REPORT ON CHARGE III

TO: THE ASSISTANT SECRETARY FOR HEALTH

FROM: TUSKEGEE SYPHILIS STUDY AD HOC ADVISORY PANEL

TOPIC: FINAL REPORT ON CHARGE III

I. INTRODUCTION

In his third charge to the Tuskegee Syphilis Study Ad Hoc Advisory Panel, Dr. Merlin K. DuVal, the HEW Assistant Secretary for Health and Scientific Affairs, has asked us to determine

> whether existing policies to protect the rights of patients participating in health research conducted or supported by the Department of Health, Education, and Welfare are adequate and effective and to recommend improvements in these policies, if needed.

Our response to this charge, embodied in this report, should not be viewed simply as a reaction to a single ethically objectionable research project. For the Tuskegee Syphilis Study, despite its widespread publicity was not an isolated phenomenon. We believe that the revelations from Macon County merely brought to the surface once again the unresolved problems which have long plagued medical research activities. Indeed, we hasten to add that although we refer in this report almost exclusively to physicians and to biomedical investigations, the issues we explore also arise in the context of non-medical investigations with human beings, conducted by psychologists, sociologists, educators, lawyers and others. The scope of the DHEW Policy on Protection of Human Subjects, broadened in 1971 to encompass such research, attests to the increasing significance of non-medical investigations with human beings.

Our initial determination that the protection of human research subjects is a current and widespread problem should not be surprising, especially in light of the recent Congressional hearings and bills focusing on the regulation of experimentation. In the past decade the press has publicized and debated a number of experiments which raised ethical questions: for example, the injection of cancer cells into aged patients at the Jewish Chronic Disease Hospital in Brooklyn, the deliberate infection of mentally retarded children with hepatitis at Willowbrook, the development of heart transplantation techniques, the enormous amount of drug research conducted in American prisons, the whole-body irradiation treatment of cancer patients at the University of Cincinnati, the advent and spread of "psychosurgery," and the Tuskegee Syphilis Study itself.

With so many dramatic projects coming to the attention of the general public, more must lie beneath the surface. Evidence for this too has been forthcoming. In 1966, Dr. Henry K. Beecher, the eminent Dorr Professor of Research in Anesthesia at the Harvard Medical School, charged in the prestigious New England Journal of Medicine that "many of the patients (used in experiments which Dr. Beecher investigated and reported) never had the risk satisfactorily explained to them, and. . .further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered as the direct result. . ."[1] Dr. Beecher concluded that "unethical or questionably ethical procedures are not uncommon."[2] Quite recently this charge has been corroborated by the sociologist Bernard Barber and his associates, who interviewed biomedical researchers about their own research practices.[3] Despite the expected tendency of researchers to minimize ethical problems in their own work, Barber *et al.* were able to conclude that "while the large majority of our samples of biomedical researchers seems to hold and live up to high ethical standards, a significant minority may not."[4]

The problem of ethical experimentation is the product of the unresolved conflict between two strongly held values: the dignity and integrity of the individual, and the freedom of scientific inquiry. Professionals of many disciplines, and researchers especially, exercise unexamined discretion to intervene in the lives of their subjects for the sake of scientific progress. Although exposure to needless harm and neglect of the duty to obtain the subject's consent have generally been frowned upon in theory, the infliction of unnecessary harm and infringements on informed consent are frequently accepted, in practice, as the price to be paid for the advancement of knowledge. How have investigators come to claim this sweeping prerogative? If the answer to this question is that "society" has authorized professionals to choose between scientific progress and

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1. Beecher, "Ethics and Clinical Research," 274 New Eng. J. Med. 1354 (1966)
2. *Ibid.*, p. 1355.
3. Barber, Lally, Makarushka, and Sullivan, *Research on Human Subjects: Problems of Social Control in Medical Experimentation* (Russell Sage Foundation 1973) (hereinafter, *Barber et al.)*
4. *Barber et al., supra,* footnote 3, at 52.

individual human dignity and welfare, should not "society" retain some control over the research enterprise? We agree with philosopher Hans Jonas that

> a slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.[5]

We have, as will be seen, made far-reaching recommendations for change. We do not propose these changes lightly. But throughout, in accordance with our mandate, our concern has not been just to define the ethical issues, but also to examine the structures and policies thus far devised to deal with those issues. In urging greater societal involvement in the research enterprise, we believe that the goal of scientific progress can be harmonized with the need to assure the protection of human subjects.

5. Jonas, "Philosophical Reflections on Experimenting with Human Subjects," 98 *Daedalus* 219, 245 (1969).

II. SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

A. Evaluation of Current DHEW Policies for the Protection of Human Research Subjects

1. No uniform Departmental policy for the protection of research subjects exists. Instead one policy governs "extramural" research – research supported by DHEW grants or contracts to institutions outside the Federal Government and conducted by private researchers – and another policy governs "intramural" research – research conducted by personnel of the Public Health Service. Furthermore. Food and Drug Administration (FDA) regulations promulgated to protect subjects in drug research, whether or not supported by DHEW or conducted by the PHS, incorporate variations of their own. The lack of uniformity in DHEW policies creates confusion, and denies some subjects the protection they deserve.

Moving to the next higher level, no uniform Federal policies exist for the protection of subjects in Government-sponsored research. Other agencies wholly separate from DHEW – most notably, the Department of Defense – support or conduct human research. DHEW policies do not govern such research. Here too, the Federal Government's failure to develop a uniform policy has been detrimental to the welfare of research subjects.

2. Under current DHEW policies for the protection of research subjects, regulation of research practices is largely left to the biomedical professions. Since the conduct of human experimentation raises important issues of social policy, greater participation in decision-making by representatives of other professions and of the general public is required.

3. The present reliance by DHEW on the institutional review committee as the primary mechanism for the protection of research subjects was an important advance in the continuing effort to guarantee ethical experimentation. Prior peer review of research protocols is a requirement which should be retained.

4. The existing review committee system suffers from basic defects which seriously undermine the accomplishment of the task assigned to the committees:

a. The governing standards promulgated by DHEW which are intended to guide review committee decisions in specific cases are vague and overly general.

b. No provisions are made for the dissemination or publication of review committee decisions. Their low level of visibility hampers efforts to evaluate and learn from committee attempts to resolve the complex problems of human research.

c. Although the informed consent of the research subject is one of the most important requirements of research ethics, DHEW policies for obtaining consent are poorly drafted and contain critical loopholes. As a result, one crucial task of institutional review committees – the implementation of the informed consent requirement – is commonly performed inadequately. In particular, consent is far too often obtained in form alone and not in substance.

d. DHEW policies do not give sufficient attention to the protection of such special research subjects as children, prisoners and the mentally incompetent. The use of these subjects in human experimentation presents grave dangers of abuse.

e. The obligation of institutional review committees to conduct continuing review of research projects after their initial approval is undefined and as a consequence often neglected.

f. Inefficient utilization of institutional review committees contributes to their ineffectiveness. Committees are overburdened with a variety of separate functions, and could operate best if their tasks were narrowly defined to encompass mainly the implementation of research policies adequately formulated by others.

g. Effective procedures for enforcing DHEW policies, when those policies are disregarded, have not been devised.

5. No policy for the compensation of research subjects harmed as a consequence of their participation in research has been formulated, despite the fact that no matter how careful investigators may be, unavoidable injury to a few is the price society must pay for the privilege of engaging in research which ultimately benefits the many. Remitting injured subjects to the uncertainties of the law court is not a solution.

B. Policy Recommendations

1. Congress should establish a permanent body with the authority to regulate *at least* all Federally supported research involving human subjects, whether it is conducted in intramural or extramural settings, or sponsored by DHEW or other government agencies, such as the Department of Defense. Ideally, the authority of this body should extend to all research activities, even those not Federally supported. But such a proposal may raise major jurisdictional problems. This body could be called the National Human Investigation Board. The Board should be independent of DHEW, for we do not

believe that the agency which both conducts a great deal of research itself and supports much of the research that is carried on elsewhere is a position to carry out dispassionately the functions we have in mind. The members of the Board should be appointed from diverse professional and scientific disciplines, and should include representatives from the public at large.

2. The primary responsibility of the National Human Investigation Board should be to formulate research policies, in much greater detail and with much more clarity than is presently the case. The Board must promulgate detailed procedures to govern the implementation of its policies by institutional review committees. It must also promulgate procedures for the review of research decisions and their consequences. In particular, this Board should establish procedures for the publication of important institutional committee and Board decisions. Publication of such decisions would permit their intensive study both inside and outside the medical profession and would be a first step toward the case-by-case development of policies governing human experimentation. We regard such a development, analogous to the experience of the common law, as the best hope for ultimately providing workable standards for the regulation of the human experimentation process.

3. The National Human Investigation Board should develop appeals procedures for the adjudication of disagreements between investigators and the institutional review committees.

4. The National Human Investigation Board should also develop a "no fault" clinical research insurance plan to assure compensation for subjects harmed as a result of their participation in research. Institutions which sponsor Federally supported research activities should be required to participate in such a plan.

5. With the establishment of adequate policy formulation and review mechanisms, the structure and functions of the institutional review committees should be altered to enhance the effectiveness of prior review. In place of the amorphous institutional review committee as it now exists, we propose the creation of an Institutional Human Investigation Committee (IHIC) with two distinct subcommittees. The IHIC should be the direct link between the institution and the National Human Investigation Board, and should establish local regulations consistent with national policies. The IHIC should also assume an educational role in its institutions, informing participants in the research enterprise of their rights and obligations. The implementation of research policies should be left to the two subcommittees of the IHIC:

a. A Protocol Review Group (PRG) should be responsible for the prior review of research protocols. The PRG should be composed mainly of competent biomedical professionals.

b. A Subject Advisory Group (SAG) should be responsible for aiding subjects in their decision-making whenever they request its services. Subject must be made aware of the existence of the SAG. The primary concern of the SAG should be with procedures for obtaining consent, and with the quality of consents obtained. The SAG should be composed of both professionals and laymen.

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III. DEVELOPMENT OF CURRENT DHEW POLICIES

A. Historical Background

Experimentation with human beings is not a modern phenomenon; it dates back to the beginning of recorded history. However, until the advent of scientific medicine, "research" was largely conducted unsystematically in the context of clinical practice which benefited, harmed or did nothing to untold patients. Indeed, harmful consequences most often accrued to countless patients who were given treatments whose value had not been established by carefully controlled clinical investigations.[6] Since the individuals involved in "research" were generally also considered potential recipients of the knowledge gained, few questions were raised about the propriety of these interventions by either the medical or legal profession. As far as the medical profession was concerned, the systematic use of human beings for research purposes, a trend which began in the late nineteenth century and has accelerated ever since, did not lead until relatively recently to a sustained exploration of the need to safeguard research subjects. A notable exception was Claude Bernard who in 1865 published his influential *An Introduction to the Study of Experimental Medicine,*[7] in which he not only demonstrated the need for experimentation on human subjects but also began to formulate rules of ethical conduct.

Similarly the law has had little to say about the rights of human subjects in the research enterprise. Indeed prior to the nineteen-sixties, no specific federal or state statutes regulated research institutions or investigators in their use of human subjects for experimental purposes. Though beginning with the English case of *Slater v. Baker and Stapleton*[8] in 1767 and the American case of *Carpenter v. Blake*[9] in 1871, courts were from time to time confronted with the claim of experimentation in malpractice actions, the resulting opinions evinced concern about "experimentation" but did not provide any meaningful legal guidelines for investigators to follow. Perhaps the fact situations in these cases, which often raised other important issues besides experimentation, precluded judges from speaking out more clearly on the legal limits to human research. Through the first third of the twentieth century, the generally accepted legal rule seemed to be that a physician experimented "at his peril" if his patients were harmed thereby.[10] Eventually, the distinction between rash human experimentation and careful, scientific and ethical experimental practice was acknowledged by the courts. In 1935, the Supreme Court of Michigan stated in a malpractice case:

> We recognize the fact that if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on; but such experiments must be done with the knowledge and consent of the patient or those responsible for him and must not vary too radically from the accepted method of procedure.[11]

Although this dictum was a broad generalization, made in a therapeutic context, and was not directed at nontherapeutic investigations, it signalled the ascendency of a more balanced judicial attitude toward medical research involving human beings.

This posture was sorely tested by the revelations of the horrifying atrocities perpetrated under the Nazis by German physicians and scientists in the name of clinical research.[12] The disclosures at Nuremberg disturbed the medical community, and many physicians and research scientists called for worldwide acceptance of ethical standards to assure the protection of subjects in biomedical research. However, the impact of their concern was blunted by the cruelty of the concentration camp experiments which obscured the fundamental fact that similar problems of research ethics, though not of the same magnitude, had characterized the research enterprise from its beginnings. Nonetheless, the trial of the Nazi physicians led the Military Tribunal to set forth ten basic principles, the so-called Nuremberg Code,[13] which must be observed in human experimentation "in order to satisfy moral, ethical, and legal concepts." The following principles illustrate the nature of the Code:

1. The voluntary consent of the human subject is absolutely essential. . . .
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods of study, and not random and unnecessary experiments in nature.

* * *

6. The degree of risk to be taken should never

6. See, e.g., Modell, "Let Each New Patient Be a Complete Experience," 174 J.A.M.A. 1717 (1960).

7. Bernard, *An Introduction to the Study of Experimental Medicine,* H. C. Greene (Transl.) (Macmillan, 1927).

8. 95 Eng. Rep. 860 (1767).

9. 60 Barb. 488 (N.Y., 1871).

10. See Curran, "Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," 98 Daedalus 542, 543 (1969).

11. Fortner v. Koch, 272 Mich. 273, 282; 261 N.W. 762, 765 (1935).

12. See *Trials of War Criminals Before the Nuremberg Military Tribunals. Volumes I and II, The Medical Case.* Washington, D.C.: U.S. Government Printing Office (1948). For excerpts which indicate the nature of the offenses and the resulting judgments, see Katz, *Experimentation with Human Beings,* pp. 292-306 (Russell Sage Foundation, 1972) (Hereinafter *Katz).*

13. *Katz, supra* footnote 12, at 305.

exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

The widely felt need to supplement and modify the provisions of the Nuremberg Code led to the proliferation of other "improved" codes of research ethics. The World Medical Association's Helsinki Declaration (1964),[14] the American Medical Association's Ethical Guidelines for Clinical Investigation (1966)[15] and the draft code of the American Psychological Association (1972)[16] are three which have received the most attention.

The promulgation of such documents helped to focus attention on the ethical problems inherent in research activities involving human subjects. However, as the number of documents increased their limitation become more evident to concerned observers. As one of us has elsewhere remarked:

> The proliferation of such codes testifies to the difficulty of promulgating a set of rules which do not immediately raise more questions than they answer. By necessity these codes have to be succinctly worded and, being devoid of commentary, their meaning is subject to a variety of interpretations. Moreover, since they generally aspire to ideal practices, they invite judicious and injudicious neglect. Consequently, as long as they remain unelaborated tablets of exhortation, codes will at best have limited usefulness in guiding the daily behavior of investigators.[17]

Furthermore, discrepancies between codes have helped to sow confusion. Discussing the Helsinki Declaration and the A.M.A. Guidelines, Professors Katz and Capron observed:

> The significant discrepancies between these two documents highlight the need for mechanisms which would permit their reconciliation... Unlike the Helsinki Declaration, the AMA guidelines propose that "(m)inors or mentally incompetent subjects may be used as subjects only if (t)the nature of the investigation is such that mentally competent adults would not be competent subjects." On the other hand, the Declaration of Helsinki states, and the AMA guidelines do not, that "(a)t any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued." No explanation is provided for the differences nor is any mechanism available to guide physician-investigators in adopting or rejecting part or all of either document, based on its disagreement with the other or for any additional reasons.[18]

In retrospect, the promulgation of so many varying codes of ethics can be viewed as a tacit recognition within the professions that self-regulation by investigators could not be relied on to control research practices. When it was also realized that the codes themselves had serious shortcomings, new and quite different proposals for ordering the research process began to emerge. Procedures were gradually developed to apply the general principles contained in codes of research ethics in the formal evaluation of individual research projects by institutional review committees.

The National Institutes of Health (NIH) first developed such procedures in order to regulate clinical research performed at its Clinical Center in Bethesda, Maryland. Since 1953, human research has not been conducted there without prior approval of a review committee responsible for the protection of subjects.[19] In 1966, Surgeon General William H. Stewart extended the requirement of prior review by "a committee of (the investigator's) institutional associates" to all "extramural" research supported by United States Public Health Service (PHS) grants and awards.[20] This review was to

> assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation.[21]

Prior committee review was also instituted, in 1967, for all "intramural" research programs of the Public Health Service.[22] The Tuskegee Syphilis Study, conducted by PHS investigators, was an intramural activity.

14. 271 N. Eng. J. Med. 473 (1964).

15. American Medical Association, *Opinions and Reports of the Judicial Council*, pp. 9-11 (Chicago, 1969).

16. American Psychological Association, *Ethical Principles in the Conduct of Research with Human Participants* (Draft Document, 1972).

17. Katz, "The Education of the Physician-Investigator," 98 *Daedalus* 480, 482-3 (1969).

18. Katz and Capron, *Social Factors Affecting the Modern Treatment of Catastrophic Diseases* (Unpublished Manuscript, 1973) (hereinafter, *Katz and Capron*).

19. Sessoms, "Guiding Principles in Medical Research Involving Humans, National Institutes of Health," 32 *Hospitals, Journal of American Hospital Association* 44 (1958).

20. Memorandum of Surgeon General William H. Stewart to the Heads of Institutions Conducting Research with Public Health Grants, (February 8, 1966).

21. *Ibid.*

22. DHEW – Public Health Service, *Protection of the Individual as a Research Subject* – Intramural Programs (May 1, 1969) (hereinafter *Intramural Guidelines*).

In 1971, the Department of Health, Education, and Welfare formulated its policy for the protection of human subjects[23] which superseded the Public Health Service extramural program guidelines. Institutional committee review was retained as the central feature of the new DHEW policy. The DHEW regulations apply to all research supported by Departmental grants or contracts, regardless of whether the research is medical in nature. However, the new regulations do not apply to intramural PHS activities, which are still governed by separate and sometimes divergent PHS guidelines. Also in 1971, the Food and Drug Administration promulgated additional regulations,[24] patterned on the DHEW framework, to govern the testing of "investigational new drugs." And recently, in response to the Tuskegee Syphilis Study revelations, Senator Jacob Javits introduced a bill which would enact most of the current DHEW requirements into law.[25] Senator Hubert Humphrey also responding to the Tuskegee Study, introduced another bill, quite different in conception.[26] It would create within the executive branch an independent board to establish guidelines for human experimentation, to review research practices and to enjoin the conduct of certain investigations.

Due to the Federal Government's prominent role in funding biomedical research, the PHS-DHEW regulations have had a noticeable impact on the conduct of human research in this country. Over 700 American research institutions have established review committees in order to satisfy DHEW or PHS requirements.[27] Although these committees are required to review only Federally-funded research, they often have extended their review to all research on human subjects conducted at their institutions.[28]

B. Description of DHEW Policy[29]

At present DHEW policies vest primary responsibility for the protection of research subjects in institutional review committees. These committees are charged with the initial review of all project proposals and are also expected to subject research activities to "continuing review." Once a committee has approved a research protocol, its decision is reviewed again by the DHEW study section which considers the protocol for funding. When either group disapproves a protocol, that decision cannot be appealed to the Department, and the protocol cannot be Federally funded. In contrast to the DHEW requirements, PHS intramural policy does not require continuing review. Instead, the burden is on the investigator to bring "significant proposed changes in protocol and emergent problems of investigation. . .to the attention of the review group involved."[30] Nor does PHS intramural policy specify distinct stages of protocol review.

DHEW requires institutional committees to review all aspects of "any activity" which might expose a subject to the possibility of harm if the activity "goes beyond the application of those established and accepted methods necessary to meet his needs."[31] Recognizing that this jurisdictional standard leaves much to the discretion of committees and investigators the Department concedes that "(a)cceptance is a matter of professional response, and determination as to when a method passes from the experimental stage and becomes 'established and accepted' is a matter of judgment."[32]

Before the committee can approve an activity under review, it must "determine that the rights and welfare of the subjects involved are adequately protected, that the risks to an individual are outweighed by the potential benefits to him or by the importance of the knowledge to be gained, and that informed consent is to be obtained by methods that are adequate and appropriate."[33] Like the jurisdictional standard, these review standards are phrased in general terms, although the "basic elements" of "informed consent" are set forth in greater detail.[34] DHEW policy also requires each institution to provide written assurance that it will abide by DHEW policy. The assurance must include "a statement of compliance with DHEW requirements for initial and continuing committee review of the supported activities; a set of implementing guidelines, including identification of the committee, and a description of its review procedures."[35] As part of the "implementing guidelines," each institution is asked to adopt a "statement of principles that will assist the institution in the discharge

23. DHEW Grants Administration Manual Chapter 1-40 (1971) (hereinafter *Grants Administration Manual*). The Department publishes *The Institutional Guide to DHEW Policy on Protection of Human Subjects* (1971) (hereinafter *Institutional Guide*) to help institutions sponsoring research to implement DHEW policy.

24. 36 Fed. Reg. 5037-38 (1971).

25. S. 3935, 92d Cong., 2d Sess. (1972).

26. S. 3951, 92d Cong., 2d Sess. (1972).

27. For a description of the spread of institutional review committees following the promulgation of the PHS guidelines, see *Barber et al., supra*, footnote 3, at 145-148.

28. Barber *et al.* estimate that 85% of the institutional review committees they surveyed review "all clinical research" conducted at their institutions, regardless of funding. *Barber et al., supra*, footnote 3, at 149.

29. This description is based on the *Intramural Guidelines, supra*, footnote 23, and the *Institutional Guide, supra*, footnote 23. Hereinafter, the policy of the Manual and the Guide will be referred to as "DHEW" policy, while the policy of the Intramural Guidelines will be referred to as "PHS intramural" policy.

30. *Intramural Guidelines, supra*, footnote 22, at 5.

31. *Grants Administration Manual, supra*, footnote 23, § 1-40-10.

32. *Institutional Guide, supra*, footnote 23, at 3.

33. *Grants Administration Manual, supra*, footnote 23, § 1-40-20(A). The PHS *Intramural Guidelines, supra*, footnote 22, contain essentially equivalent standards for review, at 4-5.

34. See *infra.*, pp. 31-32.

35. *Grants Administration Manual, supra*, footnote 23, § 1-40-40 (A).

36. *Grants Administration Manual, supra*, footnote 23, § 1-40-40 (C) (2) (a).

37. *Ibid.* See also *Institutional Guide, supra*, footnote 23, at 5, footnote 2, and at 23.

of its responsibilities for protecting the rights and welfare of subjects."[36] These statements are typically derived from existing codes of ethics not much more explicit that the DHEW review standards themselves.[37]

Unlike DHEW policy, the intramural guidelines of the PHS make specific, albeit limited, reference to "(s)tudies involving children, the mentally ill or the mentally defective."[38] Such studies "shall be carried out only when there is no significant risk of physical or mental harm to the subject or when direct benefit to the subject is anticipated."[39] The intramural guidelines also explicitly provide that "(s)tudies of individuals with limited civil freedom shall also be subject to group consideration and approval."[40] Although the references to minors, incompetents, and prisoners do not impose additional substantive restrictions on research, they may alert review committees and investigators to the special problems presented by research with such subjects.[41]

Since institutional review committees are entrusted with such difficult decision-making responsibilities, their composition is a matter of Departmental concern:

> The committee must be composed of sufficient members with varying backgrounds to assure complete and adequate review of projects and activities commonly conducted by the institution. The committee's membership, maturity, experience, and expertise should be such as to justify respect for its advice and counsel. No member of an institutional committee shall be involved in either the initial or continuing review of an activity in which he has a professional responsibility, except to provide information requested by the committee. In addition to possessing the professional competence to review specific activities, the committee should be able to determine acceptability of the proposal in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The committee may therefore need to include persons whose primary concerns lie in these areas rather than in the conduct of research, development, and service programs of the types supported by the DHEW.[42]

Beyond this, the Department does not specify any particular size or membership requirements, believing instead that disparity in institutional situations demands flexibility. For the same reason the Department does not provide any directions for the conduct of initial or continuing review. Instead, as already noted, institutions are required to submit for Departmental approval a description of the procedures their committees will follow to implement review.

When DHEW funding is sought, a research proposal approved by an institutional committee is reviewed again within the Department.[43] A study section, composed of scientists not connected with the proposal or its sponsoring institution, examines the proposal and transmits its recommendation to the particular National Advisory Council authorized to grant the requested research funds. This Departmental review is not restricted to a reconsideration of the "ethical soundness" of the proposed research. Instead, it encompasses all other factors which enter into any research funding decision, such as the scientific rigor of the proposal, the scientific significance of the proposed project, and the relationship of budgetary estimates to the proposed study. As a result, the review of ethical issues at this stage cannot be as thorough as it is intended to be at the institutional level.

The adoption of this institutional review committee approach promised to be a significant advance toward the goal of ethical human research. For the first time, codes of research ethics were to be applied in concrete situations by means of a definite procedure providing for independent scrutiny of individual research proposals. Moreover, a decentralized, pluralistic approach, emphasizing decision-making at the institutional level, seemed to offer other advantages. The exploration of problems from different points of view could ultimately lead to a fuller appreciation of the issues requiring resolution. Concern for the rights and welfare of subjects could be more easily communicated to individual investigators. The review of research protocols could be handled in depth and yet with dispatch.

Despite these hopes, the present DHEW regulatory framework can only be considered a qualified success. The continued existence of two varying sets of guidelines to govern intramural and extramural human research activities respectively serves no purpose and generates confusion. As to the content of the guidelines, although from a historial perspective institutional committee review was a major improvement over prior practices, many deficiencies, to which we now turn, have precluded successful supervision of human experimentation for the protection of human subjects.

38. *Intramural Guidelines, supra,* footnote 22, at 10.
39. *Ibid.*
40. *Ibid.*
41. PHS intramural policy does impose stricter consent requirements for experiments with such subjects. These consent requirements are discussed *infra,* at pp. 25 ff.
42. *Grants Administration Manual, supra,* footnote 23, §1-40-40 (C) (2) (b).
43. *Grants Administration Manual, supra,* footnote 23, §§1-40-20 (B) and 1-40-50 (B). See also NIH Manual §4107 "Grants Involving Human Subjects," §4107 (G) (1972).

IV. CRITIQUE OF DHEW POLICY

A. Vagueness of Standards

At bottom, the difficulties which face review committees derive from the generality of the standards which are to guide their determinations in specific cases under either the intramural or extramural policies. To illustrate, if a review committee had evaluated the Tuskegee Syphilis Study under current guidelines, questions calling for searching examination would have surfaced.

(1) If the requirement of informed consent[44] is to be taken seriously, should impoverished and uneducated Blacks from rural Alabama have been selected as subjects in the first place? Or should a concerted effort have been made to find subjects from among the most educated within the population at large, or at least to select from the given subgroup those subjects most capable of giving "informed consent"? Put more generally, what general principles should guide the selection of subjects? The philosopher Hans Jonas has given one answer to this question: "(O)ne should look for (subjects) among the most highly motivated; the most highly educated, and the least 'captive' members of the community."[45]

(2) If "(t)he welfare of the individual is paramount (and) the subject must have available to him the facilities and professional attention necessary for the protection of his health and safety,"[46] what special efforts should have been made by investigators to provide medical treatment beyond the economic reach of the subjects before enlisting them in the Tuskegee Study? Or should the institutional review committee have turned down the Tuskegee Syphilis Study because no adequate treatment facilities were available in Macon County?

(3) How should "continuing review" operate? For example, at what point in time, after penicillin treatment for syphilis became available, should the subjects of the Tuskegee Syphilis Study have been apprised of this new development? Since it generally takes time before medical consensus is reached on the value of a new medication and is reported in the medical literature, when should the subjects have been told that a drug was available which at least some competent physicians considered effective treatment?

(4) How should the risks inherent in this study have been weighed against the predicted advancement of medical knowledge? The rule that "the risks to an individual. . .(must be) outweighed by the potential benefits to him or by the importance of the knowledge to be gained,"[47] is perhaps the most difficult guideline for review committees to implement. The seeming simplicity of this command belies its complexity. How are such tangibles as "risks," "benefits," and "importance of knowledge" to be measured and weighed? Can serious harm to research subjects ever be outweighed solely by additions to the sum of human knowledge?[48] If so, what kind of knowledge, in what circumstances, would outweigh what risks to subjects? The difficulties inherent in evaluating the scientific merits of a particular study are demonstrated by the ongoing differences of opinion among scientists of the PHS as to whether continuation of the Tuskegee Syphilis Study can still be defended on the ground of scientific merit. It is necessary for review committees to scrutinize carefully the research design of every proposed study if the requirement that risks be balanced against benefits is to be taken seriously, for the acquisition of knowledge depends so much on the soundness of the research protocol.[49] Does the informed willingness of the subject to accept certain risks have any bearing on the committee's balancing of risks against benefits? Finally, since the design of the Tuskegee Study could not completely exclude the possibility that non-subjects might contract syphilis from untreated subjects, how should a review committee have balanced risks to nonsubjects against benefits to society?[50]

(5) Review committees are also required to "determine that the rights and welfare of the subjects involved are adequately protected."[51] What rights did the Tuskegee Study subjects possess? The tremendous confusion which exists in the area of patient subjects' rights is in part the result of the traditional but largely unexamined prerogative of professionals

44. The requirement of informed consent is analyzed in greater detail *infra*, at pp.31 ff.

45. Jonas, "Philosophical Reflections on Experimenting with Human Subjects," 98 *Daedalus* 219, 235 (1969).

46. *Intramural Guidelines, supra*, footnote 22, at 1.

47. *Grants Administration Manual, supra*, footnote 23, §1-40-20 (A); see also *Intramural Guidelines, supra*, footnote 22, at 2, 4-5.

48. Although PHS policy does proscribe seriously risky experimentation which cannot benefit the subject, *Intramural Guidelines, supra*, footnote 22 at 2, DHEW policy for extramural research does not categorically prohibit such research. The *Institutional Guide, supra*, footnote 23, states at 6: "If the potential benefits are insubstantial, or are outweighed by risks, the committee may be justified in permitting the subjects to accept these risks in the interests of humanity."

49. *Intramural Guidelines, supra*, footnote 22, at 1.

50. The *Intramural Guidelines, supra*, footnote 22, at 1, state: The health and safety of persons other than the subject, if endangered by the research procedures, must be protected. DHEW policy neglects this problem.

51. *Grants Administration Manual, supra*, footnote 22, §1-40-20 (A); see also *Intramural Guidelines, supra*, footnote 22, at 1, 4-5.

to intervene in their patients' behalf without full disclosure whenever it is supposed to be "in their patients' best interests." The doctrine of "informed consent" has had little impact on this longstanding professional practice. Since much medical research is carried out in the context of "patient care" the right to make decisions for patients has more often than not unwittingly been carried over into the research domain. The confusion about patient-subjects' rights is bolstered by the scientist's felt obligation to advance knowledge for the good of society, although society has inadequately defined the extent of this obligation.

To illustrate the confusion about subject's rights: Can the subject claim the right to be indemnified for any harm he suffers as a result of the research, regardless of the investigator's fault and in spite on consent? Is so, who is responsible for informing him that an injury has occurred which is not the result of the natural progression of his illness? Do Tuskegee Study subjects have a cause of action because they did not receive suitable medical treatment? If so, who may be liable–the individual investigators, the PHS, the Milbank Memorial Fund, the Tuskegee Institute? The intramural guidelines of the PHS and *The Institutional Guide to DHEW Policy on Protection of Human Subjects* also identify confidentiality as a right which must be protected.[52] Does confidentiality extend only to the subject involved in the study or does it also include the group of which he is a part? If the latter, what are the limits of group confidentiality? The Tuskegee Syphilis Study, in common with many other studies, singled out one particular group and revealed much that was intimate and private about all its members. Where can review committees seek guidance in devising procedures which safeguard subjects' rights in general, and their rights to confidentiality, privacy and respect, in particular?[53]

(6) The jurisdiction of institutional review committees encompasses "any activity which goes beyond the application of those established and accepted methods necessary to meet. . (the subject's) needs."[54] How are "established and accepted" methods to be ascertained? Among "established" treatments should distinctions be made between those of "proven" and those of "dubious" value? What are the criteria for a "necessary" intervention? Since there is so much professional disagreement as to when a procedure becomes "therapeutic," the question must be posed: "accepted" by whom? Was the withholding of arsenic and heavy metal treatments at the beginning of the Tuskegee Study a "therapeutic" intervention since the effectiveness of such treatments was in doubt, particularly for late syphilis? When did penicillin treatment become an "established and accepted method"? What degree of certainty is required of investigators and review committees? Certainly no clear line can be drawn between experimental and routine treatment since, as has so frequently been asserted, "the therapy of disease is, and always will be, an experimental aspect of medicine."[55]

The vagueness and generality of the governing standards have disadvantaged all participants in the research decision-making process. For conscientious review committees, they have meant hard work and, insofar as the committees are overwhelmed by the enormity of their task, superficial examination of protocols. For subjects, the inevitable result has been to deprive them in some measure of the protection which review committees were supposed to provide. For investigators, the pervasive uncertainty about what kind of human studies are now permissible has impeded their research. And for society, fears about the protection of its citizens in the research enterprise have not been stilled. Especially because review committees work in isolation from one another and no mechanisms have been provided for disseminating the knowledge gained from their individual experiences, each committee is condemned to repeat the process of finding their own answers to all the questions we have raised. This is an overwhelming, unnecessary and unproductive task for which they are not prepared and which we doubt they are willing to assume.

What is needed, is an overall official body authorized to formulate more detailed policies with respect to research on human beings. The need for such a policy making body has in point of fact already been perceived, and other bodies, official and non-official, have partially and on an *ad hoc* basis attempted to fill the gap. For example, the FDA has promulgated comprehensive rules for the conduct of drug research,[56] although on many crucial issues of subject protection it has simply copied DHEW policy.[57] Similarly, in the wake of organ transplantation, an *ad Hoc* Committee of the Harvard

52. *Intramural Guidelines, supra,* footnote 22, at 9; *Institutional Guide, supra,* footnote 23, at 6.

53. The *Institutional Guide, ibid.,* does make an effort to suggest procedures for safeguarding confidentiality.

54. *Grants Administration Manual, supra,* footnote 23, § 1-40-10 (B); see also *Intramural Guidelines, supra,* footnote 22, at 2-3, 7-8.

55. Ivy, "The History and Ethics of the Use of Human Subjects in Medical Experiments" 108 *Science* (July, 1948). Barber *et al.* have recently documented the prevalence of professional uncertainty over the definition of "research." See *Barber et al., supra,* footnote 3 at 150.

56. See 21 C.F.R. § § 130.3, 130.37.

57. *Ibid.*; see also 36 Fed. Reg. 5037 (1971).

Medical School redefined the criteria of "death" in order to facilitate the removal of needed organs.[58] Moreover, the Division of Research Grants of NIH,[59] which at present supervises the implementation of DHEW policy, has occasionally transmitted memoranda to review committees "concerning the interpretation and implementation of (its) policy."[60] Recent memoranda focused on potential hazards of screening programs for sickle cell trait, the definition of "human subject," and guidelines for fetal studies. These policy making activities need to be consolidated, under the auspices of a broadly representative body, about which we shall have more to say below. Such a body would not only provide guidance to review committees but would also enable them to obtain advice whenever difficult problems arise.

B. Invisibility

The creation of institutional review committees could have led to increased visibility of decisions regarding the protection of subjects. But since neither publication nor free access to their findings was specifically planned for, increased visibility has not been realized. A low level of visibility hampers efforts to evaluate and learn from attempts to resolve the complex problems of human research. Especially so long as guidelines for human research remain so indefinite, high-visibility decision-making is an essential feature of a well-functioning regulatory framework. Moreover, since committee disapprovals can block research, with no recourse to higher level review, invisibility may impede the acquisition of valuable knowledge.

The 1969 committee review of the Tuskegee Syphilis Study illustrates the problems which a low level of visibility creates. Our knowledge of that proceeding comes from an unofficial summary which constitutes the only available report on that committee's deliberations. From this summary it is impossible to determine the factors which the committee considered or the grounds on which the committee based its decision to approve a continuation of the study. This state of affairs is not atypical. Because institutional committee decisions are not published, committee decision-making operates at a primitive level, uninformed by pertinent prior decisions of other committees or by scholarly outside criticism. A mechanism for self-improvement over time is lacking. Professor Guido Calabresi has observed:

> ...The best way of broadening the imputs to the committee–lies in another device: publication of the cases decided by the committees. Such cases could well be anonymous (at least at first). They could be collected and published in much the same way that decisions of courts are collected. The reports on any case could include, first a factual part describing, among other things, the experience of the experimenter, the antecedent tests in non-human subjects, the major risks perceived, the scientific gains perceived possible, the availability of subsequent controls to limit the risks, the origin and life expectancy of the subjects, and the nature of the consent and the manner in whcih it was obtained; and, second, a jurisprudential section containing the decision of the committee (whether favorable or unfavorable), together with the principal arguments made for and against the decision reached.
>
> Such published cases would soon become the subject of intense study both inside and outside the medical profession. Analyses in learned journals by lawyers, doctors, and historians of science would inevitably follow. These would undoubtedly re-argue the more important or path-breaking cases. If law cases are any guide, the analyses would sometimes conclude that the cases were wrongly decided, but frequently that they were rightly decided, and perhaps more frequently that they were rightly decided but for the wrong reasons. To the extent that Law Reviews consider themselves courts of last appeal beyond the highest courts in the land, so would the learned journals in which this *giurisprudenza* would be dissected. From all this, a sense of what society at large deems proper in medical experiments might well arise. This sense would, in turn, guide the committees and make their decisions more sophisticated. The result would not only be better thought out decisions, but also a more complex system of controls, which, in effect, took into account much broader sources of information as to societal values. . . .[61]

In the Recommendation section of our report we incorporate Calabresi's suggestions in a comprehensive framework for the regulation of human experimentation.

C. Subject Consent

1. The Definition of "Informed Consent"

Institutional review committees are expected to

58. *Ad Hoc* Committee of the Harvard Medical School, "A Definition of Irreversible Coma," 205 J.A.M.A. 337 (1968).

59. *Grants Administration Manual*, *supra*, footnote 23, § 1-40-50 (A).

60. Memorandum of January 24, 1972, from Stephen P. Hatchett, Director, Division of Research Grants, NIH, DHEW, to Officers Responsible for Institutional Implementation of DHEW Policy on Protection of Human Subjects.

61. Calabresi, "Reflections on Medical Experimentation in Humans," 98 *Daedalus* 387, 400-401 (1969).

scertain "that informed consent is. . .obtained by ıethods that are adequate and appropriate."[62] The)HEW Grants Administration Manual, in contrast to its reatment of other important matters, defines "informed onsent" in some detail:

> Informed consent is the agreement obtained from a subject, or from his authorized representative, to the subject's participation in an activity.
>
> The basic elements of informed consent are:
>
> 1. A fair explanation of the procedures to be followed, including an identification of those which are experimental;
> 2. A description of the attendant discomforts and risks;
> 3. A description of the benefits to be expected;
> 4. A disclosure of appropriate alternative procedures that would be advantageous for the subject;
> 5. An offer to answer any inquiries concerning the procedures;
> 6. An instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.[63]

The PHS Intramural Guidelines also explicate nformed consent in some detail:

> The individual must be free to choose whether or not to be a subject in research. His participation shall be accepted only after he has received a fair explanation of the procedures to be followed, benefits, and attendant hazards and discomforts, and, suited to his comprehension, the reasons for pursuing the study and its general objectives. He must be informed of his right to withdraw from the study at any time.[64]

For no apparent reason, two "basic elements" of nformed consent identified in DHEW policy are ignored)y the PHS intramural policy. Nothing is said in the ntramural policy statement about disclosure of alterna- ive procedures ("basic element" number four) or esponse to inquiries ("basic element" number five).

Despite the commendably greater detail with which)HEW policy on obtaining informed consent is set orth, major gaps do remain. For instance, the DHEW lirectives permit consent to be obtained from the ubject's "authorized representative" in lieu of the ubject himself. But the circumstances in which third arty consent may properly be substituted for the onsent of subjects are undefined. Committees are not advised as to who can validly consent in place of the subject or whether consent can be obtained from another person besides the subject only for certain investigations, such as those specifically designed to benefit the subjects themselves. Thus, committees are left to their own devices in fashioning rules about the participation in research of such subjects as the very young or the very old, the mentally incompetent or the emotionally disturbed, the imprisoned or those otherwise under duress, or, as in the Tuskegee Study, those who are ill-prepared as a consequence or cultural deprivation or inadequate education.

In contrast to the DHEW extramural guidelines, the PHS intramural research rules do address the problems of substitute consent for special subjects in more detail:

> Studies involving children, the mentally ill or the mentally defective should be carried out only when there is no significant risk of physical or mental harm to the subject or when direct benefit to the subject is anticipated. . . . In general, written informed consent of the parent or guardian shall be required for all medical or dental studies with such subjects, except in studies of an observational nature or in those conducted during the administration of accepted health care procedures that do not require specific informed consent in ordinary practice. Any exception shall be carefully considered and fully documented. Written informed consent of parent or guardian may be desirable in certain other studies with these groups and shall be required if conditions warrant. . . . Studies of individuals with limited civil freedom shall also be subject to group consideration and approval. Informed consent of the responsible institutional authority shall be required in all cases. Written informed consent of the individual shall also be required except for studies of an observational nature conducted during the administration of accepted health care procedures that do not require specific informed consent in ordinary practice.[65]

The major difficulties with these provisions result from the exceptions to the general requirement of substitute consent. "Studies of an observational nature" and "accepted health care procedures that do not require specific informed consent in ordinary practice" are phrases too vague to be meaningful. For example, was the Tuskegee Syphilis Study "of an observational nature"? In what "other" kinds of studies may investigators dispense with the consent of parent or guardian unless unspecified "conditions warrant" it?

52. *Grants Administration Manual, supra,* footnote 23, § 1-40-20 (A).
53. *Grants Administration Manual, supra,* footnote 23, § 1-40-10 (C).
64. *Intramural Guidelines, supra,* footnote 22, at 1.
65. *Intramural Guidelines, supra,* footnote 22, at 10-11.

Moreover, the PHS instructions ignore the issue of the capacity of third parties to represent the interests of special subjects adequately, and the subtle inducements which may persuade prisoners to consent.

Prisoners in particular are a group whose participation in research has long been controversial.[66] Because prisoners are a captive group, the danger is great that their consent to participate in research will be obtained by duress. Jessica Mitford has recently documented some of the abuses to which prisoner participants in experimentation have been subjected, and she comments:

> The (Institutional) Guide expresses a "particular concern" for "subjects in groups with limited civil freedom. These include prisoners. . . ." Having uttered this praiseworthy sentiment, HEW has apparently let the matter drop. Dr. D.T. Chalkley, chief of the Institutional Relations Branch, Division of Research Grants, and signer of the Guide, tells me that HEW does not even maintain a list of prisons in which HEW-financed research programs are in progress and has "no central source of information" on the scope of medical experiments on prisoners by drug companies. . . .
>
> What efforts have been made by HEW to enforce its guidelines in HEW-financed medical research behind prison walls? "We do give some grants that involve prisoners. But there's no convenient way of recovering the information as to whether our guidelines are being followed," said Dr. Chalkley. "That responsibility lies with the principal investigator. . . ." has HEW ever brought any action to enforce its regulations in any prisons anywhere? "None, to date."[67]

Most new drug testing is initially conducted on prisoners, and is subject to FDA regulations, but the FDA also has no list of persons in which such research is carried out.[68]

We regard the failure of the DHEW policies to include comprehensive guidelines for safeguarding prisoners, children, mental incompetents, and other special subjects in research, as a major shortcoming which must be rectified. Detailed policy must be formulated specifying the kinds of research which may be carried out with special subjects of different types, the inducements which are permissible, the circumstances in which third-party consent is necessary, the identity of those who can validly consent for the subject, additional precautions which must be taken for such subjects, and other matters.

2. Exceptions to the Consent Requirement

In its *Institutional Guide to DHEW Policy on the Protection of Human Subjects*, the Department sets forth the following additional exceptions to the requirement of informed consent:

> The review committee will determine if the consent required, whether to be secured before the fact, in writing or orally, or after the fact following debriefing, or whether implicit in voluntary participation in an adequately advertised activity, is appropriate in the light of the risks to the subject, and the circumstances of the project.
>
> Where an activity involves therapy, diagnosis, or management and a professional/patient relationship exists, it is necessary "to recognize that each patient's mental and emotional condition is important. . .and that in discussing the element of risk, a certain amount of discretion must be employed consistent with full disclosure of fact necessary to any informed consent."[69]

The first exception which permits obtaining consent "after the fact," is so general in scope and so extensive in the discretion it accords review committees that it almost staggers the imagination. What are "the circumstances of the project" which could ever permit such an invasion of subjects' rights to self-determination and privacy? Is this exemption limited to investigations with normal subjects employing placebos or to deception studies so frequently employed by psychologists? In one sentence the requirement of prior[70] informed consent is seriously undermined.

Furthermore, another exception provides for a departure from informed consent in situations in which "a professional/patient relationship exists." Since most medical research is carried out in such settings, it can apply to almost all medical interventions. It is particularly in clinical settings that overreaching in obtaining consent, however unwitting, is a constant danger.[71] Thus the unqualified provision that "a certain amount of

66. See, e.g., Lasagna, "Special Subjects in Human Experimentation," 98 *Daedalus* 449 (1969); *Katz, supra*, note 12, pp. 1018-1052; Mitford, "Experiments Behind Bars," *The Atlantic Monthly* 64 (January, 1973).

67. Mitford, "Experiments Behind Bars," *supra*, footnote 67, at 67-68.

68. See Mitford, "Experiments Behind Bars," *supra*, footnote 67, at 68.

69. *Institutional Guide, supra*, footnote 23, at 8.

70. It is implicit that consent is normally to be obtained prior to the subject's participation in research, although DHEW policy nowhere so states.

71. See *infra*, pp. 40ff.

discretion must be employed consistent with full disclosure of fact" is particularly unsatisfactory.[72]

PHS intramural policy also contains loopholes in its consent provisions. First, the guidelines state that

> An explanation so detailed as to bias his response or otherwise to invalidate findings is not necessary in those procedures that involve no risk of physical harm to the subject.[73]

This qualification is apparently designed to minimize interference with behavioral and other studies common to the social sciences. This guidelines elsewhere state that

> a major class of procedures in the social and behavioral sciences does no more than observe or elicit information about the subject's status by means of tests, inventories, questionnaires or surveys of personality or background. In such instances, the ethical considerations of voluntary participation, confidentiality, and propriety in use of the findings are the most generally relevant ones. The procedures may in many instances not require the fully informed consent of the subject or even his knowledgeable participation.[74]

The lack of concern in the quoted passages for psychological–as opposed to physical–harm to subjects is striking. Despite acknowledged ethical problems, the guidelines suggest that in "many instances" the "knowledgeable participation" of the subject may be unnecessary. Here again, the regulations fail to provide meaningful guidance to review committees.

3. The Quality of "Informed Consent"

Another difficulty which seriously undermines the implementation of informed consent has not been dealt with at all in the DHEW policies. It has long been recognized that consent is far too often obtained in form alone, and not in substance. As the Department itself admits in its Institutional Guide (quoting Doctor Henry K. Beecher of Harvard Medical School):

> "The informed consent of the subject, while often a legal necessity is a goal toward which we must strive, but hardly ever achieve except in the simplest cases."[75]

For as Doctor Beecher has written elsewhere,

> Lay subjects, sick or well, are not likely to understand the full implications of complicated procedures, even after careful explanation.[76]

Even with the best of intentions, investigators may fail to "get through" to their subjects for a variety of reasons. The subjects themselves may have great difficulty in understanding or little interest in knowing the nuances of what the investigator tries to explain to them. As Senator Hubert Humphrey recently lamented in response to the Tuskegee Syphilis Study:

> Who are the people who have been the subjects of medical experiment? The clear and shocking implications of the most recently revealed experiments indicate that the powerless, the poor, the least educated, and members of minority groups are the likeliest human guinea pigs. . . .
>
> It is those who cannot understand what is being done to them that constitute by far the largest numbers among human experimentation subjects.[77]

Moreover, the circumstances in which consent is sought may foster or hinder an informed and voluntary decision. The subject may be under stress or distracted by other pressing concerns. For example, he may be a patient, desperately hoping for successful treatment of his condition, whose judgment is distorted by the natural tendency to grasp at any straw in reach. The likelihood of this result is magnified by the profound dependence which many patients develop on their attending physicians, who are often responsible for obtaining consent. Indeed, however wrongly, the patient may well fear that his refusal to consent to experimental

72. Compare the more satisfactory provisions on informed consent adopted by the FDA, 21 CFR § 130.37, which require that consent be obtained "in all but exceptional cases." This is defined as follows:

> (d) "Exceptional cases," as used in paragraph (b) of this section, which exceptions are to be strictly applied, are cases where it is not feasible to obtain the patient's consent or the consent of his representative, or where, as a matter of professional judgment exercised in the best interest of a particular patient under the investigator's care, it would be contrary to that patient's welfare to obtain his consent.
>
> • • •
>
> (f) "Not feasible" is limited to cases where the investigator is not capable of obtaining consent because of inability to communicate with the patient or his representative; for example, where the patient is in a coma or is otherwise incapable of giving informed consent, his representative cannot be reached, and it is imperative to administer the drug without delay.
>
> (g) "Contrary to the best interests of such human beings" applies when the communication of information to obtain consent would seriously affect the patient's disease status and the physician has exercised a professional judgment that under the particular circumstances of this patient's case, the patient's best interests would suffer if consent were sought.

73. *Intramural Guidelines, supra*, footnote 22, at 1-2.

74. *Intramural Guidelines, supra*, footnote 22, at 9.

75. *Institutional Guide, supra*, footnote 23, at 7.

76. Beecher, *Research and the Individual* (Little, Brown and Co. 1970).

77. 118 Cong. Rec. S 14041 (Sept. 5, 1972). Senator Humphrey's assertion is corroborated by the recent study of research practices conducted by Barber *et al.* In the two institutions they analyzed, they found that studies in which the risks were relatively high in proportion to therapeutic benefits to the subjects were "almost twice as likely as more favorable studies to be done using subjects more than three-fourths of whom (were) ward and/or clinical patients," as opposed to private and/or semi-private patients. Moreover, this proportion is not significantly altered when studies in which the risk exceeds all possible benefits, to the subjects or to medicine generally are examined: "the 'least favorable' studies (were) still almost twice as likely as the more favorable to be done using three-fourths or more ward or clinical patients." *Barber et al., supra*, footnote 3 at 55, 56.

treatment will anger his physician and deprive him of adequate medical care.

Lastly, the investigator himself may fail to describe his own research objectively, or unwittingly create subtle pressures on a subject to consent. To suggest this is not to deny the integrity of the researcher, but only to acknowledge the reality of investigators' bias toward their work. Their scientific curiosity and excitement make it difficult for them to take a detached view of the research they wish to conduct with their subjects.

D. Continuing Review

Although extramural research projects supported by DHEW grants or contracts must be reviewed on a continuing basis, intramural research activities of the Public Health Service need not be reviewed again after initial committee approval. This omission for intramural programs of what the Department itself calls "an essential part of the review process"[78] explains the long neglect of the Tuskegee Study. Begun long before committee review became a reality, the Study was not reviewed by any committee until 1969, three years after Surgeon General Stewart had inaugurated the policy of committee review. Moreover, the 1969 review was undertaken at the behest of the principal investigators themselves, and not as the result of the Public Health Service review policy. The Tuskegee Study was not reviewed again until this Panel was appointed. We have been unable to ascertain why intramural research programs are exempt from the continuing review requirement.

Although DHEW extramural policy does require "continuing review," a better definition of the nature and extent of this obligation is needed. The present indefinite regulations invite a perfunctory performance of the continuing review function. Essentially the Department expects that the committees will

> . . . adopt a variety of continuing review mechanisms. They may involve systematic review of projects at fixed intervals, or at intervals set by the committee commensurate with the project's risk. Thus, a project involving an untried procedure may initially require reconsideration as each subject completes his involvement. A highly routine project may need no more than annual review. Routine diagnostic service procedures, such as biopsy and autopsy, which contribute to research and demonstration activities generally require no more than annual review. Spot checks may be used to supplement scheduled reviews. Actual review may involve interviews with the responsible staff, or review of written reports and supporting documents and forms. . .[79]

Institutional review committees, already overburdened by the task of examining all new research projects, are thus also responsible for re-examining from time to time all ongoing research. If something has to give first, it tends to be this assignment. Pressed for time, the review committees assume that the initial review has satisfactorily resolved all existing problems and that a cursory review is sufficient.

E. Structure and Composition of Institutional Committees

Institutional review committees are charged with carrying out a number of distinct functions. They are required to formulate policies and regulations to guide the conduct of research at their institutions,[80] often under the rubric of protocol review; to communicate these policies to investigators; to administer the policies they have promulgated through the prior appraisal of research proposals, the supervision of the attempt to obtain consent and the continuing review of approved research activities; to review the consequences of their decisions; and to keep informed of DHEW policy changes and suggestions in order to reformulate institutional policies and rules when necessary.

In recognition of the variety of tasks which have been delegated to committees, DHEW policy stresses the composition of committee membership.

> . . . In addition to possessing the professional competence to review specific activities, the committee should be able to determine acceptability of the proposal in terms of institutional commitments and regulations, *applicable law, standards of professional conduct and practice, and community attitudes.* The committee *may* therefore need to include persons whose primary concerns lie in these areas rather than in the conduct of research, development, and service programs of the types supported by DHEW (emphasis supplied).[81]

In carrying out their functions, the institutional review committees are thus also asked: "to determine acceptability of the proposal in terms of. . . applicable

78. *Institutional Guide, supra,* footnote 23, at 8.

79. *Institutional Guide, supra,* footnote 23, at 8-9.

80. Although the parent institutions are charged by DHEW with the responsibility of formulating policies to guide institutional review committees, *Grants Administration Manual, supra,* footnote 23, §1-40-40, to our knowledge this task is generally delegated to those committees. As we have previously described, the burden of formulating policy weighs heavily on local institutions because the DHEW policy is vague and incomplete.

81. *Grants Administration Manual, supra,* footnote 23, §1-40-40 (C) (2) (b).

aw, standards of professional conduct and practice, and community attitude." By assigning these tasks to a broadened committee membership, DHEW recognizes that decision-making in the human experimentation process cannot be left solely to professionals, but requires the participation of informed and concerned non-scientists. who may be laymen, lawyers, clergymen, and appropriate others. However, the functions of these non-professional participants are not spelled out. And the assumption that they can make their most effective contribution at the administrative stage, when individual protocols are reviewed, rather than at other stages of the process remains unexamined. The DHEW policies attempt to consolidate all phases of research regulation—formulation of detailed policies, administration of research, and review of decisions and consequences—in one committee structure. Asking each review committee to determine far-reaching policies by itself overburdens the review committee structure. The policy issues which must be resolved with the assistance of lay members are so complex that to require *each* committee to work them out by itself is at best inefficient and at worst self-defeating.

It would be more functional and efficient to leave the administration of research, like the administration of therapeutic interactions between physicians and patients, primarily in the hands of the professionals. If review committees were guided by comprehensive policies formulated by a broadly representative body, the review of individual protocols could focus on technical matters, such as degree of risk, likely benefits, research design, competence of investigators, safety precautions, and the like. This allocation of authority would help to reduce the widespread concern among physician-investigators about "meddlesome outsiders."

F. Enforcement

The DHEW guidelines on enforcement are written in permissive and general language:

> The Division of Research Grants (DRG), NIH, will follow up reports by reviewers, evaluators, consultants, and staff of the DHEW indicating concern for the welfare of subjects involved in approved and funded grants or contracts, and of subjects potentially involved in activities approved but not funded, and in disapproved proposals. On the basis of these reports and of other sources of information, the DRG, NIH, may, in collaboration with the operating agency concerned, correspond with or visit institutions to discuss correction of any apparent deficiencies in its implementation of the procedures described in its institutional assurance.
>
> If, in the judgment of the Secretary, an institution has failed in a material manner to comply with the terms of this policy with respect to a particular DHEW grant or contract, he may require that it be terminated in the manner provided for in applicable grant or procurement regulations. The institution shall be promptly notified of such finding and of the reason therefor.
>
> If, in the judgment of the Secretary, an institution fails to discharge its responsibilities for the protection of the rights and welfare of the individuals in its care, whether or not DHEW funds are involved, he may question whether the institution and the individuals concerned should remain eligible to receive future DHEW funds for activities involving human subjects. The institution and individuals concerned shall be promptly notified of this finding and of the reasons therefor.[82]

These enforcement guidelines delegate sole responsibility for the detection of failures to comply to the Division of Research Grants. But staff members of the DRG are probably the last persons to hear of any infractions once they have occurred, and then only when, as in the Tuskegee Study, they are of major proportions. Indeed, no procedures have been established to require institutional review committees to report to DHEW any evidence on noncompliance. Moreover, DHEW has made no efforts to define categories of noncompliance[83] which should lead to the imposition of sanctions or to specify different kinds of sanctions which should be imposed in particular cases. Finally, institutional review committees and DHEW are not authorized to take disciplinary action, except for the Secretary's prerogative to terminate grants or make the investigator or his institution ineligible to receive future funds.

G. Compensation of Subjects

Existing DHEW policy provides no mechanism for the compensation of subjects harmed as a consequence of their participation in research, in spite of the growing recognition that no matter how careful investigators may be, harm still will befall some subjects.[84] Unavoidable injury to a few is the "cost" of engaging in research which ultimately benefits the many. But unless the injured individuals can prove carelessness, failure to

82. *Grants Administration Manual, supra,* footnote 23, § 1-40-50 (E).

83. Because the requirement of "continuing review" has not been elaborated, committees themselves only haphazardly come across evidence of noncompliance.

84. See Ladimer, "Protection and Compensation for Injury in Human Studies," *In Experimentation With Human Subjects* (Paul A. Freund, ed.) 247. (George Braziller, 1970) (hereinafter *Ladimer).*

obtain informed consent, or actual malice, their participation bars recovery for the harm done to them. Those subjects whose injury does result from negligence are faced with the usual difficulties and uncertainties inherent in a law suit. For his part, any investigator who is sued as a result of his research may find that his ordinary malpractice insurance does not cover medical research.[85] If it does not—and the question is as yet unsettled—the personal liability of the investigator can be substantial. In addition, the economic vulnerability of subject and investigator adds to society's uneasiness about human experimentation, and may deter some persons from engaging in research activities.

H. Applicability of DHEW Policies

The DHEW guidelines quite appropriately were formulated for research grants and contracts to be funded by the Department. While much research in this country is supported by DHEW funds, a great deal of research is also funded or conducted by other Federal agencies, such as the Department of Defense.[86] Additionally, many research activities receive no Federal support. Is there any justification for permitting less stringent protective controls for human experimentation supported by other governmental agencies, private foundations, or other private sources than for research conducted or supported by DHEW?[87] Since a major restructuring in existing policies is necessary, we believe that serious consideration should be given to developing, through Congressional action, rules and procedures which apply to the entire human research enterprise without reference to the source of funding. A tentative step in this direction has already been taken by DHEW. Its enforcement section provides for the discontinuation of funds to any institution which has failed "to discharge its responsibilities for the protection of the rights and welfare of the individuals in its care, *whether or not DHEW funds are involved.*"[88] If it is concluded, however, that such broad coverage is beyond the power of Congress, then Congress should at least act to bring all federally funded research within a comprehensive regulatory framework.

When this is done, the existing anomaly in the applicability of DHEW policies should be corrected. We refer to the different policies described earlier which govern intramural and extramural research. We can find no justification for differential protection of subjects on this basis. Moreover, the conduct of human research by DHEW employees and under the Department's aegis lends additional support to our call for an independent Government body to oversee all research. For to expect DHEW to scrutinize and judge its own activities as critically and strictly as it supervises outside research projects is arguably unrealistic and unnecessarily strains internal Departmental relationships.

85. See *Ladimer, supra,* footnote 84 at 251.

86. For documentation of the human research conducted by the armed services, see the Legislative Reference Service's report "Medical Experimentation on Human Beings, March 1967," placed in the Congressional Record by Senator Jacob Javits, 118 Cong. Rec. S. 13789, 13793-95 (August 17, 1972). The report states:

> There is very little information available on the number and types of military persons who serve as subjects in research. Intuitively appraised, however, the number of topics and of human subjects must be large.

118 Cong. Rec. S. 13793.

87. Barber *et al.*, found that in 15% of the institutions they surveyed some clinical research was not reviewed by an institutional committee. Moreover, 35% of these institutions were medical schools, "the type of institutional setting most productive of biomedical investigations using human subjects." They concluded that "a perhaps significant volume of human research is still not subject to review by peer review committees." *Barber et al., supra,* footnote 3, at 149.

88. *Grants Administration Manual, supra,* footnote 23, §1-40-50 (E).