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**Department of
Health and Human
Services**

Office of the Secretary

Protection of Human Subjects

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Protection of Human Subjects; First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and Their Implementation for the Protection of Human Subjects in Biomedical and Behavioral Research; Report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

AGENCY: Department of Health and Human Services.

ACTION: Notice of Report for Public Comment.

SUMMARY: On November 9, 1978, the Public Health Service Act (Pub. L. 95-622) was amended, thereby creating the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. One of the charges of the Commission was to biennially report to the President, the Congress, and appropriate Federal agencies on the protection of human subjects of biomedical and behavioral research. In carrying out the above, the Commission was directed to include a review of the adequacy and uniformity (1) of the rules, policies, guidelines, and regulations of all Federal agencies regarding the protection of human subjects of biomedical or behavioral research which such agencies conduct or support, and (2) of the implementation of such rules, policies, guidelines, and regulations by such agencies, and may include such recommendations for legislation and administrative action as the Commission deems appropriate.

Pursuant to section 1802(b) of the Public Health Service Act, each Federal agency which receives a recommendation from the Commission that the agency take any action with respect to its rules, policies, guidelines, or regulations, shall publish such recommendation in the Federal Register and shall provide opportunity for interested persons to submit written data, views, and arguments with respect to adoption of the recommendations. Since the recommendations affect 19 Federal agencies, the Secretary is publishing the report on behalf of the following agencies:

Department of Health and Human Services

Department of Agriculture

Department of Commerce

Department of Defense

Department of Education

Department of Energy

Department of Housing and Urban Development

Department of Justice

Department of Transportation

Central Intelligence Agency

Environmental Protection Agency

United States International

Development Cooperative Agency

National Aeronautics and Space Administration

Veterans Administration

American National Red Cross

Consumer Product Safety Commission

National Institute of Justice

National Science Foundation

Office of Science and Technology

DATES: The Secretary invites comment on the First Biennial Report of the President's Commission. The comment period will close May 28, 1982. To facilitate analysis of the comments, it would be appreciated if they were arranged by recommendation number.

ADDRESSES: Please send comments or requests for additional information to: Carol Young, Office for Protection from Research Risks, National Institutes of Health, 5333 Westbard Avenue, Room 3A18, Bethesda, Maryland 20205; telephone 301-496-7163, where all comments received will be available for inspection weekdays (Federal holidays excepted) between the hours of 9:00 a.m. and 4:30 p.m.

Dated: March 3, 1982.

Edward N. Brandt, Jr.,

Assistant Secretary for Health.

Approved March 19, 1982.

Richard S. Schweiker,

Secretary.

Protecting Human Subjects

First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and their Implementation, for the Protection of Subjects in Biomedical and Behavioral Research

December 1981.

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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*Resignation accepted by President Reagan on December 3, 1981.

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Summary and Conclusions

Research with human beings plays an essential part in combatting disease and

in expanding the frontiers of knowledge. The Commission takes as given that only though research can proven advances be made in the prevention and cure of illness and in the relief of suffering, but in this Report it addresses another goal, which, like progress against disease, is highly valued in our society. For not only is research essential but it is equally essential that this important human activity be carried out without needless risk of distress and with the willing and enlightened cooperation of its subjects. This is an ideal to which the Federal government must be—and for many years, has been—committed. In this Report, the President's Commission responds to the request of the Congress that it report every two years on the degree to which Federal departments and agencies are meeting that high ideal.

The Commission has reviewed the policies of all Federal entities involved in some fashion in research involving human subjects. It is impressed that the officials of these agencies are for the most part concerned about the careful execution of their responsibilities and concludes that the rules and policies of the agencies largely appear adequate for the protection of human subjects if properly implemented. Certain problems in the application and interpretation of the rules, however, have emerged from the Commission's study. This Biennial Report contains the Commission's recommendation to the President, the Congress and the heads of relevant departments and agencies concerning a number of these problems. The Commission intends to make additional proposals in its next Biennial Report on the basis of its continuing examination of this field.

Some of the Commission's conclusions refer to particular Federal entities. The Commission points to (1) the need for the Department of Health and Human Services (HHS) either to accept or reject certain recommendations made in 1978 by the National Commission for the Protection of Human Subjects that were intended to provide additional procedures and standards so that appropriate decisions may be made to protect children and persons institutionalized as mentally disabled when researchers wish to involve them as subjects; (2) the need for the Department of Housing and Urban Development to establish clear standards by which its social policy research can be categorized and, when appropriate, reviewed; and (3) the urgency that several bodies, including the Department of Transportation, reach decisions on rules that have been

"under study" for many years (Recommendations 3 and 5).

Most of what the Commission has to say, however, treats issues that cut across the spectrum of federal entities involved in research. First, the Commission recommends that the movement toward "uniformity" in the regulations for the protection of human research subjects be carried to its logical conclusion, and that the Department of Health and Human Services and its present regulations become the focus of such uniform rules (Recommendations 1 and 2). This will advance four important objectives: it will improve the protection of subjects, alleviate an unnecessary burden (and source of confusion) for researchers and their institutions, eliminate the multiplicity of Federal regulations in this field, and simplify Federal oversight.

The first goal will be met as gaps in a few departments' rules to protect research subjects are filled. "Variations" now followed by other departments can be included in the new uniform rules if found useful by the government-wide task force that will formulate these rules. The remaining objectives are closely related. By eliminating more than 200 pages of governmental rules and policies that now largely repeat the HHS regulations, the steps recommended by the Commission would reduce waste and confusion as well as facilitate Federal oversight. The redundancy in agencies' current rules obscures those few variations that are actually important to the respective Federal entities. Under the Commission's recommendations, any special provisions that are needed only by a particular entity could then be highlighted as acceptable exceptions or additions to the "core" provisions of the uniform regulations. And the centralization of responsibility for implementation and oversight in HHS would relieve Federal agencies and research institutions alike of the unnecessary burdens created by multiple inspections and reporting requirements.

The second major area of Commission recommendations centers on improving the present handling of reports of harm or misconduct involving human subjects. Although such reports are not frequent, the Federal government already has a number of relevant regulations on the books. The Commission examined these regulations to determine whether they provide adequate protection to subjects and other concerned parties in a manner that is clear and simple to apply for Federal officials and research

administrators alike. The resulting recommendations fall into three groups.

First, this Report contains recommendations about the responsibilities of the Federal agencies in responding to reports of misconduct. Revisions are needed because of an apparent lack of well-defined standards and an absence of coordination among various Federal entities. The present processes are still relatively new and few cases of misconduct have been reviewed in fact, it was not until 1981 that HHS or its predecessors imposed any sanctions against an investigator for misconduct in research funded by the Department that involves human subjects. Cooperation, not merely between Federal agencies but also among them and State and professional boards, is clearly an important goal (Recommendation 9).

Second, several recommendations are made to allow institutions internal flexibility in how they will investigate and adjudicate complaints against researchers. Although perhaps not intended by the Department, the present language of the HHS regulations has been interpreted by some as making IRBs responsible for resolving allegations of misconduct and for reporting their determinations directly to the Secretary rather than through institutional channels. The IRB must have a place in the process (at a minimum, it must be kept apprised of the outcome), but it need not perform the investigatory/adjudicatory/reporting roles if those are more properly fulfilled by other offices within an institution (Recommendations 7 and 8).

Finally, the Commission recommends that the number of subjects involved in, as well as the number adversely affected by, each research project be routinely collected by Institutional Review Boards (IRBs) and reported by them to the sponsoring agencies (Recommendation 4).

In recommending ways in which the Federal regulations on research could achieve greater clarity, simplicity and realism, the Commission is not adopting the view that all problems are ultimately soluble by "better" regulations. The Commission took concerns about excessive regulation into account in framing its recommendations and in drawing up its plans for further study of this subject during the coming year. As Plato observed, in esoteric areas, one must rely also on the wisdom of the expert. If society relied totally on written rules,

the arts as we know them would be annihilated and * * * could never be resurrected because * * * this law [would

put] an embargo on all research. The result would be that life which is hard enough as it is, would be quite impossible then and not to be endured.¹

Just as society must rely on the experts' wisdom, so too must it rely on their consciences—for which reasonable and well-formulated regulations may still provide both instruction and incentive.

Chapter 1: Introduction

A. *The Mandate.* The Commission's mandate regarding the protection of subjects in research with human beings has two major parts: first, to review the Federal rules and policies governing such research (1) and second, to determine how well those rules are being implemented or enforced. Specifically, section 1802(c) of the enabling legislation provides that:

The Commission shall biennially report to the President, the Congress, and appropriate Federal agencies on the protection of human subjects of biomedical and behavioral research. Each such report shall include a review of the adequacy and uniformity (1) of the rules, policies, guidelines, and regulations of all Federal agencies regarding the protection of human subjects of biomedical or behavioral research which such agencies conduct or support, and (2) of the implementation of such rules, policies, guidelines and regulations by such agencies, and may include such recommendations for legislation and administrative action as the Commission deems appropriate. (2)

The first portion of the mandate expands the survey of Federal agencies that the Commission's predecessor, the National Commission for the Protection of Human Subjects conducted, to a detailed inquiry into the adequacy of the rules of all agencies. The second portion, which adds a new dimension to the inquiry, has emerged as a major focus of this Commission's activities in the wake of the new rules on research promulgated by the Department of Health and Human Services in January 1981.

The first biennium for this Report, which began when the Commission held its first meeting in January 1980, ends in December 1981. (The second "biennium" will end in December 1982 when the Commission's present authority expires.) This report, therefore, represents two years of study and deliberations during which the Commission held three public hearings on this subject, devoted significant portions of twelve meetings to discussion and deliberation, surveyed over 83 Federal agencies to ascertain

¹Plato, *Statesman* *229e (J. B. Skemp trans.), Yale University Press, New Haven (1952) at 208.

their involvement in—and rules governing—research with human subjects, requested detailed information from the five agencies having statutory liaisons with the Commission (the Department of Health and Human Services, the Department of Defense, the Central Intelligence Agency, the Veterans Administration, and the National Science Foundation), and participated in Congressional hearings on several issues encompassed within this aspect of the Commission's mandate. (3) During this period, frequent correspondence and meetings took place between officials of the Department of Health and Human Services (HHS) and the Commission. This introductory chapter briefly describes the Commission's activities relating to this portion of its mandate.

B. *Initial Recommendations to the Department of Health and Human Services.* In September 1980, following a public hearing held in July on social science and behavioral research, the Commission made recommendations to HHS Secretary Patricia R. Harris (see Appendix D) on the Department's proposed revisions to its rules governing research with human subjects (45 CFR Part 46). The Commission proposed specific exemptions from prior review for most forms of social science research and some categories of behavioral research that present no risk of physical or psychological harm and no invasion of privacy. These recommendations were in line with the proposals being considered by the Department, but differed from them in that they were organized so as to convey the grounds for each category of exemption to the members of local review boards at research institutions who would have to apply them.

The Commission also informed Secretary Harris of its conclusion that the Department currently lacks statutory authority to require grantee institutions to follow HHS regulations and procedures in reviewing research not supported by Departmental funds. The Director of the Office of Management and Budget and the Director of the Office of Science and Technology Policy subsequently endorsed the Commission's position. (Whether such authority should be granted to HHS or other Federal departments is a question the Commission will address in the next Biennial Report.)

The amendments to the HHS rules governing research with human subjects were published on January 26, 1981 to take effect on July 27, 1981. (4) In their final form, the regulations incorporated the recommendation made by the

Commission to limit the scope of the regulations by abandoning the proposed applicability to research neither funded by the Department nor subject to the regulatory authority of the Food and Drug Administration (FDA). The Department did not, however, adopt the Commission's formulation of the rationale and organization of the exemptions of certain kinds of social science and behavioral research. (The relevant materials appear in Appendix D.)

C. *Summary of the Commission's Activities.* 1. *Survey of Federal Rules and Procedures Governing Research With Human Subjects.* The Commission sent letters of inquiry to 83 Federal agencies that might possibly be conducting or supporting research with human subjects. The responsible officials were asked whether their agencies conduct or support research with human subjects and, if so, what regulations or guidelines they follow to assure that such subjects are protected. In all cases, agencies were asked to include copies of applicable regulations, guidelines, or policies with their response.

Chapter Two of this Report contains an analysis of the adequacy and uniformity of the rules and procedures of the 23 Federal entities reporting that they conduct or support research with human subjects, as well as of the rules and procedures of the FDA, which plays the dominant role in the regulation of biomedical research not funded by the Federal government. Among the agencies, HHS (which supports the largest volume of research and which has devoted the most attention to the subject) is widely regarded as the "lead" agency. A fuller description of the policies and procedures of HHS is set forth in Appendix B, as well as a description of the rules and procedures of each of the other Federal entities, compared with those of HHS,

2. *Review of the Adequacy and Uniformity of the Rules' Implementation.* The second half of the Commission's charge regarding the protection of human subjects is to determine how adequately the applicable rules are being implemented. This has been a major focus of the Commission's activities in 1981. The Commissioners have tried to learn, from a variety of approaches: (1) How well informed the funding agencies are about institutional compliance with the regulations (an inquiry that led the Commission to conduct a selective examination of grantee institutions' implementation of the regulations); (2) how able institutions are to handle

charges of noncompliance, misconduct or injury; and (3) how the funding agencies respond to reports that the regulations have been violated or human subjects placed at risk through acts of research fraud or other misconduct.

As part of its survey of the rules and procedures of Federal agencies conducting or supporting research with human subjects, the Commission asked each agency about the extent to which it monitors either the actual conduct of research or the performance of the IRBs at grantee and contractor institutions. A summary and analysis of those responses is contained in Chapter Three.

3. *Attempts to Clarify HHS Policies and Procedures for Responding to Reports of Misconduct.* The Commission, through its Chairman and senior staff, for more than a year has been, and continues to be, engaged in correspondence and meetings with officials at the Department of Health and Human Services in an attempt to clarify current Departmental policies and procedures for responding to reports of misconduct by grantees and contractors. (See Appendix F.) The Commission is particularly interested in learning about the extent to which standards and procedures exist for: (a) Alerting committees that review grants and contracts about serious allegations pending against a scientist; (b) protecting complainants and witnesses from retaliation; (c) protecting the subjects, if research activities must be suspended; (d) protecting the rights of those accused of misconduct; and (e) protecting the public interest by assuring the reliability of research results and the ethical conduct of Federally supported research.

4. *Case Studies.* The Commission also examined closely several reported incidents of misconduct in Federally funded research to determine what might be learned from these well-documented cases. Although the cases are few in number, particularly in light of the thousands of research projects conducted each year, the Commission found them instructive. Specifically, the cases indicate areas where procedures for responding to reports of misconduct need improvement at the institutional and the Federal levels. Problems identified in a review of these cases are described in Chapter Three; the cases themselves are described in Appendix F.

5. *Commission Hearings.* As an adjunct to its study of cases of misconduct in Federally-supported biomedical research, the Commission held hearings during 1981 in Boston and Los Angeles, the locales of two such incidents. The purpose was to learn

from administrators and IRB members at the research institutions involved, as well as from principal investigators and those who reported misconduct, how well they believe existing procedures worked and what improvements they would recommend. A number of suggestions regarding the authority of IRBs, institutional mechanisms for investigating and adjudicating reports of misconduct, and Federal procedures for monitoring compliance were received and considered by the Commission. Furthermore, in addition to its hearings and deliberations on social and behavioral science research in July and September 1980, the Commission considered aspects of its Biennial Report at its regular meetings in October, November and December 1981, at which time periods were set aside for public comments as well as Commission discussion. (A list of witnesses appears in Appendix I.)

6. *Conferences Attended.* Senior professional staff participated in a number of conferences on the role and responsibilities of IRBs, the need for improved education of investigators and members of IRBs, and the effect that the revised HHS regulations will have on IRB procedures. Such conferences included a meeting sponsored by HHS of consultants on "Education for IRBs" (December 8, 1980); two conferences sponsored by Public Responsibility in Medicine and Research (PRIM&R) on "The New Federal Regulations: What They Do and Do Not Regulate" (Boston, March 26-27, 1981 and Asilomar, November 24, 1981); and a workshop sponsored by the Institute for Society, Ethics and the Life Sciences (Hastings Center) on "Institutional Review Boards and Human Subjects Research" (Colorado College, July 12, 1981). In addition, the Commission's director participated in workshop discussions with research administrators and members of IRBs (eg., the 1981 annual meeting of the National Council of University Research Administrators and the fourth annual University of California conference on IRBs.)

7. *Workshop on Whistleblowing in Biomedical Research.* Because all Federal agencies rely on private individuals to report incidents of misconduct in research with human beings, the Commission decided to examine the availability of means for making such reports, the adequacy of procedures for evaluating the reports, and the protections afforded both the complainant and the person accused after allegations have been made. The Commission was also interested in the response of the Federal agencies once

they receive either an allegation of serious misconduct or a formal finding by an institution that such misconduct has occurred.

To clarify the issues and examine possible modes of response, the Commission held a two-day Workshop on Whistleblowing in Biomedical Research, co-sponsored by the Committee on Scientific Freedom and Responsibility of the American Association for the Advancement of Science and by Medicine in the Public Interest. Participants included physicians engaged in Biomedical research; hospital administrators; professors of law, political science, sociology, and educational administration; practicing attorneys; officials of the National Institutes of Health and the Food and Drug Administration, a member of the President's Commission and senior staff of the sponsoring organizations. (See Appendix J.) The conclusions and recommendations of the Workshop were transmitted to members of the Commission and were taken into consideration in developing recommendations on this subject. (conference papers, discussions and conclusions will be published as a separate volume in 1982.)

3. *Assistance from Liaison Representatives to the Commission.* Under section 1801(a)(2) of the Commission's enabling legislation, the heads of six agencies were directed to name officials to act as liaison to the Commission: the Department of Health and Human Services, the Department of Defense, the Central Intelligence Agency, the White House Office of Science and Technology Policy, the Veterans' Administration, and the National Science Foundation. (5) The Commission and its staff wish to thank those who served in this capacity for their conscientious attendance at Commission meetings and their valuable assistance, both formal and informal, in the preparation of this report.

9. *Contacts With the Office of Management and Budget.* In response to an OMB proposal for government-wide debarment procedures applicable to Federal contractors, (6) senior staff of the Commission have discussed with OMB its interest in developing government-wide debarment procedures that would apply to Federal grantees as well. The purpose would be to standardize debarment and suspension procedures so that a scientist, debarred or suspended by one Federal agency (for misconduct in the course of Federally funded research) could be debarred by other agencies without burdening all

concerned with additional debarment proceedings. Further, a consolidated list of persons debarred from individual agencies would be available to all Federal agencies. OMB officials have expressed interest in developing such a government-wide system applicable to recipients of research grants. (See Appendices G and H.)

D. *Report on Compensating for Research Injuries.* At the urging of the vice-chair of the Ethics Advisory Board in HHS, which was in the process of concluding its activities, the Commission decided at its first meeting to study the problem of providing compensation for research-related injuries, a subject closely related to the protection of human subjects.

A starting point was provided by the report of the HEW Secretary's Task Force on Compensation for Injured Research Subjects (1977), which concluded that there is an ethical obligation to provide compensation for persons injured as a result of their participation in Federally sponsored research. The question of how such compensation could be provided was not resolved either by the Task Force or subsequently within HHS. The Commission, therefore, confronted two distinct, but related, questions: (1) Whether it agrees that an ethical obligation to provide compensation exists and, if so, the extent of that obligation; and (2) whether feasible mechanisms exist or could be developed that would meet that obligation.

A separate report on the Commission's study of these questions and the conclusions it reached is under preparation and will be released early in 1982.

E. *Extent of Federal Involvement in Research With Human Subjects.* Annual expenditures for health-related research are now about \$8 billion, of which the Federal government contributes more than 60%.

Three-quarters of this amount comes from the Department of Health and Human Services, primarily through the National Institutes of Health (NIH). (7) The remaining quarter of Federal support for biomedical and other health-related research is contributed by some 17 other agencies, with major portions provided through the Departments of Agriculture, Defense and Energy and the Veterans' Administration. (8)

The amount of such research that involved human subjects is, however, unknown. In fact, the Commission has been hampered in its study of the magnitude of the problem of research injuries because data have not been systematically accumulated on the

number of subjects involved in Federally-funded research. In an attempt to obtain an impression of the extent of Federal involvement in research with human subjects, the Commission asked the five agencies with official liaisons to the Commission to provide the following

information for FY 1980, to the extent obtainable: (1) The number of research projects involving human subjects that were supported by their departments under grants or contracts (extramural research) or that were conducted either by departmental employees or at

facilities operated by their departments (intramural research); (2) the number of IRBs that reviewed such research; (3) the amount of money spent; and (4) the number of subjects involved. Table 1 reflects the information provided by the liaison officers.

TABLE 1.—EXTENT OF BIOMEDICAL AND BEHAVIORAL RESEARCH INVOLVING HUMAN SUBJECTS CONDUCTED OR SUPPORTED BY AGENCIES WITH STATUTORY LIAISONS TO THE COMMISSION
 [Estimates provided by agencies for FY 1980]

	No. of inst'ns receiving grants or contracts	No. of grants or contracts funded	No. of intramural research projects	No. of human subjects involved	No. of IRRs that reviewed the research		Amount spent on research involving human subjects in millions	
					extra-mural	intramural	extra-mural	intramural
Central Intelligence Agency.....	<10	<10	<10	<100	<10	<10	<0.5	<0.5
Department of Defense.....	^b 256	274	409	92,000	164	38	\$26.4	\$83.3
Health and Human Services.....	816	11,574	^c 931	^d *	1,000	^e 25	\$1,460.0	^e \$408.4
National Science Foundation.....	68	164	0	*	68	0	\$8.6	0
Veterans Administration.....	9	25	^e 3,224	*	35	104	\$0.9	\$92.1

* Agency reports that data are not available.
^a The Department of Defense provided data only for their "R&D" programs; data on their "Clinical Investigations" are not available except from the Air Force which reported 1,000 clinical studies in FY 1980. According to DoD, their clinical investigation programs are largely intramural.
^b This figure may be high due to duplication, i.e., investigations may hold contracts with more than one service.
^c These figures relate solely to intramural research conducted by NIH, ADAMHA, FDA, CDC, and the Indian Health Service.
^d Information on the number of human subjects involved in research supported by HHS is available only for certain intramural programs; the Department reports that approximately 38,600 human subjects were involved in intramural research conducted by NIH, FDA, CDC, and a portion of ADAMHA. Data on the number of subjects involved in extramural research are not available.
^e This figure may be low. It refers to the number of principle investigators that conducted research involving human subjects.

As the table makes apparent, data are not available on the number of human Subjects involved in Federally-supported research except for several intramural programs within HHS (e.g., the NIH Clinical Center and the Centers for Disease Control), the R&D programs (but not several thousand clinical investigations) conducted by the Department of Defense, and the research conducted by C.I.A. On the other hand, all five agencies were able to provide the number of grants and contracts they funded for research involving human subjects. In Chapter Five of this report, the Commission recommends procedures for assuring that all Federal agencies collect and retain in a central location data on the number of subjects participating in research that the agencies conduct or support.

Footnotes

(1) Section 1802(c) of the Commission's legislation mandates a report on the rules governing research that Federal agencies "conduct or support." The Commission has chosen, pursuant to its authority to study "any other appropriate matter which relates to biomedical or behavioral research," to include within the present study the rules of the Food and Drug Administration (FDA) governing research regulated but not supported by the Federal government. The FDA was singled out because of its preeminent role in regulating biomedical research supported by private funds (under applicable law, materials submitted to obtain FDA approval of drugs and devices must have been produced through research that

meets its requirements, including regulations for the protection of human subjects) and because of the close relationship between the FDA regulations and those applicable to research funded by HHS, of which FDA is a component.
 (2) Title XVII, Public Health Service Act, 42 U.S.C. 300v-1(c).
 (3) Commission staff was also in touch with the Commission on the Federal Drug Approval Process, sponsored by Representatives Scheuer and Gore. That body is now reported to have decided not to disturb the status quo regarding the responsibilities of IRB's or other aspects of the regulations to protect human subjects.
 (4) 46 FR 8366, reprinted in Appendix A.
 (5) Liaison was provided by: *Department of Health and Human Services*—Charles R. McCarthy, Ph. D., Director, Office for Protection From Research Risks, Office of the Director, NIH, assisted by Richard Riseberg, Chief, NIH Branch, Office of General Counsel, John C. Petricciani, M.D., Assistant Director for Clinical Research, Bureau of Biologics, FDA, and Stuart Nightingale, M.D., Acting Associate Commissioner for Health Affairs, FDA; *Department of Defense*—Captain Peter A. Flynn, MC, USN, Special Assistant for Professional Activities, Office of the Assistant Secretary of Defense (Health Affairs); *Central Intelligence Agency*—Bernard M. Malloy, M.D., Chief of the Psychiatric Division, Office of Medical Services, assisted by Dennis Foreman, Office of General Counsel; *Office of Science and Technology Policy*—Gilbert S. Ommen, M.D., Ph. D., Associate Director for Human Resources and Social and Economic Services, OSTP, Executive Office of the President, succeeded by John Ball, M.D., J.D., succeeded by Denis Prager, Ph. D.; *Veterans Administration*—Dorothy C. Rasinski, M.D., J.D., Associate Director, Medical Legal

Affairs; and *National Science Foundation*—Richard T. Louttit, Ph. D., Division Director for Behavioral and Neural Sciences.
 (6) 46FR37832 (July 22, 1981).
 (7) U.S. Department of Health, Education, and Welfare, *Basic Data Relating to the National Institutes of Health: 1980*, U.S. Government Printing Office, Washington (1980) at 4.
 (8) *Id.* at 5.

Chapter 2: The Adequacy and Uniformity of the Regulations

A survey of the regulations and policies for the protection of human subjects of Federally funded and regulated research was conducted by the Commission in 1980-81 in response to the legislative mandate that the Commission report biennially to the President, the Congress and the heads of relevant agencies on both the adequacy and the uniformity of the rules and policies of all Federal agencies regarding the protection of human subjects of biomedical and behavioral research. (1)

It is generally accepted, among Federal officials and commentators, that the benchmark of "adequacy" is provided by the regulations of the Department of Health and Human Services. Based upon the thorough review of human research regulations of HHS (then, the Department of Health, Education, and Welfare) performed by the National Commission for the Protection of Human Subjects in 1974-1978, (2) and the conscientious manner in which HHS has responded to the

National Commission's recommendations regarding the review standards and procedures for research involving competent, non-institutionalized adults, the President's Commission is satisfied that the basic regulations of that Department are adequate if not above improvement. Therefore, the Commission has focused its attention on determining the "uniformity" among other Federal agencies measured by the extent to which their rules conform to the basic regulations of HHS.

A. Methods. 1. Scope of the Survey. The methods used to conduct the survey of Federal agencies were similar to those used by the National Commission in 1975. The 1980 survey was, however, broader in scope, including 11 of the 13 cabinet-level departments, (3) the Central Intelligence Agency in the Executive Office of the President, and 56 of 87 independent commissions and agencies listed in the Congressional Directory. Agencies were excluded from the survey only when there was reason to be confident that they do not conduct or support research with human subjects. (See Appendix C.)

In March 1980, the twenty still existing Federal agencies which had reported to the National Commission that they support or conduct research involving human subjects were provided with a copy of the 1977 summary of their policies and regulations. They were asked to provide information and supporting documentation regarding any additions or deletions necessary to bring the summary up-to-date. Federal agencies not surveyed by the National Commission or who had reported in 1975 that they neither conduct nor support research involving human subjects were asked whether or not they currently conduct or support such research.

In order to improve the consistency of response, agency heads were provided with the following definitions which had been developed by the National Commission:

1. *Scientific research* is a formal investigation designed to develop or contribute to generalizable knowledge.

Comment: A research project generally is described in a protocol that sets forth explicit objectives and formal procedures designed to reach those objectives. The protocol may include therapeutic and other activities intended to benefit the subjects, as well as procedures to evaluate such activities. Research objectives range from understanding normal and abnormal physiological or psychological functions or social phenomena, to evaluating diagnostic, therapeutic or preventive interventions and variations in services or practices. The activities or procedures involved in research

may be invasive or non-invasive and include surgical interventions; removal of body tissues or fluids; administration of chemical substances or forms of energy; modification of diet, daily routine or service delivery; alteration of environment; observation; administration of questionnaires or tests; randomization; review of records; etc.

2. *Human subject* is a person about whom an investigator (professional or student) conducting scientific research obtains (1) data through intervention or interaction with the person, or (2) identifiable private information.

Comment: "Intervention" includes both physical procedures by which data are gathered (e.g., venipuncture), and manipulations of the subject or the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

All agencies that conduct or support research involving human subjects, according to the definitions supplied, were asked to provide the following information as well:

(1) A description of the nature and extent of such research;

(2) Copies of the regulations or guidelines that govern the conduct of such research

(3) An analysis of the extent to which their regulations or guidelines conform to those of the Department of Health, Education, and Welfare (codified at 45 CFR 46, as amended in 43 FR 51559, November 3, 1978);

(4) A description of their procedures for monitoring such research during the course of its conduct, and for assuring that the agency is informed of any untoward or unexpected events;

(5) A description of the nature and extent of any injuries or of any departures from approved protocols that have been reported or discovered, and the steps taken by their agency to investigate and resolve such problems;

(6) The views of their department or agency regarding recently proposed modifications to the existing HEW regulations; and

(7) Any action taken by their department or agency with respect to the proposed modifications enumerated above.

2. *Agencies Excluded From Further Review.* The definition of research involving human subjects supplied to the Federal agencies was compatible with the scope of the then existing HHS regulations which applied to, among

other things, the administration of surveys or questionnaires and the review of records. Those regulations were revised January 1981, however, and most research involving only the use of surveys and questionnaires or the review of records is now exempt from the regulations. Therefore, those Federal agencies indicating that they sponsor only research exempt from review under the HHS regulations will be noted but not discussed further in this Report (see Table 2). Only those agencies that support, conduct or regulate biomedical or behavioral research of the type HHS now requires to be reviewed and approved in accordance with 45 CFR 46 are included in this analysis of Federal regulations and policies governing research with human subjects (see Table 3).

Also excluded from independent analysis in this report are the Nuclear Regulatory Commission (which, as a matter of policy, does not conduct research involving human subjects except through health agencies, such as HHS, which impose their own regulations), the Smithsonian Institution, which conducts research under grants from HHS and is subject to the regulations of that department, and the U.S. Postal Service and ACTION which permit access to their personnel and facilities by agencies of the Public Health Service (HHS) for research related to health and safety. (4)

3. *Agencies Included in the National Commission Report That are Not Reviewed in This Report.* A comparison of this Report with that of the National Commission will reveal various differences, some of them merely superficial. (5) For example, the Commission on Civil Rights no longer has an Office of Research, and the research responsibilities formerly undertaken by that office have not been reassigned therefore, the Commission on Civil Rights no longer conducts or supports any research with human subjects. (6) The National Oceanic and Atmospheric Administration (NOAA) of the Department of Commerce conducts only research involving deep sea diving and other underwater activities: the agency is not involved in research involving humans as subjects in the underwater environment. (7) The Federal Railroad Administration, within the Department of Transportation, reports that it no longer conducts research with human subjects as described in the report of the National Commission. (8)

The National Academy of Sciences has been deleted from coverage in this Report, at its own request, because it is not a Federal agency and receives no

appropriations from Congress. Rather, it is a private institution chartered by Congress as a non-profit organization to provide advice to the government on matters of science and technology. The Academy occasionally conducts or supports research with human subjects at the request of Federal agencies and requires that such research conform to the regulations of the Department of Health and Human Services. (9)

Somewhat differently situated is the Gorgas Memorial Institute of Tropical Diseases and Preventive Medicine, located in Panama. The Institute is a non-profit organization incorporated in Delaware, which receives a significant part of its operating budget from direct Congressional appropriations. (10) In Fiscal 1980, \$1.7 million of a \$2.5 million budget came from Congress. Most of the Federal money pays administrative costs such as salaries, field work, maintenance of the plant and equipment, and publications. In FY 1980, the Institute received an additional \$952,000 in research grants from NIH, the World Health Organization, the Army, the Navy, and the Pan American Health Organization. Most of the Institute's research is related to tropical diseases; however, the Institute currently has a special assurance on file at NIH's Office for Protection from Research Risks (OPRR) for a grant from the National Cancer Institute to conduct research on cervical cancer. Except for conditions attached to grants from the NIH and the Army, however, there is no specific legal or regulatory provision requiring research involving human subjects conducted by the Gorgas Memorial Institute to undergo IRB review or to comply with provisions for informed consent. Although the direct appropriations from Congress are administered by the Fogarty International Center at NIH, the Center has no authority to attach conditions to such funds. (11)

Table 2.—Agencies Excluded From Review and Analysis in This Report

Agencies That Conduct or Support Only Surveys, Questionnaires, and Record Reviews Currently Exempt From HHS Regulations

Department of Justice:
Bureau of Justice Statistics
United States Parole Commission
Department of the Treasury:
Internal Revenue Service
General Services Administration:
National Archives and Records Service
International Communications Agency
National Endowment for the Arts
National Transportation Safety Board
Office of Personnel Management
Small Business Administration
Tennessee Valley Authority

Agencies That Are Only Involved as Sponsors of Research Carried out by Other Federal Agencies.

Nuclear Regulatory Commission
Smithsonian Institution

Agencies That Permit the Use of Their Facilities and Personnel For Health/Safety Studies Conducted or Supported by Other Federal Agencies

ACTION
U.S. Postal Service

Table 3.—Agencies Included in this Report's Review and Analysis

Agencies That Conduct or Support Biomedical or Behavioral Research of the Sort Covered by HHS Regulations (45 CFR 46)

American National Red Cross
Central Intelligence Agency
Consumer Product Safety Commission
Department of Agriculture
Department of Commerce
Department of Defense:
Army
Navy
Air Force
Department of Education
Department of Energy
Department of Health and Human Services
Department of Housing and Urban Development
Department of Justice:
Bureau of Prisons
Office of Justice Assistance, Research, and Statistics
Department of Transportation:
Coast Guard
Federal Aviation Administration
Federal Highway Administration
National Highway Traffic Safety Administration
Environmental Protection Agency
National Science Foundation
U.S. International Development Cooperation Agency
Veterans Administration
* * * * *

Food and Drug Administration (which regulates research on new drugs and medical devices)

4. *Scope of This Report.* As a result of the foregoing deletions, reorganizations, and modifications, 17 Federal departments or agencies have been identified that currently conduct or support biomedical or behavioral research with human subjects that comes within the definition provided by 45 CFR Part 46. Three of those agencies have separate subsidiary components that operate under their own policies or regulations for the protection of human subjects: the Department of Defense (the Army, the Navy, and the Air Force); the Department of Justice (the Bureau of Prisons, and the Office of Justice Assistance, Research, and Statistics); and the Department of Transportation (the U.S. Coast Guard, the Federal Aviation Administration, the Federal Highway Administration, and the National Highway Traffic Safety

Administration). Thus, there are a total of 23 separate Federal entities that conduct or support biomedical or behavioral research with human subjects whose rules and procedures are scrutinized in this Report.

The Commission has also chosen to review the rules and procedures of the Food and Drug Administration (FDA), within the Department of Health and Human Services. Under the Federal Food, Drug and Cosmetic Act, the FDA regulates research on new drugs, biologicals, and medical devices. Its basic regulatory scheme was brought into conformity with the regulations governing research conducted and supported by the new rules issued simultaneously with the 1981 HHS revisions. The FDA's method of implementation and monitoring differs from that applicable to grant and contract aspects of HHS, as noted in Chapter Three.

Draft summaries of the regulations and policies of each of these Federal entities were sent to the head of the appropriate departments or agencies in June 1981 for review. Agency heads were asked to confirm the accuracy of the summaries or to indicate necessary modifications. (Agency heads were also asked to provide a description of their procedures for monitoring the implementation of the regulations and investigating and resolving complaints. That material is discussed in Chapter 3 of this Report.) The agencies were also asked for documentation to justify significant changes. The material provides the basis for the description and analysis of this chapter.

B. *The Regulatory System Government Research Conducted or Supported by the Department of Health and Human Services (HHS).* Since 1966, when the Surgeon General issued an order requiring institutional review to assure ethical acceptability of research with human subjects supported by Public Health Service (PHS), the PHS policies and procedures have served as a model for other Federal agencies. The history and development of those policies (now embodied in (HHS) regulations) have been amply chronicled before in the National Commission's report on IRBs and elsewhere, (12) and need not be repeated here.

The National Commission found in 1978 that "of the 19 other Federal entities that have formal policies or regulations governing research with human subjects, 17 adopt HEW standards and procedures to a substantial degree, and most of these cite HEW regulations or policy as a reference." (13) Moreover, the National

Commission reported that of the departments and agencies lacking formal policies for the protection of human subjects, all but two (the Law Enforcement Assistance Administration and the Department of Housing and Urban Development) conduct or support only surveys, questionnaires or record reviews—activities not universally considered “research with human subjects”.

The survey conducted for this report yielded similar results, both on uniformity and on the preeminence of the HHS regulations. In order to understand the extent of uniformity of regulations government-wide, however, it is necessary first to describe the policies and procedures of HHS. (14) The regulations of the other agencies may then be compared to the HHS prototype.

1. *Applicability.* The HHS regulations (45 CFR Part 46), as revised January 26, 1981, apply to all research involving human subjects supported or conducted by HHS, with a few explicit exemptions. “Human subject” is defined as a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) individually identifiable private information.

The following are exempt from the regulations:

(a) Research conducted in established or commonly accepted educational settings, involving normal educational practices;

(b) Research involving the use of educational tests if identities of subjects are not recorded;

(c) All research involving survey or interview procedures when the respondents are elected or appointed public officials or candidates for public office;

(d) Research involving survey and interview procedures or observation of public behavior, unless (1) the subject's identities are recorded and (2) the information, if known outside the research, could reasonably place the subject at risk of legal liability, or be damaging to the subject's employability of financial standing and (3) the research deals with sensitive aspects of the subject's own behavior;

(e) Research involving the collection or study of existing data documents, records, pathological or diagnostic identifies.

2. *Review Procedures.* Each institution that conducts research covered by the regulations must submit an assurance to the department describing its procedures for complying with the requirements of HHS regulations (45 CFR Part 46). The assurance must contain a statement of principles the institution will follow in discharging its responsibilities for protecting human subjects in research conducted at or sponsored by the institutions (e.g.,

Nuremberg Code, Helsinki Code), regardless of source of funding. Further, the assurance must identify one or more Institutional Review Boards (IRBs) established by the institution to review and approve all research involving human subjects covered by the HHS regulations. An IRB must have at least five members of varying backgrounds, sufficiently qualified to review research proposals and activities commonly conducted by the institution, and include at least one member “whose primary concerns are in a nonscientific area” and at least one individual unaffiliated with the institution. The members of an IRB may not all be of the same gender, nor may the members come from only one professional group. IRB members must be identified to HHS by name, earned degrees, representative capacity, professional (or other) experience, and relationship with the institution.

The assurance must also describe IRB procedures: (1) For conducting initial and continuing review of research proposals and activities, (2) for determining which projects require review more often than annually and which require verification from sources other than the investigators that no material changes have occurred since previous IRB review, (3) for assuring that scientists report any proposed changes in a research activity to the IRB, and for assuring that changes are not initiated without IRB sanction except as needed to eliminate immediate hazards to subjects, and (4) for reporting to HHS unanticipated problems involving risks to subjects or others and any serious or continuing noncompliance by investigator with the HHS regulations or with the requirements and determination of the IRB.

3. *Review Standards.* No HHS funds may be awarded for the conduct of research with human subjects unless an approved IRB certifies that the following conditions are satisfied:

a. The risks to subjects are minimized by using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;

b. The risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and to the importance of the knowledge that may reasonably be expected to result;

c. The selection of subjects is equitable;

d. Informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with, and to the extent required by, the regulations;

e. Consent will be appropriately documented;

f. Where appropriate, the research plan makes adequate provision for monitoring the data collected to insure the safety of subjects;

g. Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and

h. Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

4. *Consent Provisions.* The information provided to prospective subjects or their representative must be in language they can understand. Consent should be sought only under circumstances that provide the prospective subject or the subject's representative with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. No informed consent, whether oral or written, may include any exculpatory language “through which the subject is made to waive or appear to waive any legal rights or release the investigator, the sponsor, the institution or its agents from liability for negligence.” (15) A copy of the information provided, as well as the signed consent form (if any), must be given to the subject or the subject's representative.

The following elements must be disclosed to subjects for valid informed consent:

a. An explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

b. A description of any reasonably foreseeable risks or discomforts to the subject;

c. A description of any benefits to the subject or to others which may reasonably be expected from the research;

d. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

e. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

f. For research involving more than minimal risk, an explanation as to whether any compensation will be made and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

g. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

h. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional information must be provided, when appropriate:

a. A statement that the particular treatment or procedure may involve risks to the subject (or to an embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

c. Any additional cost to the subject that may result from participation in the research;

d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

e. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

f. The approximate number of subjects involved in the study.

The regulations include additional protections and special procedures for research involving prisoners and for research involving pregnant women, the human fetus, and human in vitro fertilization. (Details are provided in Appendices A and B.)

5. *Sanctions.* If an institution or principal investigator is found to have "failed materially" to protect human subjects, the Secretary may terminate or suspend current funds or withhold further HHS research funding (whether or not HHS funds were involved in the research in which the failure to protect subjects occurred).

C. *Summary and Analysis of the Regulations of Other Federal Agencies.* The HHS regulations summarized above provide the gauge against which to measure the regulations and policies of the other Federal agencies.

1. *The Degree of Uniformity: Minor Variations.* Seventeen of the Twenty-two Federal entities other than HHS that conduct or support bio-medical or behavioral research involving human subjects have regulations or policies that substantially conform with HHS regulations (see Table 4). That is, they require review and approval of proposed research by an IRB or similar committee, using standards for review and consent provisions that mirror, or are similar to, those in the HHS regulations.

The regulations of two of these seventeen Federal entities, however, apply to some but not all of the research

conducted or supported by those agencies. The Department of Education's regulations for the protection of human subjects apply to contracts, but not to grants. NASA requires IRB review for intramural research but not for extramural research.

Among the agencies that generally conform to 45 CFR 46, however, there are minor differences that complicate the work of IRBs. For example, the Army, Navy and Air Force require that IRBs determine that prior animal studies have been conducted, where possible, prior to approving human studies. They also require IRBs to determine that facilities where the research will be conducted are adequate to handle foreseeable injuries. The Consumer Product Safety Commission has the same requirement. The National Highway Traffic Safety Administration requires IRBs to review research involving cadavers; HHS and all agencies that follow 45 CFR Part 46 limit review requirements to research involving *living* human subjects.

TABLE 4.—AGENCY CONFORMITY WITH HHS REGULATIONS (45 CFR PART 46)—CONTINUED

Department or agency	Re-quires IRB or similar com-mittee	Review stand-ards similar to HHS	Con-sent provi-sions similar to HHS	Notes
Dept. of Transportation:				
Coast Guard.....	X.....	X.....	X.....	
Federal Aviation Administration.	X.....	X.....	X.....	
Federal Highway Administration.	X.....	X.....	X.....	
Nat'l Highway Traffic Safety Admin..	X.....	X.....	X.....	
Environmental Protection Agency.	X.....	X.....	X.....	
National Aeronautics and Space Admin..	X.....	X.....	X.....	IRBs required only for intramural re-search.
National Science Foundation.	X.....	X.....	X.....	
U.S. Intern'l Development Coop. Agency.	X.....	See notes.	See notes.	(45 CFR Part 46) provides guid-ance.
Veterans Administration.	X.....	X.....	X.....	

TABLE 4.—AGENCY CONFORMITY WITH HHS REGULATIONS (45 CFR PART 46)

Department or agency	Re-quires IRB or similar com-mittee	Review stand-ards similar to HHS	Con-sent provi-sions similar to HHS	Notes
American National Red Cross.	X.....	X.....	X.....	
Central Intelligence Agency.	X.....	X.....	X.....	
Consumer Product Safety Commission.	X.....	X.....	X.....	
Department of Agriculture.	X.....	X.....	X.....	
Department of Commerce.	X.....	X.....	X.....	
Department of Defense.				
Army.....	X.....	X.....	X.....	
Navy.....	X.....	X.....	X.....	
Air Force.....	X.....	X.....	X.....	
Department of Education.	X.....	X.....	X.....	IRBs are required for con-tracts but not grants.
Department of Energy.	X.....	X.....	X.....	
Department of Housing and Urban Devel..	See Notes			Independ-ent review when more than limited potential of harm.
Department of Justice.				
Bureau of Prisons.	X.....	X.....	X.....	
Office of Justice Assist., Research, and Statistics.	See notes.	See notes.	See notes	Employs advisory boards; protects confi-dentiality.

Agencies also have a variety of rules regarding special classes of subjects. The Army has adopted special protections (similar to recommendations of the National Commission) for the participation of children, prisoners, and the mentally disabled in Army research activities. The Navy and the Air Force simply exclude prisoners and the mentally disabled; the Air Force also excludes children. The Army (but not the Navy or the Air Force) specifically prohibits the participation of prisoners of war. The Department of Agriculture excludes pregnant or lactating women from certain kinds of studies; the Air Force excludes females "unless there is reasonable assurance of no concomitant pregnancy that would place the fetus at risk and if methods adopted for contraception do not place the female subject at increased risk without complete disclosure to the female subject."

There are also minor variations regarding what must be disclosed to subjects in the consent process. A number of agencies require information regarding the Privacy Act and the extent to which research data will (or can) be kept confidential; others have no such requirement. The Office of Justice Assistance, Research, and Statistics (OJARS) of the Department of Justice supports research involving surveys, questionnaires and observational data which may deal with sensitive topics such as drug or alcohol use and illegal

conduct. With research of this kind, the significant risk to subjects is the possibility of a breach of confidentiality. Therefore, OJARS has extensive regulations that protect the confidentiality of data even from subpoena. In place of IRBs, advisory boards meet several times a year with project staff to review the progress of the research.

The Bureau of Standards provides a completely different description of informed consent. The Bureau's definition (which, among other features, equates "informed consent" with the document that records the agreement reached by investigator and subject) includes:

(a) Information on all features of the research that are likely to influence the subject's willingness to participate, such as risk of injury or possibility of embarrassment, discomfort, or emotional stress;

(b) Explanation of other aspects of the research about which the subject inquiries which is consistent with maintaining the validity of the research and

(c) An agreement, to be signed by the subject and the principal investigator, which states the responsibilities of each and the relevant features of the research and which makes explicit the right of the subject or the principal investigator to terminate the subject's participation at any time without incurring any legal liability.

The Bureau of Standards also adds that subjects must be free from undue coercion and undue pressure as well as from the inducement of excessively high rewards (monetary or otherwise). The Bureau of Prisons limits incentives for participation to soft drinks and snacks given at testing time. The Navy requires that the sponsor of the research be identified and NASA requires that subjects be informed if, for any reason, withdrawal during the conduct of the research is not an option (e.g., because it would be unwise, dangerous, or impossible).

Administrative details also vary among agencies. The Consumer Product Safety Commission and the Navy both require that all consent forms be submitted to the agency along with the research proposal; most agencies apparently do not. The Navy requires that documentation of IRB approval be signed by every member of the IRB most agencies (including HHS) accept the signature of the chairman. Most agencies require that IRB records pertaining to research activities be retained for a period of 3-5 years following completion of the research. The Navy requires that such records be retained permanently, and the Air Force requires that copies of all such records be forwarded to the Air Force upon completion of the research.

Clearly, IRBs that review hundreds of research proposals per year, many of which may be submitted to (and even funded by) more than one agency, need to have copies of the regulations of each agency at hand in order to assure compliance with these varied provisions. Furthermore, the regulations are constantly changing. Several Federal departments or entities are now in the process of developing new regulations for the protection of human subjects, including the Departments of Defense and of Transportation, which are formulating department-wide standards, the Department of Agriculture, which is bringing its policies into conformity with the most recent HHS revisions, and the Bureau of Prisons, within the Department of Justice, which is currently drafting new regulations for the protection of inmates as research subjects that generally conform to the HHS regulations.*

2. Agencies Without Formal Regulations. Four Federal entities have no formal regulations specifically for the protection of human subjects involved in research. Three of these four are components of the Department of Transportation (DOT). The Department reports that it is in the process of developing department-wide regulations for the protection of human subjects; however, in 1977 DOT reported to the National Commission that it was then engaged in such an effort. Until the new regulations, which are to conform with HHS regulations, are implemented, three of the four components of the Department lack rules specifying their means of protecting human subjects, while the remaining DOT agency (The National Highway Traffic Safety Administration) has rules that parallel the HHS regulations.

The Department of Housing and Urban Development (HUD) is the only other Federal agency conducting research with human subjects that does not have formal regulations for the protection of human subjects. In HUD's initial response to the Commission's inquiry, Donna Shalala (Assistant Secretary for Policy Development and Research) stated that except for a study co-sponsored with HEW, involving the testing of an aversive additive in paint to deter children from eating paint chips, HUD "has never sponsored any human subject or biomedical studies." (16) Moreover, Dr. Shalala challenged the statement in the National Commission's report that HUD's "housing allowance

experiment" constituted research with human subjects. (17)

The definition of "research with human subjects" and the possible inclusion of HUD's activities within such a definition was explored more fully with Dr. Shalala and her staff at hearings before the Commission in July 1980 and in subsequent correspondence. The result was HUD's acknowledgement that some of its research may present risk to human subjects. The Department has now developed a departmental memorandum that requires internally generated projects as well as "unsolicited research proposals" involving risk to human subjects to be approved by an independent review board. (18) Certification of the board's approval of the research design, as well as a description of the review board's procedures and membership, must be forwarded with the proposal (see Appendix B). The memorandum does not set forth the standards of review nor require IRB approval at the home institutions of those carrying out human research with HUD funds. Moreover, the memorandum does not supply the fundamental analysis needed to establish the differences and similarities between the concerns that motivate regulation of biomedical and behavioral research and those that are appropriate in the case of "social policy experiments" of the type supported by HUD. (19)

D. Conclusions. Concern for the adequacy and uniformity of the rules for the protection of human subjects is raised most immediately by the Federal entities that currently lack procedures and standards that conform with HHS regulations. A lack of internal consistency occurs in two agencies that apply HHS policies and standards to some, but not all, research conducted under their auspices: the Department of Education, and NASA. The Commission believes that such regulatory anomalies should be corrected. Further, the policy statements of several agencies that merely refer to HHS regulations "for guidance" should provide more explicit directives.

The Commission believes that achieving uniform regulations throughout the Federal government is an important goal. The high costs of nonuniform rules were forcefully articulated in the findings of the Commission on Federal Paperwork

If other agencies are permitted to deviate from or even to paraphrase the NIH/HEW regulations (45 CFR Part 46), the result will be unnecessary duplication of reporting, recordkeeping, and other activities on the part of the Government as well as the

*The Department of Justice wishes to note that final regulations were published October 1, 1981 (46 FR 48574).

organization involved. Some agencies, including the National Science Foundation and the Department of Agriculture, have accepted the NIH/HEW regulations by reference, without finding it necessary to paraphrase, interpret, or expatiate. Others, even while recognizing HEW's precedence, phrase their regulations so as to require conformity to their own policies. This creates conflict if future changes in their policies and in HEW's are not identical and simultaneous. In addition, it requires multiple submission of general assurances, which are frequently intricate and lengthy documents and which must be updated periodically. (20)

The achievement of uniform Federal regulations on the protection of human subjects appears to be an achievable objective, since the present HHS regulations provide common ground which most of the affected agencies can apparently accept. Moreover, HHS regulations permit sufficient flexibility for agencies whose involvement with research is limited. For example, the HHS requirements on IRB review and consent for the collection of personally identifiable information might be supplemented by OJARS if it believes that more extensive safeguards are needed to protect the confidentiality of the sensitive data that are often involved in its research projects. Similarly, the activities of the Department of Housing and Urban Development would not be impeded by inappropriate requirements since it supports primarily social science research, much of which is now exempt from HHS regulatory requirements. If any of the research funded by HUD is of the sort to which HHS regulations apply, however, it should be subjected to IRB review using the standards set forth in those regulations. The three remaining Federal entities that appear to have less than fully adequate policies for the protection of human subjects are part of the Department of Transportation which after four years continues to report that it is in the process of developing department-wide regulations to conform with those of HHS.

In summary, the President's Commission has identified the following problems with respect to adequacy and uniformity of Federal rules governing research with human subjects: (1) Lack of uniformity among component parts of a department or agency (the Department of Defense, the Department of Justice, and the Department of Transportation); (2) inconsistency with respect to applicability of regulations to all categories of research within a single Federal entity (the Department of Education, and NASA); and (3) lack of complete uniformity among all Federal departments and agencies.

The Commission believes that all research involving human subjects that is supported by public monies should conform to a uniform "core" of regulations. The provisions announced by the Department of Health and Human Services earlier this year and codified in 45 CFR Part 46 provide an acceptable starting point of any attempt to achieve uniformity. The Commission notes, however, that many of the variations adopted by other agencies appear sensible and should be reviewed for possible incorporation in the regulations of HHS which, thereafter, should become the standard for all research regulated, conducted or supported by Federal agencies or by direct appropriations from Congress. Specific recommendations for improving the adequacy and uniformity of Federal regulations governing research with human subjects appear in Chapter 5.

Footnotes

(1) The statutory definition of "Federal agency" excludes the U.S. Courts; therefore, the Commission did not review the activities of the Federal Judicial Center regarding research or experimentation in the justice system. The Commission notes, however, that the Federal Judicial Center has recently received a report on this subject, with recommendations, from an advisory committee on Experimentation in the Law, U.S. Government Printing Office, Washington (1981).

(2) National Commission for the Protection of Human Subjects, *Report and Recommendations: Institutional Review Boards*, U.S. Government Printing Office, Washington (1978) [hereinafter cited as IRB Report].

(3) The Departments of Labor and of the Interior reported in 1976 that they do not conduct or support research with human subjects. See letters to Charles U. Lowe, M.D., from John T. Dunlop, Secretary of Labor (October 1, 1975) and from Rayston C. Hugkes, Assistant Secretary of the Interior (October 14, 1975).

(4) See letters to Barbara Mishkin from: Robert B. Minogue, Director, Office of Nuclear Regulatory Research (July 23, 1981); S. Dillon Ripley, Secretary, Smithsonian Institution (April 2, 1980); William F. Bolger, Postmaster General (April 4, 1980); and James B. Lancaster, Assistant Director for Administration and Finance, ACTION (April 11, 1980 and December 31, 1980).

(5) Five Federal entities that appeared in the 1977 report of the National Commission appear under different names in this report due to reorganization. The Civil Service Commission is now the Office of Personnel Management; it conducts only surveys and questionnaires. The Agency for International Development (AID), formerly part of the Department of State, has become the International Development Cooperation Agency. The Education division of the Department of Health, Education, and Welfare became a separate Department of Education, and HEW became the Department

of Health and Human Services. Finally, the Law Enforcement Assistance Administration (LEAA) is now part of the Office of Justice Assistance, Research, and Statistics—still within the Department of Justice.

(6) Letter (March 25, 1980) from Louis Nunez, Staff Director, U.S. Commission on Civil Rights.

(7) Letter (July 31, 1981) from Joseph C. Brown, Acting Director of Personnel, U.S. Department of Commerce.

(8) Memorandum from Acting Associate Administrator for Research and Development, included as attachment to letter (May 27, 1980) from Martin Convisser, Director, Office of Environment and Safety, Office of the Secretary, DOT.

(9) Letter (April 28, 1980) from Robert W. White, Administrator, National Research Council, National Academy of Sciences.

(10) 22 U.S.C. 278, 45 Stat. 491 (1928) as subsequently revised.

(11) Personal communication (October 2, 1981) with William Doak, Executive Officer, Fogarty International Center.

(12) Briefly summarized, the HHS regulations derive from Public Health Service review requirements initiated in 1966 by the Surgeon General. These were expanded and elaborated in the 1971 Institutional Guide to DHEW Policy on Protection of Human Subjects, a description of the grants administration policy which required initial review of proposed research by committees at each institution to assure that the risks were justified by the anticipated benefits or the importance of the knowledge to be gained, and that informed consent would be obtained by methods that are adequate and appropriate. (The required elements of informed consent were defined and explained.) Continuing review of ongoing projects was also required.

Proposed regulations were published in 1973 and final rules were issued in 1974 which converted the earlier grants administration policies into regulations applicable to all research conducted or supported by HEW. An important difference between the new regulations and the old policy was that whereas formerly the review requirement attached only to research activities deemed (by the principal investigator) to present risk to human subjects, the new regulations applied to all research with human subjects, leaving it to the review boards to determine the extent of any risk involved.

The proposal and promulgation of regulations by HEW took place against the backdrop of considerable Congressional interest in 1973-74. During this period, hearings were held on legislation intended to address problems with human experimentation that had been the subject of recent publicity, such as the Tuskegee Syphilis Study sponsored by the Public Health Service between 1932 and 1972. The Congressional attention culminated in Title II of the National Research Act of 1974 (Public Law 93-348), which not only required that research institutions have IRB's but also established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, within HEW, to

study the ethical principles underlying research and to recommend means of protecting human subjects.

Between 1975 and 1978 the National Commission issued a series of reports and recommendations for amendments to the 1974 regulations, some of which have now been adopted by HHS. The most recent revisions to the regulations (published in January 1981) largely adopted the National Commission's recommendations regarding Institutional Review Boards; earlier revisions incorporated recommendations regarding research with the human fetus and research involving prisoners.

Further descriptions of the history and development of HHS regulations may be found in: Bernard Barber, *Informed Consent in Medical Therapy and Research*, Rutgers University Press, New Brunswick (1980) at 41-45; Nathan Hershey and Robert D. Miller, *Human Experimentation and the Law*, Aspen Systems, Rockville (1976) at 1-11; Robert J. Levine, *Ethics and Regulation of Clinical Research*, Urban and Schwarzenberg, Baltimore (1981) at 207-210. See also an extensive history in Chapter Two of The President's Commission's forthcoming report on *Compensating for Research Injuries*.

(13) IRB Report, *supra* note 2, at 94.

(14) A more detailed description of HHS policies and procedures appears in Appendix B to this report; Appendix A contains the full text of the regulations.

(15) 45 CFR 46.116.

(16) Letter (March 28, 1980) from Donna E. Shalala, Assistant Secretary for Policy Development and Research, Department of Housing and Urban Development.

(17) IRB Report, *Supra* note 2, at 96, 100-101.

(18) HUD Policy Memorandum (February 21, 1981) from Arthur S. Newburg, Director, Office of Management and Program Control, to "All PD&R Staff" attached to letter (February 24, 1981) from Mr. Newburg to Alexander M. Capron.

(19) See, e.g., Alice M. Rivlin and P. Michael Timpane, eds., *Ethical and Legal Issues of Social Experimentation*. The Brookings Institutions, Washington (1975); Advisory Committee on Experimentation in the Law, Federal Judicial Center, *Experimentation in the Law*, U.S. Government Printing Office, Washington (1981).

(20) *A Report of the Commission on Federal Paperwork: Education*, U.S. Government Printing Office, Washington, D.C. (April 29, 1977) at 40.

Chapter 3: The Adequacy and Uniformity of the Regulations' Implementation

In evaluating the implementation of regulations governing research with human subjects, the Commission determined that its most appropriate focus would be not on the IRBs themselves but on the procedures of Federal agencies and on the knowledge these agencies have about the implementation of their rules for protecting human subjects. The Commission reached this conclusion for

several reasons. First, it had neither the statutory life nor the budget to undertake an empirical examination of IRBs comparable to the two million dollar study supported by the National Commission for the Protection of Human Subjects from 1975 to 1977. More important, that study is recent enough so that its findings continue to have a great deal of cogency. One of those findings was that IRBs were not consistently implementing Federal policy particularly with respect to the adequacy of consent documents and IRB involvement after initial review of research proposals. Consequently, in making its recommendations on IRBs, the National Commission stressed the need for the Department of Health, Education, and Welfare (as it was then known) to engage in vigorous "compliance activities" to determine how well its regulations were being implemented and to supply necessary education, encouragement or punishment. (1)

By focusing on implementation from the Federal side, the Commission intends also to encourage an examination of some basic issues about the regulation of human research. The ambiguous nature of the IRB system for regulating human research has never been resolved; indeed, it has seldom been addressed. To answer the simple question, "What is an IRB," one must confront the tension that is so often found with organizational hybrids. Or, to borrow from the fable, the IRB is like an elephant being described by blind men each of whom perceives it differently. The central difference in perception is between a research institution's vantage point and that of the Federal government. In the view of the former, its IRB is a local body; moreover, it is an outgrowth of the traditional informal mode of "peer review" that characterizes collegial, academic settings. Yet from the Federal viewpoint—and as a matter of historical fact (2)—the IRB today is a local body established under, and responsive to, Federal rules; in effect, it performs delegated functions under the supervision of Federal officials. (3)

Thus, while past descriptions have emphasized the institutional aspects of the IRB system it seemed appropriate for the Commission to begin its examination of the "adequacy and uniformity of the implementation of the regulations" by focusing on the Federal aspects. In taking up this specific statutory mandate, the Commission does not want to be understood as denying the importance of trust in the IRB system nor as pointing inevitably toward the displacement of such trust by formal review mechanisms. Rather, the

Commission began its study of "the implementation of the regulations" by asking responsible officials to report on their means for knowing that the authority delegated to local institutions was being exercised so as adequately to protect human subjects. The result of this initial inquiry was the finding that most agencies, including the grant and contact wings of HHS, have only limited first-hand knowledge of the actual performance of IRBs. The paucity of systematic data was acknowledged by responsible officials, who described for the Commission efforts that have recently been made or that are planned to provide a better ongoing picture of the regulations, actual application. A richer and more detailed understanding of "the implementation of the regulations" came from a second source, namely the Commission's examination of the response of Federal agencies to several reports of regulatory violations or of other serious misconduct by grantees and contractors. While the few instances of alleged misconduct and institutional or Federal failings are not regarded by the Commission as representative of contemporary research or of the functioning of the system to protect human subjects, the Commission is acutely aware of the vulnerability of the present system to (probably unjustified) adverse judgements in the absence of systematic data that would allow the "problem cases" to be viewed in proper perspective.

The Commission sought information not only from the relevant Federal agencies but also through testimony from IRB members and institutional administrators, papers prepared under contract, conferences attended by members of its staff, and recent articles that have appeared in the literature. (In this discussion, as in the previous chapter, the primary focus will be on the policies and procedures of HHS with which other Federal agencies will be compared and contrasted.)

A. *Do Federal Agencies Know How IRBs are Performing?* Within HHS, two methods are used for obtaining information about IRBs. One approach was developed in NIH for grantee institutions; the other was developed by FDA for research in support of new drug applications. The former approach relies largely on a promise of faithful execution of certain regulatory responsibilities by those at local institutions who have agreed to undertake those responsibilities; the FDA system relies primarily on a system of routine inspections performed during or after the conduct of the research.

1. *The Negotiation of "Assurances" by HHS.* The procedures set forth in 45 CFR Part 46 require all grantee institutions to provide written assurance that they will comply with the HHS regulations to protect human subjects. An institution's assurance of compliance must be approved by the Office for Protection from Research Risks (OPRR) within the Office of the Director, NIH. The information contained in an assurance provides the basis on which a determination is made that the composition and operating procedures of the institution's IRB meet regulatory requirements and that the institution is, therefore, eligible to receive HHS grants and contracts for the conduct of research involving human subjects. In the wake of the revisions to the regulations that took effect in July 1981, new assurances of compliance must be negotiated by all institutions. This process will take a year or more. Indeed, the Director of OPRR reports that negotiations for new assurances implementing the regulations issued May 30, 1974, began in mid-1975 and took more than two years to complete. (4)

Although the process of providing an assurance of compliance with the regulations might ideally provide an occasion for careful consideration by institutions of how they will meet their responsibilities toward human subjects, some aspects of the manner in which new assurances are being negotiated decrease the likelihood that grantee institutions will take advantage of the opportunity to review their responsibilities.

A sample assurance (dated July 3, 1981, rev. August 11, 1981) has been distributed by HHS to each institution having a general assurance on file with HHS under the old regulations. OPRR had described plans to offer institutions a variety of model formats for re-negotiating their general assurances; (5) instead, one sample was provided. In order to affirm its intent to comply with 45 CFR Part 46 an institution following this 22 page document would have to recite each individual section and subsection of the regulations almost in their entirety. (6) This recitation has the effect of a litany, rather than focusing an institution's thinking on the specific administrative and structural arrangements through which it will carry out the commitment to abide by 45 CFR Part 46. Not only is such reiteration unnecessary—a one sentence promise to comply with all regulatory requirements would serve the same function—but it may discourage thoughtful self-scrutiny and actual compliance.

OPRR has explained its choice of format for negotiating assurances by stating that when such a detailed assurance is distributed within an institution "the relevant parts of the regulations would [thereby] be in the hands of the individuals with responsibility for complying with them." Yet this laudable objective is defeated by the chosen format. The sample assurance makes oblique cross references to the regulations; this would make it necessary for anyone expecting to understand the assurance to have a copy of the regulations in hand as well. (7)

The Commission realizes that while another approach might have been preferable, the single sample assurance is already in use. Moreover, the Department has told the Commission that it shares the Commission's concern that the negotiation of new assurances by all research institutions be regarded as an important opportunity for self-examination and appropriate ingenuity on the part of research institutions as they develop administrative mechanisms responsive to their particular needs. The effort devoted to this can yield great dividends in institutional sensitivity to, and readiness to provide effective protection for, the subjects of research.

2. *The Steps Taken by OPRR to Improve Implementation.* A more serious limitation of the assurance procedure as it presently exists is its emphasis on providing only a prospective picture of the process of research review that an institution will follow. Recognizing that this provides very little information about the actual performance of the IRB, OPRR has taken several steps. The first, which has been in existence for some time, is to respond to any serious problems that come to the office's attention. Mechanisms exist to bring to OPRR's attention some problems in IRB operations, though they are far from complete or systematic. In any case, most of the "problems" uncovered have not proven to be serious; most are disposed of through a phone call to the institution or through an exchange of correspondence.

To increase its awareness of the adequacy of IRB functioning, OPRR has instructed each "study section" (initial review groups which advise the Institutes on the scientific merit of applications for grants and contracts) to evaluate the investigators' descriptions of six factors bearing on the protection of human subjects (see Appendix B). The "Summary Statement" for each research application, prepared by the executive secretary of the study section,

provides a means for the section members to express any concerns about the description of risks, the adequacy of protection against risks, and the balance between risks and benefits. If problems relating to the protection of human subjects are identified by a study section, they are called to the attention of the Institute's advisory council or board when the project is under consideration for funding. OPRR plays a coordinating role in resolving any such problems before HHS funds are permitted to be expended.

OPRR reports that it is planning to systematize the information available from the "Summary Statements" into a data base which could be used to evaluate the IRB system in general and the performance of each IRB in particular. The Commission hopes to learn more about these efforts as part of its work on its next *Biennial Report*. The sensitivity of such a system is a matter of special concern; for example, will it be able to differentiate serious problems from clerical errors on the part of an investigator or IRB, or to separate those instances in which concerns raised by study sections that are found to be "justified" from those which are merely "differences of opinion" between a study section and a conscientious IRB?

Study section review does not provide OPRR either with general information about IRB functioning (since each study section looks only at the "end product" of IRB action in the cases it is reviewing and not at overall IRB activities) or with particular information about the manner in which an IRB follows up on research once approved. Some first-hand information is available to OPRR, however, through various site visit mechanisms. Although OPRR itself has conducted only a few such on-site inspections, the routine institutional site visits conducted by scientific review groups in the General Clinical Research Centers Program (which is operated by the Division of Research Resources at NIH) include meetings with IRB members and review of IRB practices. Summary reports of those site visits are viewed by OPRR; none has triggered further review of an IRB by that Office. (8)

In responding to the National Commission's recommendation of "compliance activities," such as IRB audits and site visits, the Department in August 1979 said that Congressional action would be unnecessary on this point, since such practices were already part of HHS procedures. As already described, systematic efforts in the direction of "compliance" (as opposed to "assurance") mechanisms are still far

from complete. Indeed, representatives of the Department have explained that steps toward auditing IRB performance which were described to the Commission in May 1980 remain in the planning stages because OPRR's limited resources are largely devoted to the regular process of reviewing all NIH research proposals for compliance with the regulatory requirements and to the negotiation of new assurances under the regulations promulgated in January 1981.

Although OPRR has not yet instituted regular site visits, it reports that some site visits have been conducted. Yet, since well-defined procedures for auditing IRBs are lacking, OPRR had difficulty in giving a complete picture of the site visits it has conducted. In a letter to the Chairman of the Commission in May 1980, the Director of OPRR defined site visits to include "examination of IRB minutes and interviews with the chairmen and members of the IRB, administrative staff, and research investigators" and reported that OPRR carried out two such site visits in Fiscal Year 1979 and three in Fiscal '80. (9) The Deputy Director of OPRR testified in November 1981, however, that his office had conducted a total of 80 site visits between 1975 and 1981, although many of these were "of a routine nature to assist institutions in complying with the regulations in circumstances of special complexity (cooperative research projects of a large scale) or to provide guidance and information on HHS policy and to discuss general problems of IRB operation." (10) Clearly, the November 1981 statement reflects a very different (i.e., more expansive) notion of what constitutes a "site visit." Indeed, the OPRR officials agree that the number of such visits that could properly be termed "audits" of IRB operations was probably "very small," and that few if any of those conducted were in response to allegations of serious problems or to reports from FDA inspection teams, or from the reports of NIH study sections' concerns. (11) The additional contacts with research institutions do, however, provide OPRR with "extensive general information about IRB functioning even though the information lacks the precision that might come from formal IRB audits and site visits (in the narrow sense)." (12)

In order to mount effective "compliance activities," OPRR will need a schedule of, and defined procedures for conducting, either routine or "spot" audits of IRBs. Such steps would permit genuine "site visits" to be readily distinguished from visits to provide guidance or information, on the one

hand, and from extraordinary investigations of alleged misconduct, on the other. In order to help HHS obtain more than sporadic glimpses of the performance of IRBs, the Commission is working with OPRR (and the FDA) to develop means of obtaining information about IRBs that are both economical and likely to promote the system's highest aspirations. (Further information on this point is contained in Chapter Four.)

3. *Food and Drug Administration.* An approach that is very different from that of NIH is followed by the Food and Drug Administration (FDA), even though it is also a component of the Public Health Service within HHS. The FDA regulates research, regardless of the source of funding, that is performed in support of applications for approval of new drugs, biologicals, and medical devices to be sold in interstate commerce. Research of this type often presents the greatest need for protection of human subjects.

With the 1981 revisions, the FDA regulations on research involving human subjects have become almost identical to those of 45 CFR Part 46, with one important exception (and several minor ones). The FDA does not require prior agency approval of the composition and procedures of IRBs. Instead, FDA makes site visits ("inspections") to approximately 400 IRBs annually to monitor compliance with the requirements of its regulations. *Routine* inspections include initial inspections and subsequent inspections every 2-3 years for those IRBs found to be in full compliance, or within 2 years for IRBs found to have only minor deficiencies. Directed inspections are conducted within 6 months after a routine inspection reveals serious noncompliance with the regulations or when FDA receives information that calls into question the practices of a particular IRB. These site visits are built

around the "paper trail" of studies of particular drugs and devices selected by the FDA inspectors. In other words, the performance of the institutions and its IRB are judged on the basis of its documentation of compliance with the regulatory requirements as applied to one or more investigational drugs or devices. (See Appendix B for further description.)

Thus, the FDA does not necessarily know whether an IRB is properly constituted (or even that it exists) unless or until a routine inspection is conducted or some problem arises that triggers an investigation "for cause." (13) The site visits do provide FDA with a means of evaluating the performance of IRBs although, as described in Appendix F, both the quality of the inspections and the communications of findings to OPRR deserve further attention.

4. *Other Federal Agencies.* Outside HHS, of the 17 Federal agencies that have adopted the IRB (or similar committee) as a mechanism for assuring the protection of human subjects, 12 report that they rely entirely on an agency review of IRB membership and an assurance of compliance similar to that required by HHS in its approval of institutional assurances (see Table 5). Indeed, six of these agencies require grantees and contractors to have an assurance approved by HHS: the CIA, Department of Commerce, Department of Education, National Highway Traffic Safety Administration (a component of the Department of Transportation), the Environmental Protection Agency, and the National Science Foundation. Eleven accept either an assurance approved by HHS or their own review of IRB composition and procedures. Of these, the Red Cross relies on a system of general assurances, but reports that many of the IRBs have been inspected by the FDA.

TABLE 5.—AGENCY PROCEDURES FOR MONITORING PERFORMANCE OF EXTRAMURAL IRBS

Department or Agency	Requires IRB or similar committee	Prior approval of IRB compositions, etc.	Conducts site visits	Notes	
				To monitor	For cause
American National Red Cross.	(¹)				Supports no extramural research.
Central Intelligence Agency....	•	•	(¹)		Site visits are made "where applicable". Agency must approve all consent forms.
Consumer Product Safety Commission.	•	•			
Department of Agriculture.....	•	•			
Department of Commerce (Bureau of Standard).	(¹)				Supports no extramural research.
Department of Defense					
Army.....	•	•	(¹)		Site visits prior to approving each contract.
Navy.....	•	•			
Air Force.....	•	•			
Department of Education.....	•	•			
Department of Energy.....	•	•		•	IRBs are required for contracts but not grants.
Department of HHS:					
NIH Grants and Contracts...	•	•		•	
FDA-Regulated tests.....	•	•	•	•	400 site visits are conducted each year.

**TABLE 5.—AGENCY PROCEDURES FOR MONITORING PERFORMANCE OF EXTRAMURAL IRBs—
Continued**

Department or agency	Requires IRB or similar committee	Prior approval of IRB compositions, etc.	Conducts site visits	Notes	
				To monitor	For cause
Department Of Housing and Urban Development.					
Department of Justice: Bureau of Prisons.....	•	•	•		Site visits are made at least once every 2 years.
Office of Justice Assist., Research, and Statistics.					
Dept. of Transportation: Coast Guard.....					Fed. Air Surg. must approve all research.
Federal Aviation Admin.....					
Federal Highway Admin.....	•	•			
Natl. Highway Traffic Safety Administration.	•	•			
Environmental Protection Agency.					IRBs are required only for intramural research.
National Aeronautics and Space Administration.	(1)				
National Science Foundation	•	•			
U.S. Intl. Development Co-operation Agency.	•	•			
Veterans Administration.....	•	•	•	•	

¹ See notes.

Six agencies monitor extramural IRBs via procedures that go beyond a review of IRB membership and acceptance of an institution's promises to comply with regulations. The CIA reports that it conducts site visits "where applicable" and that CIA program managers provide continuing review of the conduct of research projects. Within the Department of Justice, the Federal Bureau of Prisons conducts site visits at least once every two years to inspect both IRBs and ongoing research programs; and both the Law Enforcement Assistance Administration (LEAA) and the National Institute of Justice monitor research via weekly phone calls and periodic site visits. The Veterans Administration has a system of regular site visits through which the Research Advisory Committee in Washington monitors both IRB performance and the conduct of research at V.A. facilities, and through which IRBs (regional "Human Rights Committees") monitor the conduct of research in the cooperative study programs.

Finally, within the three components of the Department of Defense, intramural IRBs are responsive to a commander who approves all IRB proceedings, and IRBs at institutions receiving Defense Department contracts are subject to review by contracting headquarters. There is no mechanism, however, for systematic monitoring of either the conduct of extramural research or the performance of grantee or contractor IRBs except in the Army, whose Medical Research and Development Command conducts site visits to each contractor prior to

approval of the contract. One of the site visitors must be qualified to perform technical review, the other must be qualified "to evaluate the contract as an advocate of the human subjects."

A modest check on IRB performance is provided in some agencies through review of consent forms. At the Consumer Product Safety Commission, consent forms must be approved by the agency prior to initiating research and all signed consent forms are reviewed—and retained—by the agency. Within the Public Health Service, by contrast, routine submission of consent forms to be used in proposed research activities is generally not required. The study sections do not routinely examine consent forms, and OPRR reports that, given the volume of research projects flowing through that Office, it cannot undertake this added function. At one time ADAMHA reviewed all consent forms for research it supported, but this practice has now been curtailed. The lone present exception in HHS arises when the government (most usually, the National Cancer Institute) is acting as a "sponsor" of a drug or device being tested, since the FDA requires all sponsors to review consent forms.

B. Are IRBs Able to Understand and Fulfill Their Obligations? This is plainly a time of transition for the IRB system. The National Commission for the Protection of Human Subjects gave careful consideration to the institutional review system and issued recommendations supportive of the basic elements of that system while at the same time seeking to strengthen certain of its important facets. The new regulations, issued by HHS early in

1981, are based substantially on the National Commission's recommendations, and institutions are now at various stages in revising their procedures and negotiating with HHS to accept their assurances of compliance with the regulations. Moreover, HHS is in the process of developing educational materials and conferences to assist IRBs in understanding their responsibilities under the new regulations. Thus, while a new general assessment of the basic institutional review system would be premature, it is appropriate to examine particular problem areas which arose prior to 1981 and appear to be incompletely resolved by the new regulations. Two requirements that seem to pose the greatest difficulty are: (1) continuing review by an IRB of projects it has approved and (2) IRB reporting of adverse affects of serious and continuing noncompliance.

1. *Initial Review.* The IRB Study Undertaken by the National Commission for the Protection of Human Subjects suggested that IRBs had a fairly good understanding of most of their responsibilities for initial review of research involving human subjects, although 25% of IRB members felt that they, and researchers, needed more information (i.e., better definitions and cleared guidelines) from the Department. (14) The recent revisions in the HHS regulations provide more explicit guidance than previously offered as to what constitutes research with human subjects and what categories of such research must be reviewed or, alternatively, need not be reviewed. It remains to be seen how well the new regulations and the planned educational programs will meet the IRBs' needs for further guidance. Many of the most important decisions made by IRBs are matters of interpretation and judgment. These are best left to the IRB, as they are not likely to be improved by ever more detailed regulations.

2. *Continuing Review.* In contrast to the IRB's role in initial review, available information strongly suggests that many IRBs do not understand what is expected in the way of "continuing review" of projects that the IRB has approved. Although continuing review has been required since 1971, (15) the survey conducted for the National Commission between July 1, 1974, and June 30, 1975, found that only 20% of IRBs routinely designated members or other representatives to observe the manner in which a research project was being conducted; 63% reported that they never did, and 17% said that they did under certain circumstances. Moreover,

38% of the IRBs reported that in few or none of the proposals they reviewed was there even an understanding that the project would be reviewed again after a specified period of time and 47% seldom or never received copies of interim reports. (16)

The problems manifested in these statistics clearly need attention. Some improvement might even occur as part of the current process of negotiating assurances with research institutions, if certain definitional difficulties were overcome. For example, "continuing review" and "annual review" appear in the HHS regulations to refer to separate functions (with distinct purposes and justifications). Yet the regulations do not make clear the meaning of the two terms nor the resulting expectations for institutional behavior. (17)

Moreover, anecdotal information received by Commission staff at IRB conferences, and testimony presented to the Commission at hearings in Boston and Los Angeles, indicate the need for better guidance as to the Department's expectations. It appears that few IRBs perform ongoing review of the actual conduct of research; and those that do sometimes meet with resistance. (18)

In addition, there is evidence that at least some IRB members disagree among themselves as to the nature of their responsibility to provide continuing review. (19) Indeed, some IRBs may even be unaware whether their conclusions and directives are being carried out. For example, in testimony before the Commission a member of one IRB told of her surprise, when her group was called upon to provide an annual reapproval of an ongoing project, to discover that the investigator had been using the consent form found inadequate a year earlier by the IRB rather than the one that they had approved as modified. (20) Two Commissions with extensive IRB experience agreed that this is not uncommon. (21)

What is known is that, since HHS funding agencies requires certification of IRB approval at least annually, certification is provided for continued HHS funding. This reapproval by the IRB is clearly intended by the Department to be as serious a matter as a project's initial approval; it is to be based on reports from principal investigators as to the progress of their research and its effects on subjects. The Department lacks data on whether or not this responsibility is generally carried out in the intended manner.

Furthermore, beyond this annual review, HHS has not shown that the amount or nature of "continuing review" performed by IRBs has improved since 1975. At the very least, it is apparent

that whatever the procedures followed by IRBs they were not sufficient to identify even those cases of alleged misconduct reviewed by the Commission which involved research reviewed and approved by an IRB (with the possible exception of the incidents at UCLA), all of which came to light outside these channels. Thus, the Commission has no basis for judging whether or not the requirement of continuing review is being implemented, although it does not doubt that many IRBs are attempting to, and succeeding in, executing this responsibility in a conscientious and even creative fashion.

Within the other Federal agencies, the situation is essentially the same because they follow the HHS regulations and therefore provide no clearer or more detailed direction to their IRBs than is provided by HHS. In highly structured departments, however, some oversight is possible. Thus, the C.I.A. reports that program managers provide continuing review of ongoing research actually being conducted under the Agency's auspices. Similarly, in the Veterans' Administration, the IRBs ("Human Rights Committees") of each of four regional Cooperative Study Coordinating Centers make at least three site visits per year to the various medical centers participating in the cooperative studies. The visits are designed to determine the degree of compliance with, and implementation of, requirements for informed consent an adherence to both the letter and the spirit of guidelines for protecting the rights and welfare of human subjects. During the site visits, IRB members hold discussions with principal investigators and other members of the research team as well as with some of the research subjects. In addition, when deemed appropriate, they review individual medical records. Members or representatives of the V.A.'s Research Advisory Committee (under the direction of the Assistant Chief Medical Director for Research and Development, in Washington) visit the larger V.A. medical centers (those with annual research budgets in excess of \$500,000). These site visits look primarily at the administration of the medical center's research and development program, through the operation of Subjects their IRBs ("Human Studies Subcommittees"), the Research and Development Committee, and the Office of the Assistant Chief of Staff for Research and Development.

3. *Reporting Requirements.* The requirement that IRBs report any unanticipated problems involving risk to subjects or to others that arise during the conduct of research was introduced

in HHS regulations in 1974. (22) The Director of OPRR testified to the Commission that this is interpreted to require reporting only of adverse effects not anticipated by the investigator and thus not reflected in the research proposal and consent documents at the time of initial review. (23) The result is that theoretically, at least, one could expand the catalogue of "risks" in advance, and thus reduce the obligation to report harm to subjects, even when some of the risks are so improbable that their manifestation would, in common sense terms, be "unanticipated."

In the review of IRB practices conducted for the National Commission by the Survey Research Center at the University of Michigan during the first year the 1974 regulations were in effect, fewer than half of the IRBs had either a formal or an informal policy with regard to investigators' reporting research-related injuries or harm to subjects to the IRB. (24) From data developed during its study of compensation for research injuries, the Commission is aware that present procedures do not lead all events reasonably regarded as adverse effects to be reported. Indeed, only two adverse effects associated with HHS-supported research were apparently reported to OPRR by either IRBs or investigators from 1975-1980. OPRR staff testified that "a small number" of additional reports have been received, through telephone complaints from individuals, most of which "have proved to be unfounded or unverifiable." (25) In 1981, a third serious injury was reported in research supported by the Department: "cardiac arrest with successful resuscitation and no permanent damage." (26) Thus, both in this interpretation of its regulations and its guidance to IRBs on this point, the Department should encourage more active implementation of the requirement that injuries be reported. The Commission is pleased to note, however, that the regulations issued in 1981 now specify a particular HHS office and address to which reports should be addressed rather than simply "to the Secretary."

Besides specifying the office to which reports ought to be sent, the 1981 revision of the HHS regulations added a new reporting requirement: IRBs must report not only unanticipated problems involving risks to subjects but also any serious or continuing noncompliance with the regulations or with the IRB's determinations. (27) The regulations as written, however, appear to contemplate that the responsibility for investigating and reporting rests with the IRB, and the sample assurance promulgated by

OPRR, in describing this provision, states:

For reporting purposes, the IRB will follow the procedures described below:

(1) Any serious or continuing noncompliance by research investigators with the requirements of the IRB—This information shall be reported promptly to the ORA (an administrative office within the research institution to be specified in the new assurances) and OPRR. (28)

As encouragement to implement this provision, local institutions require guidance on the meaning of the terms, *i.e.*, whether or not certain behavior is sufficiently serious or continual as to warrant reporting to OPRR and institutional officials. Although no definition of "serious and continuing noncompliance" has yet been provided, OPRR's plan to issue an official commentary to the regulations may meet the IRBs' need for guidance. A review of a random selection of general assurances now on file at HHS suggests, however, that not all IRBs currently have the authority within their institutions to fulfill this obligation. It is also not clear whether all IRBs would have sufficient autonomy to report to HHS any conduct that the institution's administration attempted to conceal if disagreement were to arise on the matter between an IRB and the institution's administration.

The role the IRBs currently have in investigating or resolving reports of misconduct is far from consistent. Indeed, the notion that IRBs should have any role in such activities has been strongly challenged. In testimony received in Boston and Los Angeles from IRB members as well as from hospital and university administrators, and in papers prepared for and discussions held at a 2-day workshop on the role of the IRB in responding to reports of misconduct, the consistent recommendation was that IRBs not be required to perform monitoring, investigative or adjudicative functions. Some people stressed that in most institutions IRBs have neither the time, the resources, nor the expertise to discharge such responsibilities. Others added that adoption of such a role would interfere with the primary function of IRBs: to educate and advise research scientists and to resolve problems in a constructive way. Finally, it was pointed out that most hospitals already have quality assurance mechanisms and other investigative and dispute-resolution bodies in place, as do many universities.

Many witnesses and consultants strongly urged that, through a reversal of the chain-of-command-and-information

now specified in the regulations, IRBs *be kept informed* of all reports and investigations conducted by other responsible institutional bodies relating to misconduct in research involving human subjects, and that IRBs retain the authority to call for such an investigation when reports of misconduct come to their attention. To make such an arrangement effective, an IRB would, of course, need a defined relationship to the quality assurance committee and its activities. The prevailing view was that the primary responsibility for investigating and resolving complaints not be assigned to the IRB.

Among the other Federal agencies that conduct or support research with human subjects, only four indicated that there had been any adverse effects arising in the course of such research: The Bureau of Standards (reporting two injuries,) the Federal Bureau of Prisons (citing one lawsuit in which injury was alleged), the Environmental Protection Agency (reporting one adverse reaction) and the Veterans' Administration. Within both HHS and the Department of Defense, it is possible that adverse reactions are sometimes reported to project officers or others within the Department. However, there is no central office to which all such reports are referred or any other coordinated system for obtaining and recording such information.

Although not themselves free of all problems, the methods and standards of the FDA indicate that more complete and informative reporting is feasible. Regulations governing research subject to FDA regulation require that clinical investigators report unanticipated problems involving risk to subjects to the IRB and also report "any adverse effect which may reasonably be regarded as caused by, or is probably caused by, the new drug" to the sponsor of the research (*eg.*, the drug company, the National Cancer Institute, etc.). The sponsor, in turn, must investigate promptly and report to the FDA and to all investigators "any findings associated with (the) use of the drug that may suggest significant hazards, contradictions, side-effects, and precautions pertinent to the safety of the drug." The FDA Acting Associate Commissioner for Health Affairs estimates that such reports number in the hundreds. (29)

C. How Do Federal Agencies Respond to Reported or Documented Violations of the Regulations or Other Serious Misconduct of Grantees or Contractors?
The uncertain response at the institutional level to reports of alleged misconduct in Federally funded

biomedical research is mirrored by a similarly uneven response at the agency level. The Commission's review of agency policies and procedures in this regard is based upon a study of several widely reported incidents of alleged misconduct and upon a series of questions posed to the heads of departments and agencies that conduct or support research with human subjects.

1. *Case Studies.* A series of allegations of misconduct on the part of principal investigators and/or junior researchers has been widely reported in the press over the last several years. The cases are summarized in Table 6 and described in Appendix F. Having investigated the procedures followed in each instance, including the Federal response to these incidents, the Commission concludes that policies and procedures for a coordinated, timely, and consistent federal response still need to be developed.

Specifically, taken together these cases indicate a need for: (a) Identification of a particular office within each research institution to which reports of alleged misconduct should be directed; (b) clarification of the role of IRBs in responding to allegations of misconduct; (c) clarity about the responsibility of institutional officials to report formal findings of misconduct to the cognizant Federal agencies; (d) better guidelines for the timing and mode of the Federal agencies' response; and (e) better coordination and communication among Federal agencies with respect to investigations of reports of serious misconduct, formal findings of facts, and imposition of sanctions based upon such findings.

2. *Questions Posed to the Secretary, HHS.* On September 18, 1980, after reviewing materials relating to the allegations concerning the University of Kansas and Boston University, the Commission through its Chairman, Morris B. Abram, wrote to Patricia Roberts Harris (then Secretary of HHS) that "if correct, these reports raise serious concerns particularly with respect to implementation of the Department's rules." Mr. Abram asked for copies of any and all reports related to the two incidents. The heart of the Commission's interest lay, however, with several matters of general policy: (a) Whether (or when) it was expected that IRBs and review groups within HHS would be told of serious allegations or findings of misconduct on the part of a scientist whose application for funding is under consideration; (b) the extent of a principal investigator's accountability

for research performed under his direction; (c) the Department's interpretation and application of its regulatory provision that research funds

may be withheld from researchers who "fail materially" to protect human subjects; (d) the procedures designed to protect the rights of those who make

allegations and those against whom allegations are made; and (e) the effects on human subjects of falsification of research data.

TABLE 6.—SUMMARY OF INSTITUTIONAL AND HHS RESPONSES TO REPORTED INCIDENTS OF RESEARCH FRAUD, ABUSE OR VIOLATION OF REGULATIONS

Became known to university	Became known to HHS	Allegations	University action	HHS action (as of Nov. 30, 1981)
Unknown independent psychiatrist.	FDA Inspections: Apr./May 1978; Hearings; Sept. 26. and Oct. 29, 1979.	Deliberately and consistently violated FDA rules by giving patients potent drugs not approved for human studies; also, unable to provide records and signed consent forms. Repeatedly ignored FDA warnings to comply with regulations.	(Independent researcher; worked at psychiatric research institute. No Institutional response on record).	FDA disqualified psychiatrist from further studies with investigational new drugs (Nov. 13, 1980). NIH placed name on "alert" list to notify appropriate officials if psychiatrist submits new applications for support. No action taken on institutional grant to research facility of which he is Director.
June 1981 (by letter from National Cancer Institute): M. D. Anderson Hospital and Tumor Institute (University of Texas System Cancer Center).	June 1981—NCI staff member read Journal abstract reporting on work. NCI/NIH conducted investigation and site visit: July 1981.	Administration to human subjects of new drug not approved for human use. Also, failure to obtain approval of IRB and committee on radioactive substances. Inadequate procedures for informed consent.	Following investigation, formally censured researcher and barred him from further involvement in research with human subjects. Also, relieved him of all current responsibilities as principal investigator or co-principal investigator on federal grants and contracts. (Both sanctions are of indefinite duration).	NCI/NIH terminated all work under the researcher's contract (except for two "high priority studies" for which a new principal investigator was named. Also, will bring the misconduct to the attention of NCI Advisory Council if researcher applies for a grant or contract in the next two years. Barred researcher from service on NIH advisory committees or site visits for two years. FDA Inspection is pending.
September 1980 UCLA.	September 1980.....	Physician conducted experimental bone marrow transplants (involving DNA) in Israel and Italy without disclosing to subjects or review committees the use of recombinant materials. The procedures had not been approved by UCLA's IRB or Biosafety Committee.	Following investigation, censured the physician and accepted his resignation as Chief of Hematology and Oncology.	NIH Director appointed ad hoc committee to investigate; then implemented its recommendations: requiring prior NIH review of physician's new grant applications involving human subjects or DNA and forwarding ad hoc committee's report to National Advisory Councils (May 1981). The Council voted to end two grants at the end of the current year and accepted a new principal investigator for a third.
March 1977: (reported by graduate students on research team) University of Kansas.	Reported to Region VII officials in Sept. 1977. Reported to NIH (OPRR) Nov. 4, 1977.	Anthropologist at Univ. of Kansas diverted NSF and HEW funds to research involving human subjects that was not approved by the IRB. Also, used inadequate consent procedures and improper fiscal management.	Jan 1978, Vice Chancellor for research reported formal finding that the project had not undergone required IRB review and the investigator was "less than candid" when he indicated on an application for research funds that his project did not involve human subjects. Investigator was warned that future violations might result in more severe sanctions.	Inspector General's report is said to have been completed but is not available. NIH investigation of possible violations of human subjects regulations is still in progress. The anthropologist received an additional NIH research grant while the investigation was under way.
June 2, 1978: (reported by members of research team) Boston University Medical Center.	National Cancer Institute notified July 31, 1978.	Principal investigator and team falsified research data in study funded by NCI; entered false information on patients' medical records.	Investigators and members of team forced to resign; also, notified Eastern Cooperative Oncology Group (ECOG) June 14-15, 1978; ECOG Investigation resulted in purge of all B.U. data and expulsion of research unit from the study. (November 1978). NOTE.—grievance procedures in university by-laws were followed by B.U. administration.	NCI Director wrote B.U. officials that "NCI cannot intervene in the internal affairs of institutions." 1978) Following press accounts in July 1980, NCI Acting Director asked for NIH investigation—which is still in progress. Investigator moved to N.Y. Medical College: received major new NCI grant in 1980.
Early 1979: (Nurses reported to Medical Center's IRB) UCLA.	Dec. 1980 (via press accounts).	Physicians performed experimental bone marrow transplants without IRB approval, sometimes with high doses of drugs also not approved by IRE.	Investigating panel of M.D.s appointed (Aug. 1979); report completed in March 1980; IRB notified of findings in July 1980. Researchers warned that serious violations of rules would result in cutoff of federal funds.	Investigation in process.

In April 1981, HHS Secretary Richard Schweiker replied that the answers to most of the questions about policy and standards posed by the Commission would depend upon the particulars of a given case. For further guidance, the Secretary referred to the Department's debarment regulations (45 CFR Part 76) issued on October 8, 1980. (30) Yet, as earlier noted by Donald Fredrickson (then Director of NIH), those regulations were designed to preclude persons guilty of fiscal mismanagement or fraud from receiving further HHS grants or contracts. As written, the regulations do not specifically refer to violations of the regulations governing research with human subjects or to scientific fraud. (32) The debarment regulations do provide for notice, formal hearings, and

other "due process" protections for individuals accused of fraud and abuse or serious violations of applicable regulations or conditions governing an HHS grant or contract. The procedures set forth in those regulations have yet to be invoked by NIH, however, although at least two scientists accused of violating the human subjects regulations have had their research funds curtailed in the year since those regulations took effect (see Appendix E).

On several subsequent occasions, the Commission inquired of HHS officials about the Department's interpretation of its rules and how one determines what course of action to take in response to allegations of misconduct or formal findings that misconduct has occurred. Following Secretary Schweiker's letter

referring to the department regulations, the Commission's chairman wrote the Secretary asking for a meeting to explain the Commission's continuing concerns more fully. (32) The Secretary declined to have such a meeting at that time but indicated that Charles McCarthy, the official HHS liaison to the Commission would continue to provide assistance. (33) The Commission staff, therefore, arranged for Dr. McCarthy to testify at the September 1981 meeting of the Commission in order to fill in certain points that remained unresolved. In a memorandum confirming that agreement, written in order to provide advance notice of the questions to be asked and to focus discussion at the meeting on policy rather than on individual cases, the

issues relating to the Department's debarment procedures were set forth as follows:

Implementation of the Department Regulations (45 CFR Part 76)

a. What are the roles and responsibilities of the various offices at NIH (e.g., OPRR, General Counsel, Associate Director for Extramural Research and Training, etc.) with respect to decisions to initiate debarment proceedings?

b. Who has final authority with respect to such decisions?

c. May suspension of funds or similar sanctions be imposed without invoking the debarment process?

d. If alternative procedures are available, by whom, and according to what standards, are choices made as to which procedure to follow in a particular case?

e. At what point in consideration of debarment will a subject of investigation be formally notified so that he or she may request a hearing under § 76.14(b)?

f. What factors will be considered in deciding when that point has been reached? Who will make the determination?

g. May a grantee institution or principal investigator, who is the subject of an investigation regarding alleged misconduct, request that debarment proceedings be initiated in order to invoke the hearing provisions? (34)

Although he had originally agreed to discuss these matters, Dr. McCarthy notified the Commission on September 1 that he now felt it inappropriate to do so because some investigations were still in process. (35) He then agreed to meet with Commission staff to discuss the possibility of a written response. When the written response was delivered to the Commission in mid-November, Dr. McCarthy stated that it would be premature to answer the series of questions about debarment procedures because Secretary Schweiker had by then agreed to a meeting to discuss those issues, among others. (36)

On December 3, 1981, Secretary Schweiker, together with the Assistant Secretary for Health, the Assistant Secretary for Planning and Evaluation, and two members of the Executive Secretariat, met with Commission Chairman Abram, and the Executive and Deputy Directors of the Commission. As a result of a full exploration of the issues, the Secretary proposed that the Assistant Secretary for Planning and Evaluation work with senior Commission staff to spell out standards under existing regulations for the Department's response to reports of misconduct that would meet the concerns of the Commission as well as those of HHS and the research community. The Commission welcomes this collaborative effort and fully expects that its next *Biennial Report*

will describe the articulation—and implementation—of the relevant policies and procedures.

3. *The FDA's Disqualification Procedures.* The FDA has had disqualification procedures in place for a number of years, and since 1964 has invoked those procedures to disqualify 42 scientists from further research under that agency's jurisdiction for varying periods of time. Twenty-six of those disqualifications occurred within the last five years. (37) Serious deficiencies in the conduct of research, including fraudulent reporting of data or noncompliance with regulations for the protection of human subjects, can form the basis of a disqualification proceeding at FDA.

As explained more fully in Appendix E, however, the process of systematic sharing between NIH and FDA of information about scientists who are the subject of an investigation or who have been subject to agency sanctions is not yet fully developed. Active sharing of information regarding formal findings of misconduct with other Federal agencies or with appropriate state licensing bodies or professional societies is limited to a "need to know" basis (i.e., if the investigator was employed by a state or is known to have received NIH support). Thus, although the formal findings following an investigation are publicly available on request, only limited efforts are made to alert other organizations that a physician or scientist has been found guilty of serious misconduct in research involving human subjects.

4. *Questions Posed to Other Federal Agencies.* On June 11, 1981, the heads of each of the 18 agencies known to conduct or support research with human subjects were asked to provide a description of:

1. Policies or procedures (formal or informal) by which their agency evaluates or monitors the actual performance of agency or extramural Institutional Review Boards (e.g., reporting requirements, site visits, record reviews);

2. Standards and procedures to guide the investigation of complaints regarding the review or conduct of research involving human subjects;

3. The number and character of any such reports or complaints received in the last 5 years (FY 1976-1980); and

4. The manner in which these complaints were disposed of, the findings that were made, and the sanctions, if any, that were imposed.

As a result of that inquiry, the Commission finds that the situation in the other Federal agencies that conduct or support research with human subjects is virtually identical to that existing at the NIH, insofar as most of those

agencies follow the policies and procedures set forth in the HHS regulations (45 CFR Part 46).

Outside of HHS, only five agencies report having received complaints. The Bureau of Standards, within the Department of Commerce, reported two injuries to subjects, the Bureau of Prisons reported one tort action (arising from research supported by the CIA and conducted between 1955 and 1961); the CIA reported the same complaint and one other also arising out of research conducted in the 1950s; the Environmental Protection Agency reported an incident of accidental exposure of subjects to a throat and eye irritant; and the Veterans Administration reported 5 incidents. (See Appendix B for further details.) Of the five complaints noted by the VA., two proved to be unfounded, two are under investigation, and one resulted in an official reprimand of the principal investigator and his exclusion from further research with human subjects.

Most of the agencies reported that they have no formal procedures for investigating or responding to complaints. The exceptions were the Bureau of Prisons, NASA, the Department of Defense and the VA. At the first two, complaints are referred to the Office of General Counsel for investigation. Within the Department of Defense and the Veterans Administration, complaints are dealt with first at the local level and, if necessary, are referred up through normal channels. Within the VA, complaints made directly to the Office of the Medical Inspector in Washington may be investigated either by a local team or by a team designated for that purpose operating out of the Washington Central Office.

Footnotes

(1) See, National Commission for the Protection of Human Subjects, *Report and Recommendations: Institutional Review Boards* (hereinafter, *IRB Report*), U.S. Government Printing Office, Washington (1978) at 9-12 (Recommendation 2 and comment).

(2) B. Barber, J. J. Lally, J. L. Makarushka and D. Sullivan, *Research on Human Subjects—Problems of Social Control in Medical Experimentation*, Russell Sage Foundation, New York (1973) at 145-48.

(3) Although many IRB members may feel uncomfortable with such a description of their role, the reality of their Federal responsibilities cannot be denied. Nonetheless, an IRB is not confined to the functions required by the Federal rules nor need it allow such responsibilities to prevent it from playing a role or *internal* leadership within its institution. Robert Levine has written tellingly of the cost to an IRB's "local

credibility" if it identifies the source of its authority and responsibility as resting outside the institution. Robert J. Levine, *Ethics and Regulation of Clinical Research*, Urban and Schwarzenberg, Baltimore (1981) at 227.

(4) Letter from Charles R. McCarthy to Morris B. Abram (May 7, 1980) at 2.

(5) See e.g., statement of Charles R. McCarthy at the PRIM&R Conference on "The New Federal Regulations: What They Do and Do Not Regulate," Boston (March 26-27, 1981) at 38.

(6) To the extent that the "sample assurance" does go beyond the regulations, questions of a different sort are raised. The sample is not formulated as a series of issues of administration and structure that OPRR believes ought to be addressed. Rather, it sets forth a structure which—by its very conjunction with many requirements of the regulations—HHS seems to expect of an institution. In effect, by including a number of items not covered by the regulations (e.g., the whole concept of an "appeals IRB"; 7 of the 15 elements of "institutional policy" in Sec. I.C. of the "sample" assurances; etc.), the Department appears to adopt policies, principles or rules that have not been subject to the usual process of scrutiny and comment that is necessary in promulgating federal regulations under the Administration Procedure Act. The "sample" assurance notes at several points that facets which have been made up out of whole cloth (e.g., the creation of an "Office of Research Administration" to exercise administrative responsibilities, including some which, under 45 CFR Part 46, appear to rest with the IRB) "will not be appropriate for some institutions and are not required by the HHS regulations." Yet this disclaimer is not provided about many of the amendments to the regulations and, in any event is dissipated by the overall impression created that the model assurance represents the Department's expectations. For example, the cover letter informs each institution that "In preparing this sample assurance we have attempted to include all of the elements necessary for compliance with the new regulations."

(7) For example, there are many statements of the sort that the institution will act "in accordance with 45 CFR 46.116" or "will comply with the policies set forth in 45 CFR Part 46 Subpart C." The baldest example of the need for an accompanying set of regulations occurs on the very first page (Sec. I.A.2) of OPRR's model assurance: "Only provisions II.A.16; II.B.1.a,b,d,e,f; and III. of this assurance are applicable to the activities listed above if the only involvement of human subjects will be in one or more of the categories exempted or waived under 45 CFR 46.101(b)(15) or 46.101(e)."

(8) Letter from Dr. McCarthy to Morris B. Abram (May 7, 1980) at 3; see also testimony of Dr. McCarthy, transcript of 2nd meeting of the President's Commission (May 16, 1980) at 81-82.

(9) Testimony of Charles MacKay, Deputy Director, OPRR, transcript of 14th meeting of the President's Commission (November 14, 1981) at 320. See also, "Response to Request for Comments and Corrections of Biennial Report" (undated, distributed by Dr.

McCarthy to members of the Commission and Staff on November 14, 1981) part II at 7.

(10) Testimony of Charles McCarthy, transcript of 14th meeting of the President's Commission (November 14, 1981) at 321.

(11) Testimony of Dr. McCarthy and Dr. MacKay, 14th meeting of the President's Commission (November 14, 1981) at 333-4.

(12) Letter to Commissioners from Dr. Charles McCarthy (December 28, 1981).

(13) In a case in which a criminal indictment was recently handed down in Pennsylvania, a scientist allegedly conducted drug research over a period of years without benefit of IRB review. It was only when an FDA reviewer questioned some of the data submitted that an investigation was initiated and it was discovered that the IRB which had purportedly reviewed the protocols had never existed. (*United States v. Levine*, No. 81-203, E.D.Pa., Indictment, July 9, 1981, Count 18(e) at 8.)

(14) *IRB Report*, *supra* note 1, Appendix at I-263 (Table XVII-10).

(15) Department of Health, Education and Welfare, Public Health Service, NIH, *The Institutional Guide to DHEW Policy on Protection of Human Subjects*, U.S. Government Printing Office, Washington (December 1, 1971) at 8.

(16) *IRB Report*, *supra* note 1, Appendix at I-207 and at I-44. In fact, 60% of IRBs never received a copy of final reports.

(17) 45 CFR 46.103(b)(4) sets forth in separate subsections that an institution's assurance must contain the "written procedures which the IRB will follow" for "conducting its * * * continuing review of research..." and for "determining which projects require review more often than annually * * *" 45 CFR 46.109(e) states that an IRB "shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less the once per year..."

(18) See, e.g., Erica J. Heath, "The IRB's Monitoring Function: Four Concepts of Monitoring," 1 *IRB* (5) (Aug./Sept. 1979); Testimony of Leonard Glantz and Judith Watkins, Tenth Meeting of the President's Commission, Boston (June 5, 1981); papers prepared for the Workshop on Whistleblowing in Biomedical Research, sponsored by the President's Commission, the AAAS Committee of Scientific Freedom and Responsibility, and Medicine in the Public Interest, Washington, (September 21-22, 1981).

(19) Testimony of Leonard Glantz and Judith Watkins, *supra* note 18.

(20) Testimony of Judith Watkins, *supra* note 18.

(21) Comments of Commissioners Jonsen and Medearis, 15th meeting of the Commission, Washington (December 12, 1981), at 137A.

(22) 45 CFR 46.6(d), 39 FR 18914, 18918 (May 30, 1974).

(23) Testimony of Charles R. McCarthy, Second Meeting of the President's Commission, Washington (May 16, 1980) at 93-96.

(24) *IRB Report*, *supra* note 1, Appendix at I-35, I-205.

(25) Letter from Charles R. McCarthy to Morris B. Abram (May 7, 1980).

(26) "Response to Request for Comments and Corrections of Biennial Report" (November 10, 1980); see also chart submitted by Charles R. McCarthy (November 25, 1981).

(27) 45 CFR 46.108(c) 46 FR 8366, 8388 (Jan. 28, 1981). Such reports may become the basis for a determination by the Secretary to suspend, terminate or withhold research grants or contracts as provided in 45 CFR 46.123.

(28) Sample Assurance issued by OPRR (July 3, 1981 as revised August 11, 1981) at 17.

(29) Memorandum from Acting Associate Commissioner for Health Affairs (FDA) to Director, OPRR (NIH) (November 10, 1981) commenting on a preliminary draft of this report on the Protection of Human Subjects.

(30) 45 CFR Part 76; 45 FR 67262 (October 8, 1980).

(31) Memorandum entitled "Rogues in Science" from the Director, NIH to the Secretary, HHS (August 7, 1981).

(32) Letter from Morris B. Abram to Richard S. Schweiker (May 11, 1981); see Appendix F.

(33) Letter from Richard S. Schweiker to Morris B. Abram (Aug. 24, 1981); see Appendix F.

(34) Memorandum from Deputy Director, President's Commission to NIH Legal Advisor and Director, OPRR (August 17, 1981); see Appendix F.

(35) Letter to Barbara Mishkin from Charles R. McCarthy (September 1, 1981); see Appendix F.

(36) "These questions overlap with many of the questions answered in Secretary Schweiker's letter of April 15. Since the Secretary has agreed to meet with the Chairman and Commission staff, it would be premature to amplify what was said in the April 15 letter." Letter to Barbara Mishkin from Charles R. McCarthy [November 10, 1981]; see Appendix F.

(37) FDA list entitled "Investigators Found Ineligible to Receive Investigational New Drugs" (December 7, 1980).

Chapter 4. Activities of the Commission Extending Into 1982

A. *Site Visits to IRBs: An Exploratory Study.* The Commission decided against conducting another study along the lines of the survey of IRB procedures and performance that was conducted under the auspices of the National Commission for the Protection of Human Subjects. The present Commission's resources of time and money made such a study infeasible. Also, since the system is in some flux after the issuance of new regulations in 1981, the value of such a study would be problematic. Most importantly, however, the Commission concluded that a study of IRBs themselves would fall outside its proper focus: the procedures of Federal agencies and their awareness of the implementation of their own rules. Instead, the Commission has begun an empirical exploration of new approach that Federal agencies might employ to develop information about the

implementation of rules for the protection of human subjects. The approach involves site visits to IRBs by teams of experienced IRB members and administrators from other institutions, with the support of the Commission staff.

The Commission's interest in site visits grew from several considerations. First, as has been said, little information currently exists as to how requirements for the protection of human subjects are actually carried out at institutions that receive support for human research from HHS, the largest sponsor of such research. This limitation on existing knowledge has been previously recognized and, indeed, was a factor leading to the National Commission's IRB study. Second, most Federal agencies, including HHS, have no procedures for routinely obtaining such information about IRBs. Third, a new approach for developing such information was proposed by the National Commission, but has not yet been implemented by HHS. Specifically, the National Commission recommended that the then Department of Health, Education, and Welfare carry out "compliance activities, including site visits and audits of Institutional Review Board records, to examine the performance of the Boards and their fulfillment of institutional assurances and regulatory requirements." (1) These site visits, said the Commission, should be conducted "routinely" and, in addition to assuring "quality control," should be aimed at "educating, improving performance of IRBs, and providing needed advice." (2)

In the Commission's view, this recommendation merits serious consideration. The President's Commission determined that it could play a useful role by specifying the meaning of this recommendation in detailed, operational terms and by exploring on a pilot basis the strengths and weaknesses of this approach. Thus, in late 1981 and early 1982, site visit teams formed by the Commission will visit 10-12 institutions. The sites will be selected for their diversity, and will not be "representatives" in any statistical sense. The purpose of these exploratory site visits will be to learn whether visits of this type would offer a useful way to develop and share information about IRB functioning. Various methods will be explored, including meetings with IRB members, reviewing records, meeting with investigators, and attending IRB meetings. Each site visit team will be made up of three persons who are experienced IRB members or

administrators, in addition to a Commission staff member.

The site visits will provide material for a report focusing on the possible processes through which information could regularly be developed by the Federal agencies that sponsor human research about the implementation of their regulations. The report is not envisioned as a critique of IRBs in general or of the specific IRBs visited in particular. Rather, the project is intended to illuminate what can be learned through a process of peer-based site visit and what problems exist with this approach. If the method is successful it might also replace the multiplicitous inspections now performed by Federal entities other than HHS which support research and by the FDA. (3)

B. *Guidebook for IRBs.* In 1974, in enacting the National Research Act, Congress directed (then) HEW to provide "a program * * * for clarification and guidance with respect to ethical issues raised in connection with biomedical and behavioral research involving human subjects." (4) Very little has been developed thus far, yet it is clear that researchers and IRB members desire help both in understanding the policies and principles that underlie the regulations governing research with human subjects, and in identifying the issues to which one should be sensitive in designing or reviewing research proposals. The Commission has embarked on a project, in collaboration with NIH and FDA, to develop a guidebook for IRBs. A contract was negotiated with a Boston-based organization well-known for sponsoring educational conferences for IRBs throughout the country, to prepare portions of the guidebook under the direction of senior staff of the Commission. Other portions of the book are being developed by NIH/FDA staff.

A draft of the guidebook is under preparation and will be distributed to the Commissioners for review early in 1982. Comments and suggestions from the Commissioners will be incorporated in a final version which should be completed by April 1982.

C. *Consideration of the Extension of Federal Regulations and Review Requirements to Research Not Federally Funded.* In September 1980, the Commission concluded that "extension of HHS regulations to research that is not conducted or supported by the Department should be based upon clearer Congressional and statutory authority than now exists in the ambiguous language of Section 474 of the Public Health Act." (5) In

communicating this conclusion to HHS Secretary Patricia Roberts Harris (by whom it was adopted), the Commission indicated, however, that it would consider, at some later date, whether to recommend statutorily-mandated IRB review of research with human subjects regardless of source of funding and, should it conclude that such a requirement is advisable, to recommend appropriate Congressional action. Consideration of this topic, along with other issues about the role of the Federal government, through IRBs, in the protection of human subjects, will be taken up in the *Second Biennial Report*.

D. *Possible Consideration of the Definition of "Phase I" Drug Testing in Cancer Chemotherapy.* The recent attention of Congressional committees and the press to informed consent in cancer research has spotlighted a problem regarding early "Phase I" testing of new anti-cancer drugs. The FDA defines the first two stages of drug research as follows:

Phase I starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; Phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. (6)

In non-cancer studies, Phase I drug tests are usually conducted with healthy volunteers, so that the subject's pathological condition will not interfere with the measurements of the drug's activity in the human body. In such cases, there is no suggestion that the subjects should expect any health benefit from their participation in the research. With cancer drugs, however, toxicity is such that even Phase I tests are usually conducted on persons with cancer, often desperate patients for whom all other possible treatments have proven unavailing.

There is considerable confusion as to whether Phase I tests of new cancer drugs can be described as "therapeutic" for the patients who will be asked to participate as subjects. IRB members disagree, at times, on this question, (7) but cancer researchers have testified that they always have therapeutic intent in Phase I tests of cancer chemotherapy. (8) Further, in a recent letter to Representative Henry Waxman (commenting on testimony of the Commission's staff), the Assistant Secretary for Health wrote:

Notwithstanding the fact that some individuals within HHS may not concur, the official position of the Department, including

NCI, NIH and FDA, is to regard Phase I trials of anti-cancer drugs as *potentially* therapeutic. The often small, but real possibility of benefit must be weighed against the nearly 100 percent probability of death if experimental therapy is not attempted for the advanced cancer patients who participate in Phase I studies. (9)

At a recent meeting of the HHS Secretary's Task Force on NCI/FDA (Regulations of) INDs (Investigational New Drugs), the Commission's Executive Director and Deputy Director urged that this definitional problem be given serious attention. The contrast between the FDA regulations and Dr. Brandt's statement of the Department's "official position" is striking. Perhaps the classifications or nomenclature of Phase I and 2 should not be applied to research on cancer chemotherapies. More important, attention should be paid to the ambiguity in the term "therapeutic research" as applied to the initial use of new anti-cancer agents in human beings, in research usually designed to test pharmacokinetic and toxicologic matters. Clarity and candor are needed as much of courage, both in the communication between physician-investigators and patient-subjects and in the unflinching self-appraisal by the cancer research community of the personal (as well as the scientific) meaning of such "heroic" experimentation. The Task Force has indicated a willingness to consider these issues and the Commission awaits its report with great interest.

E. *Report on Problems Identified at IRB Workshops.* Senior staff of the Commission will be attending a number of IRB workshops and conferences during the next year. Some of these are under the sponsorship of NIH and FDA; others are being planned by Commission staff to the extent permitted by reduced fiscal resources. If the workshops indicate that IRB members and research administrators have continuing problems understanding or implementing HHS regulations (or those of other Federal agencies), the Commission will consider what remedies might be appropriate.

F. *Informed Consent and Problems of Privacy in the Research Setting.* The Commission will consider, as part of its next *Biennial Report*, whether more needs to be said regarding (a) informed consent and (b) privacy in the research setting. The former will depend largely upon whether HHS (and other Federal agencies) adopt the recommendations of the National Commission regarding research involving children and persons institutionalized as mentally disabled; the special principles and procedures set forth in those reports may prove helpful

in resolving some difficult issues that have arisen concerning research with patients suffering from senile dementia of the Alzheimer's type. The second topic (privacy) turns on possible enactment of Federal laws that would add statutory guarantees of confidentiality for individual's medical records.

Footnotes

(1) National Commission for the Protection of Human Subjects, *Report and Recommendations: Institutional Review Boards*, U.S. Government Printing Office (1978) at 10.

(2) *Id.* at 11.

(3) Some hope for success with the peer site visit approach can be derived from the observation of Robert Levine, the long-time chair of the Yale Medical School IRB, on a related phenomenon: Members of IRBs with credibility seem to be invited into the realities of the institution by colleagues who want their advice and assistance in fostering mutual goals. Inspectors without credibility, on the other hand, are shown records (appearances of reality) and then only those to which their access is authorized by regulations. Robert J. Levine, *Ethics and Regulation of Clinical Research*, Urban and Schwarzenberg, Baltimore (1981) at 226 (citations omitted).

(4) Section 474(b) of Part I, title IV, Public Health Service Act.

(5) Letter from Morris B. Abram to Patricia R. Harris (September 18, 1981).

(6) 21 CFR 321.1(a). *see* para. 10(a) of Form FS-1571 described therein.

(7) One IRB member reviewing the protocol for Phase I tests of MHTTF at M.D. Anderson indicated that it was a *therapeutic* research project; another, that it was *nontherapeutic*. *See* IRB review check lists of Alexander Y. M. Wang, Ph.D., and W. W. Sutow, M.D., reflecting their review of protocol DT 78-31 discussed in Chapter 3.

(8) *See* testimony of Drs. Emil Freireich, James F. Holland and John E. Ulmann before a joint hearing of the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, and the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, U.S. House of Representatives (October 27, 1981).

(9) Letter from Edward N. Brandt, Jr., M.D., Assistant Secretary for Health, HHS, to the Honorable Henry A. Waxman, Chairman, Subcommittee on Health and the Environment (November 20, 1981) at 3-4 (emphasis added).

Chapter 5: Recommendations

A. *Recommendations for Improving the Adequacy and Uniformity of Federal Laws and Regulations for the Protection of Human Subjects.* Analysis of the Federal regulations surveyed in Chapter Two reveals that rules governing research with human subjects are now largely uniform among, and within, the agencies. The Commission regards this uniformity as a salutary development for

several reasons. First, it facilitates administration, resulting in an easing of the regulatory burden on research institutions. Second, uniformity makes oversight simpler and more efficient; deficiencies are more readily identified and improvements have a more pervasive effect.

The survey of the present Federal rules and regulations also reveals, however, small variations among the requirements of the different agencies. Varied regulations for the review of research protocols impose upon local institutions unnecessary complexity and uncertainty in assuring appropriate review. Moreover, since IRBs review protocols prior to submission for funding, at the time of IRB review it is not always clear which agency will ultimately support the proposed research. Also, some research activities are supported by more than one agency. Accordingly, the Commission recommends that several steps be taken to standardize the "core" elements of all governmental regulations that specify basic process and standards for the protection of human subjects. Adoption of these recommendations should provide more simplicity, economy and certainty in the Federal regulation of research with human beings.

1. *The President should, through appropriate action, require that all Federal departments or agencies adopt as a common core the regulations governing research with human subjects issued by the Department of Health and Human Services (codified at 45 CFR Part 46), as periodically amended or revised, while permitting additions needed by any department or agency that are not inconsistent with these core provisions.*

Comment: This recommendation is intended to eliminate unnecessary and confusing regulations and lighten the burden imposed on institutions that conduct human research with Federal funds or subject to Federal supervision.

The regulations of the Department of Health and Human Services already serve as the model for most other Federal agencies and departments that conduct or support research with human subjects. Some Federal entities make explicit reference to 45 CFR Part 46 in their own rules and rely on HHS accreditation of institutions receiving funds from them, while others set out procedural and substantive requirements (*i.e.*, risk/benefit ratio, informed consent) for review and approval of research projects that are similar to the HHS rules.

The Commission on Federal Paperwork acknowledged the

preeminent position that HEW (the predecessor to HHS) has held in the protection of human subjects, and it recommended that the Federal government "speak with one voice" through the Department. (1) The present recommendation by the President's Commission is consistent with the findings and conclusions of the Paperwork Commission and with a similar recommendation made three years ago by the National Commission for the Protection of Human Subjects. That Commission recommended that:

Federal law should be enacted or amended to provide that each institution which sponsors or conducts research involving human subjects that is supported by any Federal department or agency or otherwise subject to Federal regulation, and each Federal department or agency which itself conducts research involving human subjects, shall give assurances satisfactory to the Secretary of Health, Education, and Welfare that all research involving human subjects sponsored or conducted by such institution, or conducted by such department or agency, will be reviewed by and conducted in accordance with the determinations of a review board established and operated in accordance with the regulations promulgated by the Secretary * * * (2)

The President's Commission is satisfied that the preeminent role of HHS is deserved. Its leadership rests not only on its role as the major source of Federal funds for health research (as described in Chapter One) but, more importantly, on the attention it has paid to the regulatory issues in this field and to the thoughtful analysis and recommendations concerning its policies and procedures made by the National Commission for the Protection of Human Subjects between 1975 and 1978.

The HHS regulations provide a sensible "core" stating the essential elements for protecting human subjects, specifically: (1) The characteristics of IRBs (including the minimum requisites for their membership), (2) the role of IRBs in providing prior review of research protocols, including their duties and authority in relation to investigators, to their institutions, and to the sponsors of research, and (3) the standards and procedures that should govern IRB decision-making and investigators' behavior. Standardization of these core regulations for research conducted, supported or regulated by all Federal entities would not merely eliminate the need for more than 200 pages of duplicative provisions in the Code of Federal Regulations and departmental directives but would also remove the uncertainty and confusion created for research institutions and their IRBs by minor variations now

buried in the regulations of the various Federal entities.

These small differences in rules (about the composition of IRBs, for instance) do not seem intended to lead to different outcomes in the process of reviewing and approving research protocols. The Commission does not believe, for example, that the regulations of any other agency or department on IRB composition promise better protection for the rights of research subjects than that offered by the HHS regulations. Nevertheless, the pursuit of uniformity around a common set of regulations should be a two-way street: Those provisions in other agencies' regulations that vary from the present HHS regulations in wording or in substance should be considered with an open mind. It may be that certain of these variations in procedures or concepts would improve the HHS formulation and ought to be incorporated as part of the "common core" applicable to all agencies. Once this process is completed, not only would the substance of the regulations be improved, but institutions conducting Federally supported research could be certain that in following the HHS regulations, they will be in compliance with the basic requirements of any and all Federal entities that sponsor research.

In addition to the core requirements there may be a few special restrictions that one or another governmental department or agency may need to impose on research to serve a special objective beyond the basic protection of human subjects' rights and well-being. For example, some government entities may have a policy against the use of certain categories of people in research they sponsor. Or their regulatory obligations may necessitate additional information being disclosed to subjects: for example, since the FDA needs to be able to inspect patient records to assure the accuracy or authenticity of data submitted in support of a New Drug Application, the possibility of FDA inspection of those records is an added element in the informed consent requirements for FDA-regulated clinical trials. Additional requirements such as these are acceptable so long as they do not conflict with or confuse the core requirements of the uniform regulations. Moreover, by consolidating *all* agencies' regulations at 45 CFR Part 46 (by means of cross references from those titles of the *Code of Federal Regulations* germane to the activities of the other agencies), any remaining *additions* to the core requirements will be highlighted rather than being hidden

amongst a mass of repetitious requirements.

The Commission believes that the President has authority to bring about the necessary coordination and simplification of the rules recommended here. Indeed, the President has just issued an Executive Order which requires seven different agencies (or groups of agencies) that constitute the Intelligence Community to comply with HHS regulations governing research with human subjects. (3) Drawing upon this authority, the President could order the initiation of a government-wide process of consolidating the rules that would further the Administration's goal of regulatory reform. The task could be undertaken by an interagency group under the direction of the Office of Management and Budget, with participation by the President's Commission. The support of many of the affected agencies and departments can be anticipated; indeed, the Commission's official liaisons from several agencies have acknowledged the leadership role that they already assign to HHS and that they believe should be encouraged.

A timetable of 180 days should be established by the President to provide an incentive for the interagency group to resolve any remaining questions about the HHS core regulations and identify an initial set of special rules beyond the core that are needed by various departments and agencies. If action is not prompt, the Commission suggests that Congress enact legislation directing the Executive branch to establish by a specified date a uniform set of regulations under a lead agency.

2. The President should authorize and direct the Secretary of Health and Human Services to designate an office with government-wide jurisdiction to coordinate, monitor and evaluate the implementation of all regulations governing research with human subjects of Federal departments that conduct, support or regulate such research.

Comment: The central reasons for the first recommendation—a desire to eliminate needless complexity and duplication, and a recognition of the leading role already played by HHS—underlie this recommendation as well. At the moment, the President's Commission has such responsibility on a *study* basis, but the Commission's statutory life is a limited one and it does not have the supervisory duties and powers of a line agency. Further, once the core regulations have been consolidated, a substantial economy for the Federal government would be realized by assigning responsibility for

the review and implementation of the regulations to a single office. For example, it not only wastes Federal funds and personnel but creates needless trouble and expense for a research institution to have the functioning of its IRB monitored separately by each Federal entity that has a funding or regulatory role in research conducted at the institution. Thus, systematic responsibility for the adequacy of the rules and their implementation ought to be lodged in a single Federal office, and that office ought to be located within the Department of Health and Human Services. Should the Secretary choose to designate an already existing office within NIH or FDA to fulfill this function, the office so designated should be elevated to the level of the Office of the Secretary to emphasize its government-wide supervisory authority.

The existence of a lead office within HHS with coordinating and monitoring responsibilities for the system of regulation will relieve the other Federal entities of some of the substantial burdens of oversight and monitoring. Each Federal entity will still have to make its own administrative arrangements for the review of individual research projects. Some may have need for an office to ascertain that attention has been paid in each case to the regulatory requirements and to propose to the director of the agency and to the designated lead office within HHS any special regulations that are particularly appropriate for that entity's activities. Other Federal agencies may find that this function can be adequately executed by existing subunits within the agency that pass upon the scientific or fiscal aspects of grants and contracts. Still others may be involved in so few research projects involving human subjects that their internal arrangements for review and approval will involve the establishment of an *ad hoc* committee as needed for each project. All such administrative arrangements should be acceptable under the revised rules and procedures.

3. *Each Federal department or agency should have a comprehensive set of rules and procedures governing research with human subjects that applies consistently to all subunits within the department or agency.*

Comment: If Recommendations 1 and 2 are adopted, this recommendation will not need separate attention, since essential uniformity within each Federal entity would be a necessary consequence of uniformity among all entities. Unless or until the steps recommended above have been taken,

the reasons that led to those recommendations—namely, the pursuit of simplicity, economy and certainty—support the present recommendation even more strongly. Bureaucratic explanations for repetitious regulations peppered with minor variations are if not justifiable at least understandable between agencies, but not within subunits of a single agency.

Yet as described in Chapter Two, separate component parts within the Departments of Defense, Justice, and Transportation do each have different policies governing research with human subjects. The Defense Department reports that it is in the process of developing a department-wide set of regulations; the Department of Transportation reports likewise, but it gave the same report to the National Commission in 1977.

In addition, two departments have regulations that cover research supported through one administrative mechanism but not through another. The Department of Education requires IRB review for research supported by contracts, but not for grants. NASA requires IRB review for intramural research, but not for extramural research. No reason is offered—or apparent—for the different treatments afforded the different categories of research by these two departments.

The Commission believes that each Federal department or agency should have one set of rules and procedures applicable to all research with human subjects supported by the department. If the rules are sufficiently flexible, they can be applied to all modalities of research (*e.g.*, biomedical, behavioral, surveys, questionnaires, record reviews, and so forth). Therefore, the Commission sees no justification for differentiating among funding mechanisms or individual departmental components. This recommendation is made, as a formal matter, under § 1802(b) of the Commission's enabling statute (42 U.S.C. 300v-1(b)) to the Secretaries of Defense, Education, Health and Human Services, Justice and Transportation, and to the Administrator of NASA, for action within the specified time periods.

4. *All Federal departments and agencies that conduct or support research with human subjects should require principal investigators to submit, as part of their annual reports to the IRB and the funding agency, information regarding the number of subjects who participated in each research project as well as the nature and frequency of adverse effects.*

Comment: This recommendation, like the preceding one, is intended for implementation whether or not the full uniformity and centralization of Recommendations 1 and 2 are achieved. In any event, the Commission suggests the reporting requirements recommended here be uniform so that comparable data are available on a government-wide basis. (The timetable established by § 1802(b) of the Commission's authorizing statute applies to this recommendation unless the government-wide task force proposed under Recommendation 1 is at work within 60 days on a uniform set of rules and has published such rules within 180 days thereafter.)

In preparing its report on *Compensating for Research Injuries*, the Commission was disappointed to discover that data on the number of human subjects who participate in Federally funded research are not routinely and systematically compiled. Data regarding the incidence and severity of injuries that occur in such research are also not collected. The inability to obtain such information was one of the most frustrating aspects of the Commission's attempt to determine whether a program to compensate individuals for injuries resulting from their participation in research is needed. Federally funded investigators are already required (under the terms of their grants and contracts) to report on their projects at least once a year. A requirement that they note in such reports the numbers of subjects and of injuries during the period in question would add only a trivial burden while yielding a large benefit.

The Commission recommends that copies of such reports be collected and reviewed by the IRB at the institution in which the research is conducted and then forwarded to a specified office within the funding agency to be collated. Those with oversight responsibility for human research—at Congressional, Presidential or Departmental level—will then be able to obtain information about the number of human subjects and the number of injuries from each Federal agency supporting research with human subjects as well as from each institution conducting such research with Federal funds. This information seems the minimum necessary for public accountability regarding such an important and sensitive enterprise as collectively supported research with human beings.

The Commission is aware of the difficulty of defining injuries or adverse effects in a way that will avoid massive reporting of trivia but at the same time

encourage the reporting of significant problems. The Commission notes, however, that several institutions with insurance programs have found means of categorizing harmful effects and that the Veterans Administration has recently implemented a reporting requirement along the lines recommended here. Its initial experience points to some administrative difficulties needing further attention, both by the V.A. and by other Federal entities implementing this recommendation. Concurrent with such implementation, the Commission suggests that the agencies (ideally, with coordination by the designated "lead office") work together to resolve any remaining definitional problems (e.g., determining whether *under-* or *over-*reporting occurs if transient effects such as mild to moderate headache, nausea, and the like are not reported unless they persist so long as to interfere with the subject's normal activities; determining the extent to which injuries caused by the research process can be distinguished from those caused by the treatment being tested or by the subjects' disease or condition; etc.). A certain amount of trial and error may be necessary before the optimal definition is developed; nevertheless, refinements and adjustments can be made over time. It is important to make a beginning.

5. *The Department of Health and Human Services and all other relevant Federal departments and agencies should proceed promptly to take action on the National Commission's recommendations concerning research involving children and research involving those institutionalized as mentally disabled, and other Federal agencies should also act on the final regulations of HHS governing such research.*

Comment: It is now four years since the National Commission for the Protection of Human Subjects transmitted to the Secretary, HEW, its recommendations concerning research involving children and research involving those institutionalized as mentally disabled. (4) Those recommendations address a very complex and sensitive topic: Research with subjects who are unable to give legally valid consent to their own participation. The subject is complicated because state law on "proxy consent" is not well developed or clear. The procedures and standards recommended by the National Commission were intended to provide greater protection for children and the mentally disabled than exists under the basic HHS rules. Under current regulations, children and

the mentally disabled may be enrolled in research even over their express objections on the basis of parental or guardian consent. Ironically, since the National Commission's recommendations would erect special protections, their adoption might actually facilitate research, since scrupulous compliance with their terms might lay to rest concerns over the status of "proxy consent" in research under the common law.

The legislation that created that Commission required the Secretary to publish those recommendations within 60 days of receipt, and to publish the Department's response (in the form of proposed rulemaking) within the next 180 days. (5) Although no deadline for implementation of final regulations was set forth in the National Commission's enabling legislation, the President's Commission is certain that Congress anticipated an orderly and expeditious proceeding. Surely, it did not contemplate that the Department would prolong its rulemaking over a period of years.

The President's Commission agrees with the National Commission about the importance of pediatric research and of research to prevent or alleviate serious cognitive and emotional disorders. This Commission also shares the concerns of the National Commission that the subjects of such research be properly protected. The Commission concludes, therefore, that the time is long past for action, either by adoption, rejection or modification of the National Commission's recommendations. This recommendation, like Recommendations 3 and 4, is made pursuant to § 1802(b) of the President's Commission's authorizing legislation, to the Secretary of Health and Human Services, and to the heads of all other Federal entities that conduct or support research with children or institutionalized mental patients. Within 60 days, this recommendation shall be published by each agency, and each agency is then obliged within 180 days to act upon the recommendation, favorably or unfavorably, and to announce its disposition and reasons. The President's Commission would regard this requirement to be met by a *single* publication in the **Federal Register** if the government-wide task force proposed under Recommendation 1 is at work on establishing a uniform set of rules and regulations by 60 days from the date of this Report and has published proposed uniform regulations within 180 days thereafter. Plainly, such unified action would avoid adding to the needless

duplication that already characterizes regulations in this field.

6. *Congress should attach the following condition to any direct appropriations for "private" research entities: "No funds appropriated under this Act may be used, directly or indirectly, to support research involving human subjects unless such research is reviewed and conducted in compliance with either (1) appropriate regulations of (the disbursing agency) or (2) the regulations of the Department of Health and Human Services (45 CFR Part (46))."*

Comment: It has come to the Commission's attention that Federal monies are appropriated to organizations that are established as private, non-profit corporations. In the case of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., which conducts research on tropical and other diseases in Panama, the funds are disbursed through the Fogarty International Center at the NIH, but the Fogarty Center lacks authority to require the Gorgas Institute to follow the rules on the protection of human subjects that attach to other research that receives funds from NIH. In the absence of specific legislation, such recipients of direct appropriations are not required to comply with any regulations governing research with human subjects.

The Commission recommends that Congress attach conditions to its appropriations that would require compliance with regulations for the protection of human subjects participating in research supported by those funds. As noted above, the Commission would prefer to see a uniform standard applied to all research supported by Federal monies; if this is to be accomplished, private organizations receiving "line item" appropriations should have to comply with the designated standard. Even if uniformity of regulations among agencies is not achieved, however, the Commission recommends as an alternative that Congress require such entities to comply with the regulations of either HHS or of the disbursing agency, if other than HHS.

B. *Recommendations for Improving Institutional and Federal Oversight of Research and the Response to Reports of Misconduct.* As discussed in Chapters One and Three of this *Biennial Report*, the Commission has concentrated its efforts regarding Federal regulations for the protection of human subjects on scrutinizing the adequacy of Federal oversight and the *implementation* of the regulations. Several recommendations on implementation and Federal compliance activities are made in this

Report pursuant to § 1802(b) of the Commission's statute; the process of review is ongoing and further recommendations may be forthcoming in the next *Biennial Report*.

Examining the implementation of the present regulations has, moreover, revealed certain problems with those regulations themselves. These problems emerged through the Commission's hearings on, and studies of, instances of alleged fraud or abuse in research involving human subjects. The few cases of alleged misconduct examined by the Commission should not be regarded as grounds for indicting the research enterprise in general or the IRB system in particular. Rather, the cases demonstrate the need for an oversight process that would provide the systematic data necessary to place the "problem cases" in context and to justify the confidence generally expressed regarding the present system. Furthermore, the cases bring to the fore basic questions about the role and functions of IRBs, questions that will be the subject of further study by the President's Commission during the preparation of its next *Biennial Report*.

For the moment, the Commission has identified several aspects of institutional responsibility in need of clarification in the HHS regulations (which, it is assumed, will soon have even broader applicability as the formal basis for government-wide standards). These matters are addressed in Recommendations 7 and 8.

7. *45 CFR 46.103, which specifies the minimum requirements for an institutional assurance, should be amended by inserting two new clauses under (b):*

(5) The designation of a specific office within the institution that will be responsible for: (i) receiving reports of alleged misconduct in research involving human subjects; (ii) investigating promptly and fairly; and (iii) reporting formal findings of misconduct both to the institution's IRB which approved the research and to the Secretary.¹ The institutional office so designated need not be created specifically for this purpose but may be the relevant IRB itself or another existing office already having responsibility for quality assurance within the institution. Such office shall report all ongoing investigations of alleged research misconduct involving human subjects as well as formal findings to the IRB, and shall consult with the IRB on all matters relating to the conduct of research with human subjects.

(6) Written procedures for insuring prompt reporting to designated institutional officials, and by them to the Secretary, of the results of any investigation or inquiries carried out under the preceding subsection or under § 46.108(c) that reveal research misconduct or serious or continuing noncompliance with

Federal or institutional requirements for the protection of human subjects.

Note.— Footnote 1 in the existing 45 CFR Part 46 specifies the Office for Protection from Research Risks as the place where reports should be filed within the Department.

Comment: Recommendation 7 is closely related to Recommendation 8. Taken together, the two recommendations seek to clarify the roles and responsibility of IRBs and other offices within research institutions in assuring compliance with Federal regulations. Detailed commentary follows Recommendation 8.

8. *45 CFR 46.108(c) should be revised to read as follows:*

(In order to fulfill the requirements of these regulations, each IRB shall) ***

(c) Be responsible for reporting to the appropriate institutional officials any serious or continuing noncompliance by investigators with the requirements and determinations of the IRB, or with the provisions of these regulations, or with good research practices, that is revealed during the IRB's continuing or annual review of research or through reports made directly to a member of the IRB or its staff.

(d) Establish procedures for receiving and acting upon findings of misconduct in research involving human subjects, made by the office designated pursuant to § 46.103(b)(5).

Comment: These two recommendations will add language to the HHS regulations, but they will actually simplify those regulations by making clear that institutions may employ a variety of internal arrangements to deal with alleged misconduct by researchers. These proposals result from the Commission's reexamination of the HHS rules with an eye toward the great diversity of institutional structures and administrative procedures to be found in universities, hospitals and other research institutions.

As written, the HHS regulations appear to place on the IRB responsibility for investigation and adjudication of all questions or allegations that arise about research with human beings. The regulations also appear to require that IRBs communicate their findings directly to the Department rather than through normal internal channels at their institutions. In some (perhaps most) institutions, however, the IRB may not be the body best suited, by tradition, knowledge or institutional role, to perform these functions. The Commission received forceful testimony from IRB members at several research centers as well as from institutional officials and invited consultants that IRBs should not perform monitoring, investigative, or adjudicative

functions. (6) In their view, such responsibilities would interfere with the primary role of IRBs: to educate and advise research scientists regarding their obligations toward human subjects and to resolve problems in a constructive manner. The Commission notes that most research institutions already have established appropriate quality assurance mechanisms and that efficient management would be impaired by splitting such duties between two offices.

Yet, as part of their responsibility to maintain "continuing review" of research projects they have approved (§ 46.109(e)), IRB members do need to know of any findings of misconduct. Therefore, rather than being "responsible for reporting to appropriate institutional officials" about violations of relevant rules (§ 46.108(c), emphasis added), at most institutions the IRB should be one body to which others (who are responsible for investigating and adjudicating) communicate the results of their investigations.

Relatively few incidents serious enough to warrant full-scale investigation and adjudication are expected to occur in human research that has undergone advance review and approval. To resolve such matters, it is expected that most institutions will choose to rely on an already existing body. Only under exceptional circumstances will a special office or committee need to be created within an institution's research administration to handle these functions. Flexibility in format may be retained by designating a particular official (such as "the Vice-President for Research"), who can fulfill his or her responsibilities by calling upon any standing or *ad hoc* committee that would be appropriate in light of a specific problem. In any case, the duty ought to be that of the institution itself (under § 46.103), but need not necessarily be lodged with the IRB (under § 46.108), although an IRB is not precluded from this role under the Commission's recommended amendment to § 46.103.

The Commission therefore recommends that HHS clarify its regulations to make explicit that the investigation and adjudication of alleged misconduct may be conducted by those offices already charged with such responsibilities. Representatives of the Department have assured the Commission that this is the intent of the regulations and that assurances reflecting such institutional arrangements are acceptable.

The details of process and procedure need not be recited in the institution's

assurance with HHS, but they do deserve advance thought and planning by the institution. Experience is a great teacher, but preparation can provide certainty and a better chance for order and fairness. Thus, the assurance should guarantee that whatever mechanism the institution chooses will be able to provide: (i) A prompt investigation; (ii) an impartial adjudicating body; (iii) full opportunity for the complaining parties and the accused to explain their positions, present evidence, call witnesses, etc; and (iv) protection from institutional reprisals for good faith complainants and witnesses.

Every effort should be made to encourage institutional personnel to report problems through internal channels. The responsible office should not only be identified in the institution's written assurance but should also be announced to all research personnel and subjects (*e.g.*, by a statement on the consent form giving the name of a responsible official to contact in the case of problems). The use of internal channels will also be encouraged if institutions protect those who report in good faith, resolve problems informally to the extent possible, and impose appropriate disciplinary measures for serious acts of misconduct. Procedures to protect against institutional reprisals should also be publicized and all staff should be made aware of their obligation to assist the administration in upholding high standards of conduct.

Whenever the body responsible for resolving allegations of misconduct is *not* the IRB, the institution's assurance ought also to guarantee at least that the IRB will be kept informed and consulted regarding any alleged misconduct that involves or may affect human research subjects. The institution must assure the Department that the latter will be notified of any relevant findings. Serious misconduct should be reported to the cognizant Federal agency, once a formal determination has been made. Administrators and investigators receiving Federal funds should understand that they have a legal obligation to do so and that knowing provision of false information to the Federal government is a felony. If an institution makes a formal finding that false information has been contained in a grant application, annual report, or data submitted to a regulatory agency, the institution may incur criminal liability if officials fail to report such a finding. Although an IRB should not officially be placed, as a body, in the awkward position of being a (toothless) watchdog for laxity on the part of superior officials within an institution,

neither the regulations nor institutional rules should preclude the IRB (or individual members) from making reports directly to the Department if required under unusual circumstances.

Education and attitude can play a large part in encouraging adherence to professional norms and standards. Federal administrators can aid this process by giving more precise meaning to phrases such as "material failure to protect human subjects" and by spelling out the standards governing the imposition of sanctions (issues about which the Commission is continuing to hold discussions with HHS officials). Institutional administrators can establish a clear commitment to upholding professional standards and enforcing Federal regulation by taking reports of problems seriously and by acting promptly and fairly to resolve complaints.

Professional societies and state licensing boards can also encourage adherence to scientific norms and compliance with Federal regulations governing research with human subjects. The principle of adhering to legal and regulatory requirements, like adherence to basic ethical norms, has been endorsed by many bodies in professions that conduct human research. These principles also deserve to be highlighted in professional codes of ethics and/or in the official commentary on such codes. More attention should be devoted to ethical and regulatory standards for human research as part of post-doctoral training in clinical investigation. Clear actions of this sort would provide a warning to all that misconduct in research may be a basis for disciplinary action by professional societies and specialty boards and even by state licensing boards.

9. Federal departments and agencies should establish government-wide procedures for making determinations on suspension and debarment of grantees and contractors alleged to have engaged in misconduct in Federally supported research with human subjects. Final determinations and sanctions imposed should be entered onto a consolidated list of individuals and made known to all Federal agencies involved with human research, to state licensing boards, and to appropriate professional societies.

Comment: The immediate cause for concern is the apparent need for NIH and FDA to clarify standards and procedures for response to reports of misconduct in research under their jurisdiction. All Federal entities should work together, under the lead of the newly designated "lead office" in HHS,

as proposed in Recommendations 1 and 2 above, to formulate and apply a uniform set of standards for the investigation of incidents in which any agency has a regulatory interest. Procedures to protect both those who are accused and those who make good faith reports of misconduct should be developed and made known to all agency staff who might receive such reports or participate in the subsequent investigation. Gradations in penalty—from a temporary suspension of grant support to a lengthy debarment from all Federal research activities—will be needed to reflect differences in the degree of an investigator's culpability. Consideration should also be given to methods for "rehabilitation" of a researcher or institution and for expungement of the record.

Currently, an individual who is debarred or suspended by one Federal agency from receiving further grants and/or contracts remains eligible to receive research funds from other Federal agencies. Indeed, the other agencies may not have any knowledge of the administrative sanctions imposed by the first. The Commission believes that any investigator found to have failed to protect human subjects or otherwise seriously violated the conditions of a research grant from one agency should not be eligible to receive Federal support for the same, or similar, research from other agencies for an appropriate period of time. The mechanism recommended would provide an efficient and fair procedure for assuring that scientists cannot go "forum shopping" for more lax or lenient agencies once a final administrative finding of misconduct has been made. It would also provide assurance that such findings would be made only after the accused scientist has been afforded adequate notice of the charges and an opportunity to answer those charges at an administrative hearing, with representation by counsel and an opportunity to present evidence (see Appendix G).

Formal determinations should also be actively shared with appropriate state licensing boards and national organizations such as professional societies and pharmaceutical manufacturing associations. Although such information is currently available on request, no attempt is made to forward reports to other agencies or boards unless a specific request is made.

Footnotes

(1) *Commission on Federal Paperwork Education*, US. Government Printing Office, Washington (1977), Recommendation 9 et 41.

(2) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Institutional Review Boards*, U.S. Government Printing Office, Washington (1978), Recommendation (1)(B) at 3.

(3) Executive Order 12333 (December 4, 1981) applies to all members of the Intelligence Community, which is defined (in § 3.4(f)) as including: (1) The Central Intelligence Agency; (2) the National Security Agency; (3) the Defense Intelligence Agency; (4) the Offices within the Department of Defense for the collection of specialized national foreign intelligence through reconnaissance programs; (5) the Bureau of Intelligence and Research of the Department of State; (6) the intelligence elements of the Army, Navy, Air Force, and Marine Corps, the Federal Bureau of Investigation, the Department of the Treasury, and the Department of Energy; and (7) the staff elements of the Director of Central Intelligence.

(4) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research Involving Children*, U.S. Government Printing Office, Washington (1977); National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm*, U.S. Government Printing Office, Washington (1978).

Specifically, both children (age 7 and over) and the mentally disabled would be given an explanation of the proposed procedures geared to their level of understanding and, if the research presented no likelihood of benefit to them, would have an opportunity to assent or refuse to participate. In addition, research presenting more than minimal risk and no likelihood of benefit to the subjects would be permitted to involve children or the mentally disabled if: (a) The risk is no more than a minor increase over minimal; (b) the research is relevant to the subjects' condition; and (c) the research holds out the promise of significant benefit in the future to either the subject or others with similar disorders or conditions. Finally, the National Commission recommended review at a national level (with opportunity for public participation) of proposed research that would present more than a minor increment of risk and no anticipated benefit to children or the mentally disabled but may be of major significance to the solution of a serious health problem affecting persons similarly situated. As noted earlier, action on these recommendations might clear the way for important research on severely disabling conditions such as senile dementia of the Alzheimer's type.

(5) National Research Act, Pub. L. 93348, § 205 (1974).

(6) Erica Heath has suggested several types of "monitoring" activities carried out by IRBs: (1) Periodic reappraisal of an on-going project based upon review of documents prepared by the investigator; (2) review of the actual consent process; (3) review to ascertain that the investigator is adhering to the protocol:

and (4) oversight in an institution to identify unapproved research. Erica J. Heath, "The IRBs Monitoring Function: Four Concepts of Monitoring," 1 *IRB* 1-3 (Aug./Sept. 1979). Dr. Levine raises provocative questions about the "field work" by IRB members entailed in the last three classes of activities. Robert J. Levine, *Ethics and Regulation of Clinical Research*, Urban & Schwamberg, Baltimore (1981) at 231-33.

Appendices

A. Regulations of the Department of Health and Human Services Governing Research With Human Subjects (45 CFR Part 46.)

B. Summaries of Federal Agencies' Rules and Procedures Governing Research With Human Subjects.

C. List of Agencies Included in Commission's 1980 Survey.

D. Correspondence with the Secretary, HHS Regarding Amendments to the Department's Rules Governing Research With Human Subjects.

E. Case Studies: Five Incidents of Alleged Misconduct in Biomedical Research.

F. Correspondence with HHS Officials Regarding Procedures for Responding to Reports of Misconduct.

G. HHS Debarment Regulations and Related Rules Governing Suspension and Revocation of Grants and Contracts.

H. Correspondence with the Deputy Director, Office of Management and Budget.

I. Witnesses Who Testified at Commission Hearings.

J. Participants in the Workshop on Whistleblowing in Biomedical Research.

Note.— In order to avoid excessive duplication, only Appendix E is reproduced in this prepublication copy of the Report. All appendices will appear in the published version. For further information, please contact Andrew Burness, Public Information Officer, at (202) 653-8051.

Case Studies: Five Incidents of Alleged Misconduct in Biomedical Research

During 1980 and 1981, a number of incidents of alleged misconduct in the performance of Federally regulated research received national attention in the press. Using the press accounts as a point of departure, Commission staff assembled copies of original documents from which to piece together a description of five such incidents. (Copies of all documents cited in the

footnotes are retained in the Commission's files.) In one or two instances, where the absence of a specific procedure seemed important and the documents (although suggestive) lacked precision, the matter was confirmed by telephone conversation both with the pertinent Federal officials and with other persons involved in the matter. As the material makes clear, some of the cases have been through the entire process of HHS investigation and imposition of sanctions: other cases are still under investigation. They are recounted here for the light they may

shed on local and Federal oversight processes (as discussed in Chapters Three and Five) and not as a basis for drawing any adverse conclusions about research or the IRB as a means for its regulation.

1. *Boston University*. In June 1978, junior members of a research team in the oncology unit of Boston University Medical Center reported to hospital administrators that data had been falsified both in research reports and on individual patients' medical records. They also alleged that there had been violations of HEW rules on IRB review and informed consent. Within two weeks, hospital administrators had convened an ad hoc investigative committee, received its reports, and initiated procedures to remove the principal investigator from its staff. They also alerted the funding agency (the National Cancer Institute) and the collaborative oncology group to which data from the research unit were submitted. In July, officials from the B.U. Medical Center met with high level staff at the Cancer Institute to provide further information on the incident, but were told that NCI "Cannot intervene in the internal affairs of institutions, or pass judgment on individuals, in situations in which we are not directly involved." (1)

Approximately six months later, in January 1979, the Cancer Institute approved and encumbered research funds in the amount of \$1 million for the principal investigator of the B.U. Medical Center Project who by then had taken a position at a medical center in New York. None of the review groups at NIH that approved the subsequent research grant were told of the charges against the principal investigator. Two years later, after a five-day series of articles on the incident was published in the *Boston Globe*, (2) the Cancer Institute requested an investigation of the matter by the NIH Division of Management Survey and Review. (3) That investigation is still in progress, as is a parallel investigation initiated the same month by OPRR.

2. *University of Kansas*. In March 1977, two graduate students in the anthropology department at the University of Kansas lodged a series of complaints against a professor with whom they had worked, alleging that venepuncture and genetic counseling had been performed in a project in Central America by anthropologists and graduate students who lacked proper training for such activities. They further alleged that consent procedures were inadequate and that Federal funds had been misappropriated. The Vice Chancellor for Research and Graduate

Studies at Kansas found many of the charges to be unsubstantiated, but also found that the principal investigator had embarked on the research without the necessary IRB review and approval, in violation of university rules as well as applicable Federal regulations. A formal letter of warning was issued to the principal investigator, but no sanctions were imposed and no reports were made to the cognizant Federal agencies.

The graduate students, dissatisfied with the university's disposition of the matter, formally complained to the then Department of Health, Education and Welfare in September 1977, as well as to several professional societies, including the American Anthropological Association. The Executive Board of that Association considered a report of a special *ad hoc* Committee of Inquiry in April 1980 and concluded "that there are no grounds for action under the Principles of Professional Responsibility." (4) Here, as in the Boston University case, the principal investigator subsequently received additional HHS research funds. The Department's investigation into the matter is still in progress.

In both incidents, those who reported the alleged misconduct have fared badly. At Boston University, the junior members of the research team were dismissed along with the principal investigators when the project was halted and a multi-million dollar suit has been filed by the principal investigator against some of them for tortious interference with contractual relations. At the University of Kansas, adverse actions were taken with respect to the graduate students' academic standing. (The students and the administration differ as to the basis of those actions.) A million dollar suit for slander and libel was also filed in Kansas against the graduate students, their lawyers, and others who assisted them in pursuing their complaints. It is not clear whether the investigations under way at HHS will be completed in time for the findings to be introduced as evidence in any of the pending litigation.

3. *FDA Disqualification of Dr. Nathan Kline.* On November 13, 1980, the Food and Drug Administration (FDA) disqualified New York psychiatrist Nathan Kline from further drug testing on human subjects. (5) This action followed hearings in September and October 1979, which were held as a result of an inspection of Dr. Kline's activities in April and May 1978. The disqualification was based upon Kline's persistent and deliberate violations of FDA rules by giving patients potent drugs not approved for human studies.

There were also serious breaches of rules on informed consent and on record keeping. The FDA Commissioner concluded that Dr. Kline's action adversely affected the safety of his subjects and therefore formally disqualified Dr. Kline from further investigational drug studies over which FDA has regulatory authority.

The Commission subsequently inquired of OPRR about the effect Dr. Kline's FDA disqualification would have on his eligibility to receive NIH grants or contracts. Specifically Section 76.10 of the HHS debarment regulations promulgated in 1980 applies only to "serious violation of the applicable statutes, regulations, or other terms and conditions of a previous award of financial assistance" or to "debarment from Government contracting, subcontracting or financial assistance by a Government agency (including an agency within HHS)." Therefore, it is not apparent whether debarment from activities under Federal regulation (*e.g.*, by FDA) would necessarily be interpreted as cause for debarment under Section 76.10. (6)

In reply, Dr. McCarthy, OPRR's director, reported that his office had been alerted by FDA about Dr. Kline's formal disqualification (some four or more months after the determination had been reached) and had placed his name on an "alert" system so that appropriate NIH officials would be notified if any applications for research grants or contracts are received from Dr. Kline in the future. (7) (It does not appear that the "alert" system is specified in any HHS regulations, so that the Commission is unable to evaluate the appropriateness of the criteria employed for a person's inclusion nor for the sanctions, if any, that are imposed on those included.)

Dr. McCarthy further reported that Dr. Kline currently had no research support from either NIH or ADAMHA (the Alcohol, Drug Abuse, and Mental Health Administration) and that the FDA disqualification would not automatically result in NIH debarment or even in the initiation of debarment proceedings. Instead, NIH would take the reasons for the FDA disqualification into account "along with all other pertinent information" in considering whether to initiate debarment proceedings. (8) Although it is technically correct that there are no NIH or ADAMHA research grants to Dr. Kline as principal investigator, there is—apparently unbeknownst to OPRR—an NIH Biomedical Research Support Grant to Rockland Research Institute which lists Dr. Kline as the Program Director. (9) The

most recent award under that grant (now in its 15th year) was in the amount of \$36,174 covering a period from April 1, 1981 through March 31, 1982. Dr. Kline is member of an 8-person committee at Rockland Research Institute that decides how the money will be allocated. (10) For a person "disqualified" by the FDA, the consequence in terms of research support from HHS may be both more and less than one would gather from the regulations.

4. *UCLA Medical Center.* Early in 1979, a group of nurses complained to the IRB at the UCLA Medical Center that physicians had been performing experimental bone marrow transplants without IRB approval. Although it is not entirely clear to what extent the transplants and accompanying chemotherapy were innovative, "last-ditch" therapies for seriously ill patients, and to what extent they constituted "research," UCLA rules require review of all such activities by the IRB (known at UCLA as the Human Subjects Protection Committee). In fact, in a letter to the Commission staff, Dr. Sherman Mellinkoff, the Dean of the Medical School, reported that: "the investigators made a misjudgment when they altered the protocol for the treatment *in vitro* of bone marrow obtained for patients in remission prior to its reinfusion into the patient from whom it had been obtained." (11)

Dr. Mellinkoff further reported that as a result of an inquiry by a panel of physicians appointed by the administration of the medical center, the researchers "were told that the university's policy was to follow precisely the regulations related to human subjects protection * * * [and] that serious violations of these regulations would require us to request that the funding agencies withdraw their support." Dr. Mellinkoff further noted that "since (then-applicable) Federal regulations do not require reporting of an inquiry or warning by a university to its researchers and since no patient had been endangered by the change in protocol, the funding sources were not notified." (12)

Nevertheless, one of the UCLA physicians working on experimental bone marrow transplantation, subsequently became the first biomedical investigator formally sanctioned by NIH for violations of human subjects regulations in research supported by HHS. These sanctions resulted from another experiment in which patients in Israel and Italy were treated with altered bone marrow in violation of applicable rules governing

both the use of recombinant DNA techniques and the protection of human subjects. (13) Specifically, Dr. Martin J. Cline failed to disclose to the IRB at Hadassah Hospital in Israel, or to the patients in Israel and Italy, that the bone marrow transplants would contain recombinant DNA material (14) despite the fact that the review board at Hadassah went to considerable lengths to verify that the procedure would *not* involve recombinant DNA. (15) (There are no review committees in Italy comparable to IRBs. (16)) Moreover, the procedures he used were the same as those submitted to the IRB at UCLA in May 1979 and disapproved on July 16, 1980, after four outside consultants all advised that more animal studies should be conducted prior to human experimentation. (17)

The UCLA "general assurance" with HHS specifically states that all research performed by UCLA employees (even if performed elsewhere) must be reviewed by an IRB at the collaborating institution; and UCLA must receive a report of that review. (18) Although no NIH funds were used to perform the studies abroad, or to pay the cost of the trip, the materials used in Israel and Italy were prepared at UCLA as part of research supported by NIH. (19)

The Office for Protection from Research Risks at NIH first became aware of the possibility that Dr. Cline had performed research using recombinant DNA and in violation of NIH rules in September 1980. Following a letter from the NIH Director to the UCLA Chancellor, and the Chancellor's reply, the Director established an ad hoc committee to consider the report from UCLA, determine whether NIH regulations had been violated, and recommend appropriate action. Meanwhile Dr. Cline's resignation from his position as Chief of Hematology and Oncology was accepted by the UCLA Chancellor and the Medical School Dean as appropriate under the circumstances.

The NIH ad hoc committee reported in May 1981 that Dr. Cline's activities violated both the NIH Guidelines on use of recombinant DNA and the Department's regulations for the protection of human subjects. The Committee recommended that four actions be taken and NIH Director Fredrickson accepted them all: (1) Prior NIH approval will be required for any new application from Dr. Cline for NIH support of research involving human subjects; (2) prior NIH approval will be required for each project of his involving recombinant DNA (3) the Director of each NIH Institute currently supporting

research grants for which Dr. Cline is principal investigator should forward the report of the Ad Hoc Committee to the Institute's Advisory Council for advice regarding continuation of such grants; and (4) for each application for new or competing renewal of NIH grants, the study sections and National Advisory Councils shall consider the report of the Ad Hoc Committee in making decisions regarding support of the research. (20)

All four recommendations were implemented. In September and October 1981, National Advisory Councils of the three NIH institutes that had been funding Dr. Cline's research reviewed the ad hoc committee's report and forwarded their recommendations to the Acting Director, NIH, through the Associate Director for Extramural Research and Training, who endorsed all but one recommendation. (21)

The National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases has been supporting Dr. Cline's research in "A New Method of Bone Marrow Culture," providing \$33,172 in direct costs for September 1981-August 1982, and for the next two years, \$41,232 and \$44,109, respectively. This institute recommended that each annual report be signed by a responsible official of UCLA certifying that the research was carried out "in keeping with the intent and conditions for which the award was made." (22)

The National Heart, Lung, and Blood Institute is currently supporting Dr. Cline's research on "Treatment of Hemoglobinopathies by Gene Insertion," providing \$81,647 in direct costs, the first year, and \$78,647 and \$83,787 in two subsequent years. Its Advisory Council, after considering the record and debating the issues, concluded that "the actions of Dr. Cline are reprehensible and * * * warrant disciplinary action." The Council supported the NIH actions already taken and further recommended that Dr. Cline provide assurance that he will not engage in human experimentation involving recombinant DNA for a period of three years. Finally, the Council voted to terminate the Heart, Lung and Blood Institute's support of Dr. Cline at the end of the first year (March 31, 1981.) (23)

The National Cancer Institute has been funding two grants of which Dr. Cline is principal investigator; one, a research grant, was funded through November 1981 but was scheduled to run through May 1982; the other, a project grant covering four program areas in medical oncology, has been revised by UCLA for consideration for renewal with a new principal

investigator. The National Cancer Advisory Board recommended that Dr. Cline's research grant be funded through the original scheduled termination date of May 31, 1982. The Board also recommended that the project grant be supported through February 28, 1982, to provide continuity until the revised application (with the new principal investigator) could be reviewed by the Board at its January meeting. The Board also recommended, however, that Dr. Cline not receive any further support from the extension of the grant. (24)

Although Dr. Cline had been asked to comment on a *draft* of the NIH ad hoc committee's report and had replied that he had no response to make "at this time," (25) he was not invited to respond at any other time or in any other manner to the charges against him. (26) Finally, knowing the ad hoc committee's negative conclusions but not knowing when the advisory councils would act upon them nor how to contact the councils, Dr. Cline sent a letter to the Executive Secretary of the ad hoc committee on September 17, 1981, to be forwarded to the advisory councils "providing arguments in support of his actions as well as more general comments on review and approval of innovative research." (27) That letter, however, was not received by NIH until September 28 and thus was too late to be taken into consideration by the two National Advisory Councils that reviewed his case on September 24 and 25. Only the National Cancer Advisory Board (which did not meet until October 6) had Dr. Cline's letter at the time of its consideration of the matter. (28)

Authorities cited by NIH for imposition of the sanctions included: (1) Grants administration regulations for terminating or suspending a grant and related provisions for appeal of such action to the Department's Grants Appeals Board; (2) HHS regulations for attaching conditions to grants as a consequence of poor performance; (3) the regulations governing research with human subjects that state that the Secretary may withhold or withdraw departmental support of research from investigators or institutions that "fail materially" either to comply with the terms of a grant or to protect human subjects; and (4) similar provisions contained in Guidelines governing NIH-funded projects involving recombinant DNA. (29) The regulations setting forth the procedures for debarment and suspension (that provide an accused scientist with notice and an opportunity for a hearing) were not invoked. (30)

5. *M.D. Anderson Hospital and Tumor Institute (University of Texas System*

Cancer Center, Houston). In June 1981, an employee of the National Cancer Institute (NCI) read a brief medical journal report by researchers at M.D. Anderson Hospital on the administration of a new drug, 5-methyltetrahydrohomofolate (referred to as MTHHF), to six cancer patients. The report was noteworthy because MTHHF had not been cleared for use in human subjects by either the Food and Drug Administration or by NCI at the time the research was conducted. Subsequent investigation revealed that the drug had been provided to the principal investigator by NCI under a contract explicitly limiting its use to animal research. NCI officials immediately wrote to administrators at M.D. Anderson and to the principal investigator, suspending further work on MTHHF and announcing a site visit to take place on July 13, 1981. (31)

The significance for the President's Commission of the lengthy site visit report and accompanying documents lies not solely in what was discovered about the MTHHF experiment that was conducted in 1980, but rather in the evidence that was turned up which reveals serious deficiencies in the review process at M.D. Anderson and in the response to that evidence made by officials at NCI and NIH. Equally notable was the lack of communication between the NIH and FDA (which had inspected the IRB at M.D. Anderson less than half a year earlier). (32) This suggests that the coordinated oversight of IRBs falls a good deal short in reality of the system that is set forth on paper.

Among the documents reviewed by the site visitors were a protocol by another investigator for "Phase I Evaluation of Homofolic Acid" (homofolic acid is another name for MTHHF) and an accompanying consent form, both of which had been approved by the hospital's IRB in August 1978. (33) The study was never carried out as described in the 1978 protocol, but this was the only documentation available to the NCI site visit team, since the study actually conducted during 1980 was not based on a protocol or set of consent documents approved by the IRB. The information available about the 1973 protocol suggests that the consent form employed there was a general form used for Phase I trials (*i.e.*, only the name of the drug had to be filled in), and this surmise is confirmed by a later statement of a hospital administrator, who described the consent form as the standard one in use at the time, (34)

In light of the clear violation of both FDA and HHS rules that had brought the nine member site visit team

(including one representative of OPRR) to Houston, the apparent deficiencies in the IRB review procedures and in the standards for informed consent (which are described in greater detail below) might have triggered a broader investigation of the protection of human subjects at M.D. Anderson Hospital. Instead, sanctions were directed primarily at the principal investigator; broader remedies were limited to specific steps to tighten up the procedures of the hospital's pharmacy and a formal directive that the hospital "develop a document that describes in detail the policies and procedures for clinical research using investigational drugs, including protocol review and approval, IRB procedures * * *" (35)—the absence of which demonstrates failings that ought never to have existed if the institution's "general assurance" with HHS has been adequately implemented in the first place. A follow-up site visit to determine how well the procedures described in the new document are being implemented was deferred for six months; by contrast, a representative of the NCI's Investigational Drug Branch returned to M.D. Anderson on July 28, 1981 (two weeks after the initial site visit), to review records of additional studies. This second visit turned up further problems (both in protocol review and in consent forms) which were characterized by the Deputy Director of NCI as being "general" in nature. (36)

The problems with the MTHHF protocol as approved—which might have been shown to be "general" problems had OPRR also chosen to follow up immediately with a broader inquiry—were numerous. Three stand out: the lack of clarity about the type of study subjects were being asked to join, the failure to reveal potential adverse effects, and the misleading impression created that the drug—actually in the earliest phase of testing—was being offered as treatment of a disease.

The objectives of the study, as set forth in the approved protocol, were:

- (1) To determine the maximum tolerated dose of MTHHF administered by single dose intermittent intravenous infusion;
- (2) To determine the qualitative and quantitative toxicity and reversibility of toxicity of MTHHF administered in this fashion; and
- (3) To investigate the clinical pharmacology of MTHHF and rationale for dose and schedule chosen.

These objectives fell into two groups: (1) and (2), which concerned toxic effects, and (3) which was aimed at discovering the drug's metabolism, absorption and the like. Together, these objectives define a "Phase I test," as the FDA

terms it—namely, research to answer basic questions about pharmacokinetics and safety through initial trials in the first few human beings after laboratory and animal work has been completed.

It is a matter of some importance that these two sets of purposes be made very clear, both in the protocol and (particularly) in the consent form, since the effects of the two aspects of the study are likely to be very different for the subjects. In the second branch of this experiment, it was intended to give a relatively small dose of MTHHF "labeled" with a small amount of radioactivity. This amount would be too small to be expected to have any effect on patient-subjects' tumors. The size of the dosage probably explains why the consent form would put these words into a prospective subject's mouth: "I understand * * * that the amount of drug used solely for the pharmacology studies * * * will be free of toxic effects." (37)

Any subject who understood the term "pharmacology studies" to be synonymous with the experiment itself—an understandable, indeed predictable, mistake, given the way the consent form is written—would have gotten the misleading impression that the study *as a whole*, to the extent it was not treatment, would be "free of toxic effects." Yet, the other branch of the study design was actually a search for "the highest dose which does not cause the following toxicities," which had been reported from studies on dogs and monkeys: (38)

severe hemolytic anemia, * * * congestive heart failure, life-threatening arrhythmias, * * * severe diarrhea requiring hospitalization for fluid replacement, * * * coma, seizures, nerve paralysis, progressive mental deterioration or weakness.

The standard to be used was that if three patients develop any of the above toxicities at a similar dose level during Phase I evaluation, the dose will be considered to be above the maximum tolerated dose. (39)

The amount of the drug that would produce those effects in humans was unknown; by step-wise increments (or decrements, if the initial guess on tolerable dosage was too high) the researchers intended to find the point where these (or other) toxic side effects would begin.

One would expect such possible consequences to be spelled out clearly in the consent form. They were not mentioned. Of course, under the HHS rules in effect at the time the protocol was approved, it was also (and still is) permissible to use a "short form" written consent that indicates that "the basic elements of informed consent have

been presented orally to the subject.” But in that case, “written summaries of what is to be said to the patient are to be approved by the Board.” The rules required that the form be signed not only by the subject but also “by an auditor witness to the oral presentation and to the subject’s signature. A copy of the approved summary, annotated to show any additions, is to be signed by the persons officially obtaining the consent and by the auditor witness.” (40) No such summaries were prepared for, or approved by the IRB (nor do any such forms and procedures appear to have employed in the MTHHF study actually performed 1980), which violated not only the HHS regulations but M.D. Anderson Hospital’s own general assurance. (41)

The failure of the consent form to describe the risks of the experiment is more grave because of another, perhaps central, deficiency in the form: it gives the impression that the cancer patient is being asked to consent to treatment, with perhaps some small added studies (“free of toxic effects”) on the side. The form does not make clear that MTHHF had never before been administered to humans and therefore that its possible efficacy was wholly unknown. The language of the consent form, as approved by the IRB, is instead replete with references to “therapy” and “my treatment.” Indeed, after formal language naming the physician and the “treatment,” the body of the consent form begins with the assertion: “I am about to receive a form of chemotherapy recommended by my physician. He has explained the potential benefits and hazards of this treatment to me. (42)

Although the NCI site visitors’ report did note that the consent procedures in this case failed to conform to the HHS regulations and the hospital’s general assurance, most of the attention (and subsequent sanctions) were based upon the principal investigator’s having acted on the (incorrect) assumption that in the two years since the IRB approved the protocol, appropriate clearance had been obtained from the FDA and NCI to administer the drug to humans. There was no apparent concern that the deficiencies revealed in the MTHHF consent form might be widespread or that the IRB should have mechanisms to assure that all additional certifications are in place prior to giving its final approval for a research project. (43) Nor did the site visitors find noteworthy the fact that at least two IRB members had disagreed as to whether the research would be “therapeutic” for the subjects and, moreover, had advised that

additional information be provided in the consent forms. (44)

The response of both NIH and the administrators at M.D. Anderson was to direct strong criticism and sanctions against the principal investigator. NIH terminated all work under the contract in question, except for two studies “of high programmatic priority” for which a new principal investigator was named, and the government sought reimbursement of funds used to support the unauthorized clinical studies. (45) The hospital, in addition, formally censured the principal investigator and barred him from further participation in studies involving human subjects. He was also relieved of all responsibilities as principal investigator or co-principal investigator on federal contracts or grants. Both of the latter sanctions are of indefinite duration but are subject to periodic review. (46)

A joint NIH/NCI panel that reviewed the site visit report added two additional sanctions: that the investigator’s infraction be brought to the attention of the appropriate NIH advisory council should he submit a grant or contract proposal during the next two year period and that he not be asked to serve on any NIH advisory committees or as a site visitor during that same period. (47)

The Director of OPRR reported to the Commission that his office engaged in additional correspondence and telephone calls with M.D. Anderson, following the formal imposition of sanctions by NIH, in an effort to improve the hospital’s overall review procedures. The only recommendations directed at the institution and formally endorsed by the Acting Director of NIH, however, were that its procedures for handling investigational new drugs be improved with respect to documentation, record-keeping and distribution from the pharmacy and that “documents be developed by the University which describe the policies and procedures for the clinical research utilizing investigational drugs, which will ensure compliance in the future with the NCI policy and HHS regulations for the protection of human subjects with follow-up visits by NCI and the Office of Protection for Research Risks [sic].” (48)

Throughout, officials at NIH remained unaware of the routine FDA inspection of M.D. Anderson that had taken place on March 20, 1981, (49) despite the assurances given to the President’s Commission that NIH has developed good communication with FDA and that “when FDA inspectors find any practice which may constitute noncompliance

with 45 CFR Part 46, the HEW regulations, OPRR is immediately notified.” (50) Perhaps OPRR was not notified of the clear deficiencies reported by the FDA inspectors because, although the reviewers noted a failure to conduct annual review of individual protocols (instead, the IRB reviewed and re-approved the “parent project” which might contain any number of individual protocols), the FDA classified the results of its inspection as “No Action [is] Indicated.” (51) The failure of the IRB to review each protocol, however, violates regulations governing research supported by HHS as well as FDA’s own regulations governing research with investigational new drugs. Moreover, while the FDA investigation showed that, in the case of the drug reviewed, the IRB had required modifications in the consent form, the important changes recommended by the two IRB members with primary review responsibilities in that case were not in fact incorporated in the revised form as approved. (52) Finally, the form (also for a Phase I drug study) is less than clear and candid about the likelihood (or lack thereof) of therapeutic benefit to subjects and contains “boiler plate” language that certain information has been provided, rather than a full description of the information itself. In the absence of any summary of the risks, the consent form and the IRB review process described in the FDA inspection documents appear not to meet the HHS regulations and the hospital’s general assurance, just as was true in the IRBs handling of the 1978 MTHHF protocol.

It appears, therefore, that neither the FDA nor the NIH has developed inspection procedures that are sensitive to significant factors; moreover, communication between FDA and NIH regarding their site visits is far from adequate. An additional problem is whether “Phase I” tests of new cancer drugs can be considered “therapeutic” and, if so, whether they should still be classified as “Phase I.”

Footnotes

(1) Letter to John I. Sandson, M.D., and John H. Betjemann from Arthur Upton, M.D., Director, NCI (August 3, 1978) agreeing with the position taken by his senior staff in July. A complete documentary account of the sequence of events at Boston University Hospital and NCI is contained in a chronology of events prepared by Commission staff and submitted with the testimony of the Executive and Deputy Directors at hearings held by Rep. Albert Gore, Jr., April, 1981. See, *Fraud in Biomedical Research*, Hearings Before the Subcommittee on Investigations and Oversight of the Committee on Science and

Technology, U.S. House of Representatives (March 31, April 1, 1981) at 136-139.

(2) "Spotlight" series, *Boston Globe*, Sunday, June 29 through Thursday, July 3, 1980.

(3) Memorandum from Dr. Vincent T. DeVita, Jr., Acting Director, NCI to Acting Director, Division of Management Survey and Review, NIH (July 3, 1980).

(4) Letter from Edward J. Lehman, Executive Officer, American Anthropological Association, to Anta Montet-White, Chair, Department of Anthropology, University of Kansas (April 28, 1980).

(5) Food and Drug Administration, Department of Health and Human Services *In the Matter of Nathan S. Kline, M.D., Commissioner's Decision*. (November 13, 1980).

(6) Memorandum from Deputy Director, President's Commission, to Director, OPRR (Feb. 19, 1981).

(7) Letter from Charles R. McCarthy (Director, OPRR) to Barbara Mishkin (Deputy Director, President's Commission) (May 19, 1981).

(8) *Id.*

(9) Grant #2S07RR05651-15.

(10) Letter from Dr. Thomas Bowery, Director, NIH Biomedical Research Support Program, NIH to Barbara Mishkin (December 2, 1981), attaching *14th Year Annual Progress Report* of Rockland Research Institute, which lists members of Allocation Committee at p. 6.

(11) Letter from Sherman Mellinkoff to Alexander M. Capron, Executive Director, President's Commission (February 5, 1981).

(12) *Id.*

(13) Statement of the Director, NIH, accompanying the release of the Report concerning Martin J. Cline, M.D. (May 26, 1981).

(14) Memorandum from Chairman, NIH Ad Hoc Committee on UCLA Report (transmitting the Committee's report) to Director, NIH (May 21, 1981) at 7-10, 16-21.

(15) *Id.* at 1415, 21.

(16) *Id.* at 10.

(17) *Id.* at 6. The IRB voted on July 16, 1960 to disapprove the protocol. Dr. Cline was formally notified on July 22; the procedure was performed on the patient in Israel on July 10, 1980 and on the patient in Italy on or about July 15, 1980.

(18) *Id.* at 1112.

(19) *Id.* at 20.

(20) Statement of the Director, NIH, *supra*, note 39.

(21) Memorandum from Associate Director for Extramural Research and Training to Acting Director, NIH (Nov. 12, 1981).

(22) *Id.*

(23) *Id.*

(24) *Id.*

(25) *Report of NIH Ad Hoc Committee*, *supra* note 40, at 19.

(26) Confirmed by personal communications (Nov. 23, 1981) with Dr. Charles McCarthy, Director, OPRR and Dr.

Martin Cline. Dr. Cline expressed frustration at his inability to get his explanatory letter to the Advisory Councils in time for them to take it into consideration, noting that no one told him the dates of the Council meetings or how to address communications to them.

(27) Memorandum from Associate Director for Extramural Research and Training, *supra* note 47.

(28) *Id.*

(29) *See*: 45 CFR Part 74, Subpart M; 45 CFR Part 16; 42 CFR Part 50, Subpart D; 45 CFR 74.7; 45 CFR 46.121-122; 45 FR 77384 (November 21, 1980).

(30) 45 CFR Part (45 FR 67262, October 9, 1980). In the executive summary of the regulations, Secretary Patricia R. Harris stated "the effect of the regulations will be to establish a procedure, with due process safeguards, to render persons ineligible to receive HHS financial assistance for reasonable periods of time." The regulations became effective on November 10, 1980.

(31) Memorandum from Deputy Director, NCI to Director, NCI (July 24, 1981) on: Clinical Pharmacology Study of [MTHHF] carried out at M.D. Anderson Hospital and Tumor Institute (University of Texas System Cancer Center) *Summary Report of NIH Site Visit Team*.

(32) Report of IRB Inspection of M.D. Anderson Hospital, FDA (March 20, 1981).

(33) *Summary Report of NIH Site Visit Team*, *supra* note 57. The protocol, numbered DT 78-31, the consent form, and the certification of IRB approval are among background documents attached to the site visit report.

(34) Testimony of James Bowen, Associate Vice President for Research, M.D. Anderson, before a joint hearing of the Subcommittee on Health and the Environment, Committee on Energy and Commerce and the Subcommittee on Oversight and Investigations, Committee on Science and Technology, U.S. House of Representatives (October 27, 1981).

(35) Report of NIH Site Visit Team, *supra* note 57, at 8. OPRR recently reported additional "intensive interaction" with M.D. Anderson "to develop revised procedures which explicitly bar 'Standard' or 'Master' [consent] forms." (Comments on November draft Biennial Report.) The use of Standard forms, however, was already explicitly barred by the hospital's 1975 "Code and Methods of Procedure" for activities involving human subjects.

(36) Memorandum from Deputy Director, DCT, NCI, to Director, NCI, on Follow-up on M.D. Anderson Site Visit (August 6, 1981).

(37) The consent form is contained in the *Summary Report of the NIH Site Visit Team*, *supra* note 57.

(38) *Id.*, Protocol DT 78-31 paragraph 3.14: Animal Toxicology.

(39) *Id.*, Protocol DT 78-31, Appendix A, Maximum Tolerated Dose.

(40) Section 46.110 of the 1974 regulations required documentation of the "actual procedure utilized in obtaining legally

effective informed consent and the basis for Institutional Review Board determinations that the procedures are adequate and appropriate." The documentation of consent was permitted to take one of two forms in biomedical research. When the "short form" written consent procedures was utilized, the document must indicate "that the basic elements of informed consent have been presented orally to the subject or his legally authorized representative." Sample copies of the consent form and of the summaries as approved by the Board must be retained in its records.

More typically, a subject is provided with "a written document embodying all of the basic elements of informed consent. This may be read to the subject or to his legally authorized representative, but in any event he or his legally authorized representative must be given adequate opportunity to read it." The regulation required that the document be signed by the subject or his legally authorized representative, and that "Sample copies of the consent form as approved by the Board. . . be retained in its records."

(41) Report of FDA's Inspection Report, *supra* note 58, Exhibit #2.

(42) Consent form in *Summary Report of NIH Site Visit Team*, *supra* note 57.

(43) The principal investigator has also failed to obtain approval from the hospital's Radioactive Drug Research Committee, which was required for use of radioactive "labels" which facilities study of the subjects' metabolism of the drug.

(44) *Summary Report of NIH Site Visit Team*, *supra* note 57, Reviews of protocol DT 78-81 by Alexander Y.M. Wang, Ph.D. (81878) and W.W. Sutow, M.D. (August 2, 1978).

(45) Memorandum from Director, NCI to Acting Director, NIH (August 6, 1981) forwarding Recommendations Regarding Ti Li Loo, Ph.D. and the M.D. Anderson Hospital and Tumor Institute, University of Texas System Cancer Center, and attached Site Visit report.

(46) *Id.*

(47) *Id.*

(48) *Id.* The sanctions recommended by NCI were approved by the NIH Acting Director on August 11, 1981. (See concurrence signature on p. 4 of the memorandum.)

(49) Testimony of Charles MacKay, Deputy Director, OPRR, at 14th meeting of the President's Commission (Nov. 14, 1981) at 323.

(50) Testimony of the Director, OPRR at the 2nd meeting of the President's Commission (May 16, 1980) at 82. *See also*, letter from Dr. Charles R. McCarthy to Morris B. Abram (May 7, 1980) at 4.

(51) FDA Inspection Report, *supra* note 58, at 1.

(52) *Id.* *See* Exhibits 1a-d, 4c, and 4d.

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