one year in discounted foregone earnings, and would also save $45 million in hospital costs per year if one thinks in terms of a 10% reduction in recurrent infarction from a prophylactic study.

TABLE VII
Cost-Impact of Successful RCT Demonstrating 10% Reduction in 20% CFR

<table>
<thead>
<tr>
<th></th>
<th>20,400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients required</td>
<td>20,400</td>
</tr>
<tr>
<td>Cost per patient</td>
<td>$5,000</td>
</tr>
<tr>
<td>Total cost</td>
<td>$102,000,000</td>
</tr>
<tr>
<td>Number of lives saved in U.S.A.</td>
<td>8,500</td>
</tr>
<tr>
<td>Discounted foregone earnings saved</td>
<td>$399,287,500</td>
</tr>
<tr>
<td>Hospital costs to economy saved</td>
<td>$45,050,000</td>
</tr>
</tbody>
</table>

The cost impact in compensating families for foregone earnings is presented in Table VII in which, if one assumes that the families of all patients who died would be compensated, the cost...
would be $182 million, or $9,000 per patient in the study. And if only those patients who received the worst treatment were to be compensated, the cost would be half that.

**TABLE VII**

Cost Impact of Compensating Families of All A.M.L Patients Who Died in an RCT of 20,400 Patients

<table>
<thead>
<tr>
<th>Cost per patient in study</th>
<th>Number of patients</th>
<th>discounted foregone earnings</th>
<th>Cost of all patients</th>
<th>Cost per patient in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>3,876</td>
<td>$46,975</td>
<td>$182,076,000</td>
<td>$8,925</td>
</tr>
<tr>
<td>“Worse treatment” only</td>
<td>2,040</td>
<td>$46,975</td>
<td>$95,829,000</td>
<td>$4,697</td>
</tr>
</tbody>
</table>

In the final table (Table IX) the number of trials conducted during the five-year period from 1975 to 1979 is presented along with the patients involved, and the mean reduction in CFR of 6.7%. This is intended to show that far too few studies have been performed under present circumstances when doctors were not faced with compensating patients for bad outcomes. This number would surely be reduced if doctors had to add to compensation to the complexities of doing a trial. There would be still more patients handled by less informative and less ethical innovative medicine.

In summary:

(1) There is a great need for precise clinical trial research if we are to take advantage of remarkable technological advances to reduce premature death and disability.

(2) The present rigid distinctions between practice and clinical trials with regard to requirements for peer review and informed consent are making it increasingly difficult to persuade doctors and patients to take part in clinical trials.

(3) Compensating bad outcomes *only* in those entering formal trials will further widen that gap and almost eliminate trials.

(4) Clinical research will then be disguised as innovative practice and, therefore, result in unreliable conclusions and markedly reduce the chances of saving lives and decreasing disability.

**TABLE IX**

Randomized Control Trials of A.M.L

<table>
<thead>
<tr>
<th>1975-1979</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total trials</td>
</tr>
<tr>
<td># Patients involved</td>
</tr>
<tr>
<td>Mean % reduction in CFR</td>
</tr>
</tbody>
</table>
4. Giulio J. D'Angio, M.D., Director
Children's Cancer Research Center
The Children's Hospital of Philadelphia
December 8, 1980

I am writing with respect to the Commission on Compensa-
tion for Subjects Injured in Research. Several people have testi-
fied before your group, but I would like to underline the special
circumstances concerning cancer clinical trials.

The treatments used for the management of cancer patients
all have their associated risks as well as benefits. These are bal-
anced very carefully in virtually every clinical cancer trial. The
benefits of the treatments under investigation need to be estab-
lished; they almost certainly have their deleterious side effects.
Therefore, even the patients receiving only standard therapy (for
example, surgery alone) as controls benefit from not being sub-
jected to the toxicities associated with chemo- or radiotherapy.

The situation in cancer work also is made complex because
of the side effects that may become evident only after the passage
of many years. Some of these are unpredictable, and require
observations of many patients for a long time before a clear
cause-and-effect relationship can be established. If compen-
sation were to be offered patients for this kind of unforeseen,
much-delayed injury, one can predict contention if not litigation
in future years. This is particularly applicable to possible genetic
consequences which are extremely difficult to establish, as you
know.

It seems best to restrict this whole matter of compensation to
those investigations that are not designed to benefit the patient:
There are virtually none of this kind in clinical cancer studies,
especially the cooperative group trials. I therefore would urge
you and your Commission to consider cancer clinical in-
vestigations as a separate issue, and not include them in the
general principles and recommendations that you are drafting.

5. John R. Durant, M.D., Chairman
Cooperative Group Chairmen
Southeastern Cancer Study Group
University of Alabama & Birmingham
January 7, 1981

I am writing regarding your deliberations concerning com-
pensation programs for research and the possibility of providing
insurance for that purpose.

First, let me say that it seems to me that therapeutic research
must clearly be separated from other kinds of research. In regard
to this question, I am not very confident of the experience of the
commissioners, other than yourself, in the field of therapeutic
research, particularly therapeutic cancer research.
I am the Chairman of the Cooperative Group Chairmen who conduct many of the NCI's clinical cancer therapeutic research trials. I would like to appear before your commission in order to present my concerns in this area. Briefly these concerns are:

1. If this decision is implemented, many trivial suits would be instituted which would not otherwise be instituted, and would lead to enormous escalation of administrative costs—a factor already reducing the available money for research by diverting funds from direct to indirect costs.

2. In my prior correspondence with Barbara Mishkin, she assured me that no such large costs would be incurred since two institutions have already developed self-insurance programs with the experience that very few claims for very small amounts were made. I would have to interpret such information as indicating that the problem is not very serious—therefore, hardly worth the commission's effort. I note, however, that the University of Washington was unable to obtain a commercial insurer for their program when they wished to renew it. Accordingly, I would have to believe that private insurance companies believe this program is not likely to be one that would permit accurate predictions of future cost. I believe the net effect of creating such a program in therapeutic research would be to delay the introduction of effective new therapies into American medicine much more than the GAO's recent estimate of 7 years compared to our European counterparts. It surely will raise indirect costs and probably discourage imagination. Accordingly, I believe the issue is important and hope that I may be able to have my views made known to the commission.

6. Audrey E. Evans, M.D.,
   Director, Division of Oncology
   Children's Cancer Research Center
   The Children's Hospital of Philadelphia
   November 25, 1980

I understand following the hearings in September the Commission agreed to recommend a system of compensation for people injured in clinical trials. In my own mind I think I would separate out therapeutic and non-therapeutic trials and also the diseases for which therapy are designed. I believe if a patient develops thrombocytopenia while testing a cure for the common cold it is different from one who experiences unpleasant vomiting from a drug being tried in the treatment of cancer. I must have spent 20 years in clinical cancer research where the risks and benefits to the patient are honestly addressed and I don't believe we have ever had an occasion where I believed a patient was legitimately due any financial compensation.
My concern regarding sweeping recommendations is that they can be misinterpreted and misused. In many ways I think medical care is hampered by considerations of malpractice suits (and indeed has become more expensive because of these concerns) and that it is possible that the need for compensation may inhibit good clinical research. I do not honestly believe that in the present day climate of human experimentation, that physicians "use" the poor and disadvantaged in a way that they would not use any other patient. I do believe that the unintelligent can often not understand the issues involved in the study, but that their rights are sufficiently protected by the Commission on Human Experimentation.

7. Emil J. Freireich, M.D., President
American Society of Clinical Oncology
January 2, 1981

I am writing to you in my capacity as President of the American Society of Clinical Oncology. Our organization has over 2700 members and encompasses all of the subspecialties of medicine which deal specifically with cancer research and cancer treatment. I am writing about the problem of "compensation of injured research subjects". I have discussed the matter with Dr. Denman Hammond who is the Chairman of our Public Issues Committee and I have asked Dr. Philip S. Schein of Georgetown University School of Medicine, who is a member of our Board of Directors to represent the Society at your meeting on January 9.

I am writing to express the view that cancer patients and cancer treatment research should be specifically excluded from any considerations relating to compensation. My primary reason for suggesting this is to emphasize both the importance of cancer treatment research and the research nature of most of the current cancer treatments available.

The physician in clinical science and in clinical practice is always faced with the problem of weighing the potential for benefit against the potential risk of any treatment recommendations. In the case of malignant disease the threat to the individual's life is so great that treatments which would otherwise not be considered are regularly undertaken.

It seems clear to me that in consideration of compensation one must consider the motivation for the subject participating in clinical research. In those instances where the motivation for participation is personal gain, that is where a patient is motivated to participate in research in order to benefit his own health and survival, it seems that compensation would not be indicated. In contrast when society finds it necessary to ask people to participate in clinical research where the individual himself has no potential for benefit, but where the community as a whole does have a potential for benefit, this is an area where participation in
clinical research should be accompanied by some mechanism for compensation should injury result from such investigation. If this is considered, then treatment of patients with a malignant diagnosis would be generally excluded from any compensation considerations and this would eliminate the concern of those in the field of clinical oncology about considerations of this subject.

8. Robert C. Hickey, M.D.
Executive Vice President
The University of Texas System Cancer Center
January 9, 1981

I wish to express my views on the subject of "compensation of injured research subjects". I serve as Executive Vice President for one of the major comprehensive cancer research, treatment and education centers in our country. Our institution is a major component of a university, The University of Texas System, and performs its mission under the laws of the State of Texas and the United States. Our goals and purposes reflect the great importance of the problem of cancer as an illness and a biological problem. Knowledge about the biology and treatment of cancer has evolved rapidly in recent years, with progressive improvement in our expectation of cancer control. At the present time, at least two of every five patients diagnosed as having cancer will have their disease effectively controlled by current treatment methods; however, many still will succumb. This emphasizes the great importance of continuing clinical investigation to improve our methods of cancer treatment.

Cancer treatment and research are closely interwoven. Our institution recognizes that cancer therapy is continuously evolving and improving. As a result, most therapy at an institution such as ours must be considered as developmental in nature, and therefore potentially exposed to compensation for an injury. Our physicians are obligated by professional ethics to provide the most effective treatment, even though it be an investigational treatment regimen. When considered with the additional point that almost all standard and investigative therapy for cancer has substantial undesirable side effects and toxicity, the cancer physician conducting clinical investigation is exposed to significant risks; this is true even though the clinical scientist is acting entirely in the patient's best interests. The ultimate hope is to convert an otherwise hopeless situation into one with a brighter prospect for possible long term control.

The matter of compensation in human-subject cancer research should consider the intent of the research. If the intent is therapeutic for the patient or research subject, and the patient stands to potentially benefit, if adversity is encountered, compensation should not be expected. Nontherapeutic directed research is another matter, to be handled on an individual basis.
After carefully considering the possibilities for compensation, it is clear to me that cancer treatment research conducted upon patients with a malignant disease should be excluded from any considerations of compensation. This recommendation is made because it is clear that the dividing line between research and treatment is poorly defined. Significant harm and slowing of cancer research could result from adverse rulings in this field. Because better treatments for cancer are so important in this country and the world, I feel that cancer patients and treatment of cancer patients must be excluded from any considerations in compensation. I would add that the clinical observations must be done in a proper setting and under proper surveillance to protect the subject.

9. James F. Holland, M.D.
American Cancer Society Professor of Clinical Oncology and Chairman, Department of Neoplastic Diseases
Mt. Sinai Medical Center, New York
January 7, 1981

I am concerned with the ethics of therapeutic agents, their clinical investigation and their use.

So long as there are diseases which are not prevented, therapeutics will be a major human endeavor. There are few diseases for which the therapies are entirely satisfactory, and many where no potential victim can rejoice in the modest effectiveness available today. One need only consider the human misery of cancer, parasitic diseases which wreak untold suffering on a worldwide basis, atherosclerosis, the psychoses and the arthritides to appreciate the challenge confronting therapeutic investigation.

Investigation is a step into the unknown. It is impossible to determine whether benefits will accrue. It is impossible, in advance, to determine if toxic side effects (actually true drug effects on normal tissues) will occur. It is often easy, however, to appreciate the toxicity of the unmitigated disease. Unrelieved by effective therapeutics, many of the diseases for which the quest is made cause disability, death and economic ruin.

It is manifestly impossible to guarantee that the unknown is risk-free. I believe it would inflict a lethal blow to therapeutic research to require that any adverse effect be compensated. Who compensates those who suffer or die because society has not discovered effective therapeutics for their disease? I urge you to reject compensation for toxicity or unforeseen effects of therapeutic research in consenting volunteer patients. Their risk is counterbalanced by the potential for their gain. Since hospitals are nearly all not-for-profit, and could not compensate from their own resources, the temptation would be to place the blame on the manufacturer of the therapeutic agent. This would have the effect of sharply restricting the number of drugs which ever
reached clinical trial, and then only for indications which potentially could lead eventually to a profitable market. If one considers the adverse effects of drugs a catastrophe, patients who sustain them can be categorized with all other medical catastrophes in the national attempt to deal with these.

Undesirable side effects of drugs which are no longer in the investigative realm but are part of the accepted therapeutic armamentarium are already handled by Federal and State laws. Negligence is a key item; there, and certainly should not be exculpated.

The difference between the practice of medicine, using approved therapeutic agents, and investigative drug use to find better therapies is so stark, that I believe it merits governmental reorganization. The Food and Drug Administration has exceptional strength and expertise in regulating the flow of drugs to the market. Many in academic pursuits (let alone the pharmaceutical industry) believe the manifest conservatism of the Food and Drug Administration must be judged not only on the adverse side by the effects avoided, but on the continued manifestations of disease and death which might have been corrected by effective drugs had they been available earlier. This is particularly true for therapeutic agents found active in other countries. I am aware of several instances where reputable pharmaceutical firms have been obliged to submit an application taking years to prepare, running 75,000 to 100,000 pages, to have such an active drug approved for the American market. One hopes this bureaucratic disease is reparable.

One could question, however, whether this approach to drug regulation is conductive to investigating and finding new drug leads. I suggest that the ethical burden of unrelieved illness is worthy of equal consideration, and that a new mechanism be proposed for accelerating progress in therapeutics. A separate Bureau charged with investigating drugs, disposed to encourage investigation should be established. It should be qualified to permit 250 patients, all volunteers, to undergo exploratory therapy. Only those drugs of demonstrated efficacy and safety would then be allowed to proceed toward the market, and the Food and Drug Administration should exercise the same responsibilities it now bears for further clinical investigation and for marketing. A separate investigative bureau could husband its resources well, permitting studies only in those institutions qualified by skilled personnel and facilities to make maximum contribution to human welfare. In such a climate, good research design ensures good ethics, and containment of risk.

I have taken the liberty of enclosing a recent editorial I have written for the American Journal of Medicine which deals with this problem. I hope you and your Committee will address this ethical problem: of our failed mission for every day of illness when we are not exercising best efforts to find a better treatment.
10. Jerry P. Lewis, M.D.
Professor of Medicine & Pathology
Chief, Section of Hematology and Oncology
University of California Davis, School of Medicine
November 6, 1980

As a worker in the field who cares for cancer patients and has participated in cooperative clinical trials for some two decades, I thought that my comments might be of some interest to you and your associates. My comments are made in the context of cancer patients and human subjects research.

The Commission will want to grasp the fact that insofar as well-organized cooperative clinical trials are concerned in oncology wherein the protocols have been carefully screened by competent local investigators, reviewed by duly authorized and appropriately constituted human subjects review committees locally, and in many cases have also been reviewed by the National Cancer Institute, and, finally, come under continuous peer review, that entry into such a study assures one the best known therapy or its presumed equivalent. Such studies are not designed with the assumption that the proposed new therapy is less efficacious. The implication of the Commission appears to be that standard treatment, whatever that may be, has fewer risks and side effects than “experimental therapy.” This is not the case, and, as a matter of fact, it may be at the end of the study that standard therapy actually has greater risks than does the new “experimental” regimen.

In designing clinical studies of treatment regimens in cancer, it is essential that investigators demonstrate to themselves as well as to the Human Subjects Review Committee that the benefits outweigh the risks. While participating in clinical studies of this type, the patients may be cared for without the added costs of professional fees or with free medication or grant-supported diagnostic studies. Thus, even without compensation for “harm,” the patient often receives some compensation for his participation in trials, and this compensation is equally distributed to all participants whether they are “injured” or not. This seems to be a far more fair approach than to select only those who may have been “harmed.” Since patients participating in trials may be cared for at less cost than a patient not on such treatment regimens, if one then agrees to compensate those who may have been “harmed” by the procedure, rightfully one should charge patients who benefit from such studies, since this may clearly be a benefit which they would not have received while on standard therapy.

The Commission should recognize that patients with serious and debilitating diseases whose natural course is that of deterioration, such as cancer patients, receive absolutely no benefit from nonintervention. I would hope the cancer patient would be ex-
cluded from any compensation system, since the risks of non-treatment are so tremendous that it would be unethical to deny patients therapy and since the best treatment available in many settings is participation in a well-defined, thoroughly studied, adequately documented clinical trial.

Although it is attractive to envision improved quality of care for patients as originating in a test tube, as a practical matter improved medical care has only been brought about because of the willingness of patients to participate in well-organized studies. There has been a very healthy movement nationwide in the past decade to extend the benefits of clinical studies of this type to patients cared for by community physicians. I would call the Commission’s attention to the federally funded national studies of breast cancer, which in the past 4-5 years have surely extended our understanding and treatment of this very common disease. These studies could not have been carried out without the active cooperation and support of the private sector of medicine. With the enactment of laws which will demand and dictate compensation for those who may feel they have been harmed, we will lose the vast wealth of experience of a large segment of medical practice in such trials and advances in medicine will grind to a snail’s pace.

The institution of an elaborate and, to be sure, eventually lucrative compensation system for patients with cancer entering into clinical trials will alter the reasons for patients to enter into such studies. Currently they do so out of altruism and their willingness and, at times, even eagerness to help their fellow man. Under the system which your Commission is currently attempting to erect, they would see entering such clinical trials as possibly lucrative and most surely beneficial to them. They would either improve, which, of course, would accrue to them the benefits of prolonged survival and possibly cure, or they would be awarded compensation if they did not respond, for to fail on a clinical trial is similar to having been injured by it, since there are some side effects which the patient would have experienced, and side effects without benefit is tantamount to harm and most certainly would be considered by the courts at some point in time as a compensable injury.

The definition of injury must be very carefully spelled out before any compensation system is inaugurated. As an example, a form of injury secondary to cyclophosphamide therapy, which is predictable in a small number of patients, is hemorrhagic cystitis. Given the scenario of two patients, one of whom is treated with standard therapy off protocol, which includes cyclophosphamide, and another patient who is treated on a clinical study and is randomized to the standard arm, which includes cyclophosphamide, only the patient on the formal clinical trial would receive compensation if hemorrhagic cystitis develops. The point is, of course, there is no reason to believe that participation in clinical studies is necessarily more hazardous than
not participating in clinical studies. In fact, the therapies may be identical.

Dr. Holly Smith, in her testimony before your committee, seems to have overlooked the fact that the gratitude of society is expressed for society by the researcher himself to all patients who enter into cooperative clinical trials; it is not reserved for only those who are injured. I would also point out that there are many other ways that one receives gratitude aside from the monetary route. Her comments suggest that gratitude be awarded by society to those who are injured and not those who receive only benefits from clinical trials. The risks of both patients are identical on entering the trial and both should be equally recognized for their willingness to contribute to the control of human disease.

The comments of Dr. Boxill, although on the surface reasonable, must be viewed in the broader context of historical experience in the courts with compensation for injury. There is no reason to believe that compensation set up under your Commission will remain reasonable. Most surely the concept of injury will be broadened so eventually if a good response without toxicity is not forthcoming the patient will be considered harmed.

The Commission will also wish to address the question as to how one handles the problem of suffering or “harm” which occurs in the context of a clinical trial which eventually leads to the cure of the patient. As an example, recent clinical trials have led to a 70% cure of testicular cancer at the expense of extensive side effects. The treatment is toxic (i.e., harmful); however, the results are desirable (i.e., cure). Since compensation would not be based on outcome but only upon side effects, a patient who enters such a clinical trial and experiences toxicity yet is cured would be eligible for compensation. The patient who is treated with standard therapy would not have enjoyed as great a chance of cure, but not being on study would not be eligible for compensation.

Should your commission finally elect to include cancer patients who are on well-reasoned clinical trials in the category of injured patients, I would hope that such compensation would be provided federally as long as the clinical trial was well reasoned and passed the institution’s human subjects review. It is certainly not appropriate for patients to buy their own “injured research subjects insurance.” This would limit the benefits of such research to those who could afford to pay. It is also not reasonable in a climate where funds for research are being continually restricted to limit these funds even further by insisting that institutions carry the cost of such insurance. As mentioned earlier, such a plan would also completely negate the opportunity of patients in the private sector from participating in such trials, since private hospitals will not want to purchase additional insurance so their doctors can participate in clinical studies.

In closing, I would like to assure you that I recognize the awesome task of your Commission. Through your rulings you are
in a position to bring medical research to its knees, eventually grinding progress to a standstill. Most surely this cannot be in the best interests of our patients, of society today, and future generations of mankind.

President
Association of American Cancer Institutes
September 1, 1979

As President of the Association of American Cancer Institutes (AACI), I would like to address myself to the proposal for compensation of patients involved in clinical therapeutic investigations. My viewpoint represents those from the sixty-three major cancer centers in the USA who are members of the ACCI.

The proposal for compensation of research subjects experiencing excess injury during clinical therapeutic investigations is based on the premise that society gains by such studies and must compensate for injuries incurred. Also, such proposals assume that the survival rates of untreated cancer patients are known. There is very little data available to substantiate the support of this assumption. It must be realized the situation in clinical research involving cancer patients poses a different set of circumstances from the usual setting. Cancer without treatment is inevitably fatal, and in addition often a patient experiences considerable discomfort. There is no completely standard therapy for cancer of any kind today. A recognized need exists to improve the results of treatment with currently available methods and to bring new modalities in as they become available through preclinical research. Clinical research offers the cancer patient the best available treatment in a setting in which new information can be gained. The cancer patient is the principal beneficiary of this treatment, which often is associated with some risk because of the nature of the surgical procedure, radiation therapy and chemotherapy used.

It has been demonstrated that the risk of injury during clinical therapeutic investigation is greatest for the cancer patient. We feel strongly that any consideration of the matter of compensation for injured research subjects should have knowledge provided by an investigator experienced in clinical research for cancer. Furthermore, we would urge that the Ethics Advisory Board Chairman, Dr. James Gaither, be provided with Ad Hoc members experienced in clinical research particularly when this subject is under discussion. At some time in the future, we also advise that an experienced clinical investigator be appointed to the permanent board. We think this action will be most helpful and appropriate.
The implications of the compensation issue for continued clinical research for cancer patients is serious in our opinion and needs careful review as to its appropriateness and consequence of implementation.

12. James A. Neidhart, M.D.
Associate Professor of Medicine
Deputy Director,
The Ohio State University
Comprehensive Cancer Center
November 11, 1980

Doctor Gerald Murphy recently sent some notes from the Commission’s September 15th meeting to members of the American Association of Cancer Institutes. The Commission is breaking some very difficult and treacherous ground and I would like to share a few thoughts. I will keep this letter succinct, but would be anxious to expound on any of these points if it would be helpful.

(1) It is absolutely clear that experimental treatment programs in cancer are quite often the best available to a particular patient, at a particular stage of his or her disease. Although the primary goal is to offer that patient the best therapy available, the Commission must be careful that it does not make it impossible to offer patients with cancer experimental treatments. These patients have enough problems at it is.

(2) It is much easier for physicians to treat cancer patients with standard treatment modalities even if those modalities have proven to be ineffective. Experimental treatment programs, particularly those using investigational drugs already require considerably more effort on the part of the physician and the patient despite the fact that they are often the best choice. The Commission must be careful that it does not generate further resistance to participation in research treatment programs.

(3) There are numerous examples of investigational anticancer drugs and treatment programs that have proven curative in previously untreatable cancers during the period that they were used as investigational agents. A system that discouraged clinical research in cancer would have deprived these patients of the opportunity of cure and assured their death within a reasonably short period of time. Any oncologist can generate a list of patients who are now alive solely because of their participation in clinical research programs. The Commission must be careful that it does not rob future patients with cancer of similar opportunities. Examples are: (a) cis-platinum in testicular cancer; (b) cytosine arabinoside
in acute myelogenous leukemia; (c) Adriamycin in soft tissue sarcomas; (d) combination therapy of Hodgkin’s disease and acute leukemia in children.

This is not a complete list of experimental programs that have turned around the treatment of a particular cancer in a very short period of time.

(4) Often, but not always, patients with cancer receiving investigational programs have far advanced disease and will, if that disease progresses, develop additional complications related to the disease and not the treatment. It is extremely difficult sometimes to attribute “side effects” to drug or disease. This is particularly true when that drug is being used in early clinical investigations.

(5) Should the Commission set up regulations that make physicians choose standard therapies rather than experimental ones, it is highly likely that they will not decrease the risk of “injury” to patients. You must remember that standard treatment regimens for cancer also have side effects that can be quite severe. These side effects may be much greater than those of new investigational drugs or programs. Since standard treatments have been shown not to work in many cancers, the risk to benefit ratio for the standard treatment program could be much higher. It should be pointed out that much of the effort in developing anti-cancer therapies are aimed at developing agents or combinations with less, not more, toxicities than standard agents.

I would be happy to expand on any of these points or to raise additional ones if it would be of help to the Commission. I do urge you to be very, very careful. We have made great progress in treating cancer and now have the capability of curing many tumors that were not treatable ten years ago. Progress has been slow and it is often difficult to keep the momentum of clinical therapeutic research going. I sincerely hope the President’s Commission does not enact regulations or mechanisms that are going to make therapeutic research more difficult or even impossible. Lack of access to investigational drugs for untreatable cancers may be a greater injury than the use of that drug.

13. John F. Sherman, Ph.D.
Vice President
Association of American Medical Colleges
May 7, 1980
The November 3, 1978, publication of an Interim Final Regulation requiring specific disclosure during the process of securing informed consent of the availability of compensation for human subjects injured in the course of biomedical and behavioral research caused great confusion and consternation within the Nation’s universities, medical schools and teaching hospitals. Their concern was many-faceted; but a chief contributing factor
was the fact that no institution, to our knowledge, currently has
in force insurance coverage to provide broad compensation such
as that recommended by the DHEW Task Force. Over the past
year, members of our staff have engaged in extensive consul-
tations with representatives of other education associations in an
attempt to explore the problems involved in achieving the goals
of the Task Force and the Department of Health, Education and
Welfare. The objective of this effort was to examine the feasibil-
ity of acquiring appropriate insurance coverage and to develop
positive suggestions regarding the character of a compensation
scheme which would meet the enunciated ethical and equity
considerations of the Task Force while at the same time pre-
serving an environment conducive to productive research on
pressing human problems. While we believe that we have made
substantial progress toward accomplishing this purpose, there
remain many questions which are beyond the purview and/or
competence of this group to resolve. We believe these questions
must be resolved before any compensatory mechanism can be
put in place. The purpose of this letter is to describe our efforts,
to enunciate the questions and to suggest a mechanism for their
resolution.

Background

The “DHEW Secretary’s Task Force on the Compensation of
Injured Research Subjects” concluded that there are several fea-
sible legal avenues for compensating injured research subjects;
one involves continuing reliance on the tort-negligence system,
one would require state legislation to provide coverage at that
level of government, two would require legislation to establish a
Federal compensation system, and one would establish and
administrative requirement that PHS-assisted grantees and con-
tractors establish and operate a compensation system. The publi-
cation of Interim Final Regulations on November 3 together with
the draft notice of proposed rulemaking contained in the appen-
dix to the Task Force Report suggest that the Department is pro-
ceeding with an implementation strategy which places primary
reliance on the fifth alternative. As the Task Force pointed out,
however, this approach assumes the availability of commercial
insurance.

In this connection, however, it must be realized that
such a system could operate only to the extent that
the private insurance industry is willing to under-
write such a scheme. [Report p. V-5]

The consultants commissioned by the Task Force alerted it to the
formidable obstacles to insurance industry participation.

Regular insurance of this type is not available be-
cause of the great, if not overwhelming, difficulty of
establishing actuarily proper rates. Some research
projects would have virtually no risk involved,
whereas others might have risks that would be very difficult to assess in advance, and any underwriting study thereof by an insurer in order to establish adequate premium rates would be so expensive as to preclude entrance into this field.

Similarly self-insurance would not be at all feasible. For one thing there would be great uncertainty as to the incidence of cost and the possibility of an enormous cost arising. The only way that an institution could really properly budget its cost for such a program would be through insurance, and this is not available. To self-insure would mean taking a serious risk of a catastrophic budgetary nature that could disrupt or even destroy the entire operations of the organization.

In summary, then, this approach of establishing regulations requiring grantees and contractors to provide compensation for injured subjects does not seem feasible.

Robert J. Myers
Professor of Actuarial Science
Temple University
(Appendix, p. 149)

A caution of a different nature was registered by a second consultant to the Task Force.

The cases that have generated public and governmental concern, it should be recognized, are unlikely to be representative of the cases that would be encountered once any of a variety of new administrative mechanisms is put into use. The mix of cases that will be presented, as well as their quantity, will respond to the procedure that will be employed to award compensation...

Compensation systems are highly complex instruments. Each possible system will serve or hinder a variety of purposes. A system that is designed to best meet a single goal, say provide equitable levels of compensation to injured parties, is unlikely to prove to be desirable. Its levels of achievement on other valued dimensions are almost certain to be inadequate.

Professor Richard Zeckhauser
Professor of Political Economy
Kennedy School of Government
Harvard University
(Appendix, p. 155)
Progress of Our Efforts

These two cautions expressed by consultants to the Task Force epitomize the concerns which faced our ad hoc group. Namely, the identification of circumstances under which the lack of actuarial data regarding risks could be circumscribed to such an extent as to make insurance company participation feasible and a subsequent concern which might be characterized as the "economics vs. equity trade-off." By this latter phrase we mean that the participation of insurance companies may depend upon program and coverage limitations which may diminish the degree to which the equity/ethical objectives of the Task Force can be met.

Coverage Limitation. It is our conclusion after substantial consultation with insurance industry representatives that any insurance coverage would have to have the following limitations:

It would exclude trivial injuries. While there appears to be some latitude as to the definition of what might constitute a trivial injury, some threshold of seriousness must be reached and exceeded before the risk becomes an insurable one. The reasons for this limitation are:

(A) To limit the effect of inducing claims for medical coverage.
(B) To limit the need for the administrative machinery required to process and resolve claims to those situations where the recovery is sufficiently large to warrant the administrative expense.

Comment. Under the present circumstances, trivial injuries are routinely cared for on a no-cost-to-the-subject basis. The widespread existence of this "informal" system for handling minor injuries to research subjects suggests that the exclusion of such cases from the insurance coverage would present no substantial difficulty. The fear arises, however, that the effect of assuring a research subject that total care will be provided should the subject be injured would be to induce a demand for medical care and/or compensation in many cases where it is not warranted. There is further concern that having the research institution in effect self-insure for the trivial injury may result in a situation in which the aggregation of trivial injuries during a particular time or with respect to a particular project amounts to a substantial expense which is either unrecoverable to the institution or which seriously depletes the funds dedicated to the cognate research project (and thus defeats the purpose of the project and the reason for the risk taking.)

Resultant Policy Questions

(1) Is the exclusion of trivial injuries, requisite to obtaining insurance industry participation, acceptable to the Ethics Commission?

(2) How shall trivial injuries be defined for this purpose? (Advice to date suggests that an injury lasting no more than 2-7 days would be adequate.)
Recovery for wage loss would be unavailable for an initial period. This limitation has a similar rationale to that discussed above. From an insurance standpoint, such a limitation is essential in order to limit the tendency of such a program to induce claims for compensation of dubious merit and to limit the administrative expense of processing and resolving claims to those situations in which it is clearly warranted.

Comment. While such a waiting period is standard in disability insurance contracts, it does not appear to be contemplated by the Task Force or permitted under the draft NPRM. Clearly such a limitation diminishes the level of recovery to an injured subject and thus fails to meet completely the ethical/equity objectives. Nevertheless, it appears to be an essential feature from an insurance perspective.

Resultant Policy Questions
(1) Is such a coverage limitation acceptable to the Department?
(2) What is the appropriate duration of the initial waiting period during which wage loss would not be compensable? (Advice to date suggests that a minimum of 30 days would be required.)

The total period during which claims may be made must be time limited. The draft NPRM suggests that a limitation on claims is permissible (§6 (c)(1)); App. p. 291). However, the limitation specified would allow the filing of a claim within two years of the manifestation of a latent injury without regard to when the injury became manifest. We are informed that such open-ended coverage would not be available because the risks described would be regarded by the industry as uninsurable. While such "statutes of limitations" are common in tort law, the Task Force Report and the draft NPRM do not appear to contemplate an absolute cutoff date.

Resultant Policy Questions.
(1) Is such an absolute cutoff of insurance company liability acceptable to the Commission?
(2) What should constitute the cutoff point for allowable claims in the case of latent injury? (Advice to date suggests that the typical malpractice statute cutoff of eight years is an appropriate model.)

Collateral Sources Offset. We are advised that insurance coverage for such a compensation program is feasible only if it is clearly defined as "on top of" existing mechanisms for providing funding for medical care and compensation that injured subjects may otherwise be entitled to.

Comment. The draft NPRM is silent on the issues of collateral sources entitlements and subrogation of claims. Subrogation should clearly be discarded as an option because of the associated administrative expenses and the possibility that it will stimulate unproductive litigation among carriers.
Resultant Policy Question.

(1) Is the specification of an offset for collateral sources acceptable to the Commission?

Discussion

The issues set out above are only the most fundamental and pressing that must be resolved before it is possible to expect that there is any likelihood of insurance industry participation. In each case there are two related issues: Is the limitation acceptable to the Commission in principle?; and, what would constitute an acceptable and economically feasible limitation? While the second is a detail, the nature or extent of the limitation involves the economics/equity trade-off. Insurance coverage may be available only at some thresholds and the assurance of its availability is only possible once that threshold has been defined and judged acceptable to the Commission.

There are a myriad of other questions which suggest themselves to those who consider this matter carefully. Some of these will be provided later in this document. But the preceding discussion should make it clear that there is a pressing need for the Commission to consider these and other issues identified below and to weigh the trade-offs which appear to be required.

The Task Force Report, while an admirable exploration of the philosophical imperatives of instituting such a compensation system, was able only to develop the conceptual framework and rationale for such a program. The Task Force was limited in its charge, however, so that the conceptual framework is insufficiently detailed and in some respects insufficiently cognizant of the practical difficulties facing research institutions in acquiring insurance coverage for this purpose to permit implementation without further refinement. We do not believe that the NPRM procedure is best calculated to meet this need.

In our letter of June 25, 1979 to the then Secretary of DHEW, Joseph Califano, we suggested that the matter be referred to the Ethics Advisory Board or a similar body such as the President's Commission for the Study of Ethical Problems as an intermediate step, prior to the issuance of the NPRM. This step would be calculated to resolve the issues in a fashion which takes cognizance of the dynamics of the private insurance system, the needs of academic institutions and the nature of the clinical research enterprise. The Task Force, constituted as it was solely of federal officials, was structurally incapable of performing such a function. In our view the President's Commission on Ethics with its broader representation, and with the capability of commissioning studies of, for example, the actuarial and economic implications of various configurations of such a system, is the appropriate forum for the deliberation of such issues. The policy questions mentioned above should be resolved by the Commis-
sion after consideration of the ethical issues involved. Wellconsidered recommendations which take into account the effect of the system on each of the companies, institutions and investigators which would be expected to participate as well as the desirability of providing equitable compensation to injured subjects, would provide a sound basis for proceeding with the regulatory process.

Additional Questions

(1) The Task Force Report suggests compensation for “social and psychological” injury as well as physical injury. Is it possible to define such types of injury sufficiently well to describe an insurable risk? We have serious reservations on this issue.

(2) The Task Force Report proposed to limit compensation only to injured subjects or their survivors. In addition, it is possible to conceive of injury to progeny resulting from interventions on their parents (while not involving research, the example of female offspring of mothers ingesting diethyl-stilbestrol (DES) comes to mind.) Should compensation be extended to progeny of research subjects?

(3) The draft NPRM requires minimum wage loss compensation at the rate of GS-5. There is concern with a minimum benefit which is equal to or greater than what the subject is or would have been receiving. Available information suggests that this level exceeds the average weekly wage in twenty states. Is this level set too high?

(4) The program should be structured to compensate individuals while providing inducements to enter the work force. There is a need for detailed study to spell out the exact boundaries of required compensation for individuals who are not employed at the time of the experiment. Should not the proposal cover a range of different types of non-employment including retired persons, prisoners, college students, persons unemployed because of illness and those simply unemployed?

(5) Presumably, there should be an element of consistency of coverage across research projects, within institutions and between institutions across the country. Is there not a conflict between this principle and the Task Force proposal that the mandated assurance of compensation apply only to HEW-sponsored research? It is hard to justify the availability of compensation to one subject and its non-availability to his neighbor in the next bed participating in research sponsored by another agency.

(6) What provision will be made for institutions unable to purchase insurance coverage? This eventuality is not difficult to foresee in view of the variety of institutional and insurance company characteristics. Is a residual market mechanism advisable? Feasible? Are there other alternatives?
(7) Is it equitable or desirable that subjects participating in Public Health Service-conducted research, and/or other government-conducted research be left without a compensation mechanism? If not, should not such coverage be instituted at the same time as sponsored research coverage is instituted?

(8) Can either a residual market mechanism be developed or coverage for government-conducted research be instituted without federal legislation?

(9) The Task Force Report suggests that the purchase of insurance coverage or self-insurance is an allowable cost of research projects. What are the proposed mechanisms of reporting and recovering such costs? Should it be a direct cost, an indirect cost, or some new kind of separately identified cost center? These determinations may require the resolution of prior questions.

(10) Is it possible to recover contributions to a self-insurance fund in the absence of more precise definitions of an acceptable program, allowable costs in terms of meeting audit standards, etc.?

(11) Is it desirable to require that an injured subject, at the time of making a claim, waive any rights he or she might have to pursue compensation through the tort (negligence) system? Is such a requirement consistent with the ethical objectives of the program? Is such a requirement consistent with the laws governing the tort system (state law, court decisions, etc.)?

(12) Would it be feasible or desirable to institute such a compensation system on a pilot basis, limited by time, by number of institutions or geography, to permit the gathering of relevant data on the basis of real experience rather than proceeding on the basis of untested assumptions? Analysis of experience of this sort would enhance the confidence of insurance companies and perhaps stimulate their participation. Similarly, several apparently workable configurations might be tried and the strengths and weaknesses of each might be discovered.

(13) Since the government sponsors the substantial proportion of human subjects research and will bear a similar fraction of the cost burden of it, would it be less expensive in the long run and administratively less burdensome for the government to provide directly the compensation to injured subjects?

Conclusion

In summary, the rather extensive examination of this subject over the past year leads us to conclude that:

- insurance may be available (there are, of course, no firm commitments that it will be) but only on terms substantially more limited than contemplated by the Secretary’s Task Force;
• before there can be any assurance that insurance will be available, there must be a resolution of current unresolved questions;
• further consideration to a variety of additional questions ought to be given to assure the sound development of the program;
• the nature of the threshold decisions is such that the rule-making process does not appear to be an appropriate mechanism;
• the Commission for the Study of Ethical Problems should begin at once to review this problem, should familiarize itself with the views of thoughtful researchers and research administrators and should make some of the ethical choices which will allow a workable scheme to be developed in a reasonably prompt fashion.

We appreciate the seriousness of this matter and have devoted substantial energy to it. The group which has studied the problem intensively included clinical researchers, research administrators, representatives of the insurance industry and staff members of the AAMC and other higher education associations. We trust that our observations will be viewed as a constructive and valued contribution to the efforts of the Commission. We request that you give serious consideration to our recommendations and that you call on a representative of our Association to address the Commission on May 17, 1930.

Thank you for your attention to our request.

12. Bennett Stark
Coordinator
National Committee for Victims of Human Research
January 17, 1930

I am a former research subject and a victim of research abuse. Nearly twenty-one years ago I participated in a study of college freshman who dropped out of school. I had an anxiety neurosis condition. I was a student at Columbia College. My parents were refugees from Nazi Germany; my father had died when I was 15 years of age. We were very poor, and my mother was elderly and had recently recovered from a cancer operation when I was in my freshman year. When I felt I could not handle anxiety, I admitted myself in the hospital across the street from my dormitory. A month later I volunteered in a research program held at the National Institute of Mental Health.

There were severe adverse effects. They arose quite simply because the research director was indifferent to the adjustment of subjects to his research design. In any other environment the experience would have been criminal. Indeed the most damaging part of my experience was its residual, long-term effect and
this was a consequence of my inability to deal directly and public-
licy with what is a truly insidious experience. Had the ego
disintegration I suffered been perpetrated by criminals, I would
have had a considerably better chance of coming to grips with the
trauma. That of course was not the case; it was psychiatrists
working for the United States Public Health Service.

It has been eleven years now during which I have dealt
directly with my experience. At virtually every juncture in my
contacts with the federal government, I have met with frus-
tration. I have also met with outright misrepresentation, evasion
and obfuscation. I had to enlist the services of an attorney to get
my research records and indeed we had to threaten a law suit
before they were received. Once we received them it was under-
standable why NIMH was reluctant because the damaging ef-
facts were duly noted by one psychologist.

In April 1974, former Secretary of HEW Weinberger wrote
that my case "raised vital questions about the proper conduct of
human research."

During the summer of 1975, Karen LeBacqz, after reviewing
research materials wrote that they "presented a compelling case
for investigation." No investigation ever took place.

Aside from establishing the National Committee for Victims
of Human Research and engaging in advocacy work on behalf of
individuals who claim they are victims and lobbying efforts, I
have served as a patient's rights advocate on a number of advis-
sory boards for the State of Wisconsin, the Regional Health Plann-
ing Council and Wisconsin's Center for Public Representation.

I can not think of a clearer and more compelling instance of
federal government moral irresponsibility than its policy toward
its research victims—past and present. There are of course
numerous instances of injustice in the United States. Rarely,
however, do they arise as a direct consequence of federal
government programs. Ethically this is a very simple matter about
which there can be no compromise: the government has the
moral responsibility to assist its research victims—past, present
and future—in every way that is fair and possible.

Indeed human research subjects deserve our society's appre-
ciation and respect; their involvement are a vital component
in the growth of knowledge. It is a shocking and appalling state-
ment about our society that nothing is done to compensate or
assist the nation's research victims. They are left to fend for
themselves against a research bureaucracy whose first and only
concern it is to undermine the credibility of the research subject
and the content of his charge.

The nation prides itself on being a moral example to the rest
of the world. The government's policy towards its research vic-
tims raise forceful questions about the nature of our politicians
and indirectly the nature of our society. We live in a fragmented,
heterogeneous society, in which moral issues provide little or no rewards to politicians committed to them. Obvious ethical imperatives are easily discarded. Thus there is no mention of research victims and assistance to them in Public Law 93-348 which established the National Commission for the Protection of Research Subjects in 1974. Nor is assistance mentioned in Public Law 95-622 which established the Presidential Commission. HEW’s Perry Committee did acknowledge the justification for compensation of research victims. What is extraordinary (from the ethical perspective) is that the application of the principle of compensation for injured research subjects does not extend to the vast majority of research victims and indeed those who were hurt the most—pre-1974 research victims.

The Unitarian Universalist Service Committee recently adopted the following resolution. It should be of interest to you:

"Whereas Congress made clear its intent that human research be founded upon "basic ethical principles" (Public Law 93-348 which established the National Commission for the Protection of Human Subjects), the federal government should accept responsibility for the harm done to human subjects in its own research programs. Such responsibility should entail: 1) just compensation and 2) health care for research related injuries."

March 13, 1981

Given the economic and political climate, it is clear that the most compelling human and ethical problems in human research may not be appropriately dealt with at this time. Nonetheless, I note with great disappointment, upon reading the Commission Minutes of January 9-10, that these problems are not even acknowledged.

I refer to the problem of injured subjects of fraudulent research. The full extent of human research injury is not known. The existing studies on the incidence of research injury are based upon voluntary participation and thus are methodologically flawed. Indeed, 13.4 per cent of those researchers contacted in the original sample in the University of Michigan’s Ann Arbor Study chose not to respond. Little can be inferred about the incidence of research injury from existing studies.

The Senate Hearings on Clinical Pharmaceutical Research in October, 1979, indicated a wide range of serious abuses which included: (1) falsified consent forms; (2) falsified or misleading evidence of IRB approval and; (3) flagrant disregard of FDA rules. There have also been recent disclosures about fraudulent research among prominent physicians at the UCLA Medical School. For every case of fraudulent research that the public learns about, I would conjecture that there are ten cases about which the public does not become aware. The evidence that exists suggests unambiguously that fraudulent research is not a trivial problem.
There are many reasons why litigation by injured subjects of fraudulent research is inappropriate. Many of the individuals in this population will be ill. Many will not be litigious, assuming that is, they suspect they were in some way victimized. The same traits that made them vulnerable as research subjects will render them unlikely to litigate their cases. Awareness of the possibility of fraudulent research may take years to develop. At that point it may be exceedingly difficult to reconstruct the clinical situation and to determine responsibility for acts of commission and omission. Typically, physicians are extraordinarily disinclined to criticize the professional performance of colleagues when such is warranted. After several years have passed, such cooperation is virtually impossible. In other instance, technicalities will bar litigation.

I also note with great disappointment that no mention in the January Minutes is made of retrospective research injury. All too often these individuals or their surviving family members learn of research participation by accident, after someone else has filed under the Freedom for Information Act. To date not only is there no compensation for victims of retrospective federal research in which no informed consent was given, no mandate exists requiring the federal government to notify the individual of his/her research involvement. Failure to acknowledge these two compelling human and ethical problems in human research will render a travesty of the clear ethical mandate which established the President's Commission. The President's Commission will have the dubious distinction of being more widely known for those ethical problems it carefully overlooked than those with which it dealt.

June 23, 1980

In late February I was informed that the Commission will not involve itself in matters dealing with existing human research victims. This was later confirmed by Gilbert Omenn of the Office of Science and Technology Policy of the White House. Staff Director, Alexander Capron, corroborated this in June 3rd correspondence.

It is difficult enough to explain how, in a civilized society: (1) a government human research program would bring injury and death to its citizens and; (2) that government would, dishonorably, eschew all responsibility for those it had harmed. However, it defies explanation that an advisory commission with a clear ethical mandate to deal with problems in human research would, operating in good faith, be indifferent to the plight of existing government research victims.

Nowhere in the President's Commission mandate or in the National Commission's mandate or anywhere else in the federal code is a policy recommendation proscribed which would provide compensation for existing research victims. The prescriptive nature of Congressional intent is explicitly stated in Public Law
93-348. Section 202, 1A: the National Commission was mandated to identify the "basic ethical principles" upon which the federal human research program should rest. As is evident from the title of the President's Commission and the ethical component of its responsibilities, the prescriptive thrust—central to the mandate of the National Commission—has not been modified. The President's Commission may investigate any issue "which is consistent with the purposes of [its] title". There can be no more compelling "ethical problem in medicine and biomedical and behavioral research" than the government's indifference to its human research victims.

To argue that the President's Commission has no advisory jurisdiction on behalf of existing victims is to base one's views upon political considerations. The only view that is consonant with the ethical nature of Congressional intent is that all government research victims be appropriately assisted by the government. A policy which is purported to be ethical cannot be partitioned to serve the needs of expediency and still maintain its ethical content.

It is obvious that the present political climate will not be favorable to a policy recommendation which would involve expenditures. However, political concerns should have no bearing on the ethical deliberations of the Commission. It is ethics that should determine the parameters of government responsibility, not politics. Where constraints exist, ethical considerations, not political considerations should decide priorities.

The hypocritical nature of the Administration's declarations on human rights becomes apparent when one takes into account the Chairperson's position with regard to prior research victimization. It is obvious that the Administration's domestic performance vis-a-vis human rights hardly measures up to its own standards. The government's relegation of its prior human research program to a moral limbo in which basic ethical canons have no relevance constitutes a perfidy wrought upon its citizenry which may be without precedent in United States history.
Individuals Who Presented Oral Testimony Only

Terrence F. Ackerman, Ph.D. and Jerry Lewis, M.D.,
On behalf of the Association of American Cancer Institutes
January 9, 1981

Edward Holmes, M.D., and Thomas Morgan, M.D.
On behalf of the Association of American Medical Colleges
(AAMC)
September 15, 1980

Barbara F. Katz, J.D.
Boston, Massachusetts
January 9, 1981

Charles R. McCarthy, Ph.D.
Director
Office for Protection from Research Risks
National Institutes of Health
May 16, 1980 and January 9, 1981

Mark Novitch, M.D.
Acting Deputy Commissioner
Food and Drug Administration
May 16, 1980

Philip S. Schein, M.D.
On behalf of the American Society of Clinical Oncology
January 9, 1981

Phyllis Wetherill
On behalf of the DES Registry
Washington, D.C.
September 15, 1980 and January 9, 1981

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