Charles R. McCarthy

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The Origins and Policies That Govern Institutional Review Boards

Major turning points in history are often recognized only in hindsight. One example of a significant historical change that went almost unnoticed at the time is the statement made by James A. Shannon, director of the National Institutes of Health (NIH), before the National Advisory Health Council (NAHC) on September 28, 1965.

The NAHC had been created in 1930 to deal with a budget crisis faced by what was then a single, small federal agency called the National Institute of Health. Senator Joseph Randell, backed by Surgeon General Lewis R. Thompson, introduced sweeping legislation to authorize the National Institute of Health to carry out research that would address "all the ills that flesh is heir to." In direct contrast, Senator Joseph M. Neely proposed sharply focused legislation to direct the spending of all federal medical research dollars onto a single program to overcome cancer in all its many forms.[1]

The Randell bill was modified and enacted. It is now compacted into Section 301 of the Public Health Service Act as amended.[2] It grants the NIH authority to fund research into virtually any area that may be associated with human health or disease. Although the Neely bill failed in 1930, the concept of a concentrated research effort directed or targeted at one or several diseases remained alive in the Congress, and in the public mind. In succeeding decades, the Congress has enacted legislation targeted at virtually all major diseases and conditions—judged in terms of their impact on society as measured by morbidity and mortality. The plethora of institutes that make up the NIH, each dedicated to one or several diseases or disease clusters, is due in part to the concept of targeted research articulated by Neely. In 1930 the contest between those who supported the Randell concept, which came to be known as *investigator-initiated research,* based on perceived scientific opportunities, and those who supported *targeted research* directed at public need as measured by morbidity and mortality data, created a tension that continues to the present time. In 1930 the debate threatened to stalemate the budget process and jeopardize the fragile existence of the NIH.

Congress addressed the Randell-Neely tension by a procedural compromise. It recommended creation of the NAHC—a standing committee of nonfederal advisers to establish or approve policies for both the surgeon general of the Public Health Service (PHS) and the director of the NIH (the research arm of the PHS) on a broad range of issues. As far back as 1902, the NIH had utilized ad hoc public advisory committees. But the creation of the NAHC marked the beginning of ongoing participation by nongovernment advisers in the formulation of national health research policies. The NAHC eventually evolved into a two-tiered peer review system consisting of initial review groups (IRGs—often called *study sections*) charged with assigning priority scores based on the perceived scientific merit of grant applications, and national advisory councils or boards to pass judgment on proposed research in the light of its expected social utility.[1]

When Shannon testified in September 1965, he brought to the attention of the NAHC a complex long-standing problem of medical ethics that had not previously been addressed at a policy level by any federal agency. Fragmentary stenographic notes of the NAHC meeting attribute the following statement to him:

> [R]esearch involving [humans] departs from the conventional patient-physician relationship where the patient's good has been substituted for by the need to develop new

> knowledge. . . . [The] physician is no longer in the same relationship that he is in the conventional medical setting and indeed may not be in a position to develop a purely or wholly objective assessment of the . . . ethical act which he proposes to perform. [The PHS has] a dual responsibility. One is a minor one of keeping the Government out of trouble . . . but really the major one is . . . to try to encourage the flourishing of sound clinical investigation rather than discouraging it. I am searching for some way of creating a more profound sense of an institutional awareness of the importance of this aspect of the problem without tying [investigators] down and immobilizing them in their capabilities.[3]

Shannon was seeking a policy applicable to all research involving human subjects funded by the NIH. He wanted the policy to contrast and distinguish the relationship between research investigators and their subjects from the relationship between physicians and their patients. He identified several interrelated questions, which he put to the NAHC. First, how could the NIH make physicians aware that when they are functioning as research investigators, their responsibilities to subjects differ from their responsibilities to patients? Second, how could the ethics of research be incorporated into a workable public policy that would both protect the NIH from public criticism and protect subjects from physical or moral harms, without unduly restricting investigators?

Shannon knew that medical schools and science programs of his day provided little formal training in medical ethics.[4] The dictum *Primum non nocere* ("First, do no harm") and the Hippocratic tradition of respecting the privacy of patients were conveyed by way of mentors, role models, and institutional traditions. Ethical guidance pertaining to the conduct of research involving human subjects was virtually unmentioned in the training given to medical students. At the time that Shannon met with the NAHC, responsibility for the ethical conduct of medical research was left to the untutored consciences of physician/investigators who had little formal training in ethics and whose behavior was shaped and guided by the social customs of the time. Albert Jonsen, for example, describes the ethics training in the following words:

> For doctors, medical ethics was incarnate in their behavior and social character and in the social arrangements that sustained the solidarity, respectability, and educated competence of the profession. There were ethical battles to be fought such as those against quackery, but there were few ethical dilemmas about the doctor's duties.[4]

Shannon presented to the NAHC a draft resolution that recommended that the protocol design of an investigator proposing to conduct research involving humans be submitted to the judgment of "peers" to provide an independent determination of the risks and expected benefits of research, and to assure maximum protection for the rights and welfare of those enrolled in each study.

The 1965 NAHC meeting marks the first time that what was later termed the *therapeutic misconception*—confusion of the investigator/subject relationship with the physician/patient relationship—was addressed at the level of national policy. Perhaps even more startling is the fact that Shannon recommended that nonfederal advisers—Shannon called them "*peer reviewers,*" but that terminology was soon discarded because the reviewers were not, strictly speaking, peers of the investigator—should exercise ethical oversight of federally funded research involving humans.

The policy that Shannon recommended was borrowed in part from a policy pertaining to normal research volunteers that had been implemented in 1953 when the NIH Clinical Center opened its doors. Shannon recognized, of course, that the review of protocols for scientific merit was already an established practice at the federal level. The new policy called for review of protocols for ethical integrity to be conducted at the local level by panels composed of both experts and nonexperts at the site where the research was to be conducted.

By calling for review by impartial observers, Shannon was reversing two traditions that had been in place at the NIH for more than 25 years. The first tradition held that the physician in charge of the research is the best qualified person to make the judgment of what is in the best interests of research subjects. The second held that nonscientists, that is, *laypersons,* were not qualified to pass judgment on the ethical aspects of medical research. To understand the dramatic difference between what Shannon was proposing and the prevailing practices and attitudes of the time, we need to consider a few historical facts.

David Rothman tells us the following:

> Until World War II, the research enterprise was typically small-scale and intimate, guided by an ethic consistent with community expectations. Most research was a cottage industry: a few physicians, working alone, carried out experiments on themselves, their families, and their immediate neighbors. Moreover, the research was almost always therapeutic in intent, that is, the subjects stood to benefit directly if experiments were successful. Under these circumstances the ethics of human investigation did not command much attention.[5]

Rothman acknowledges that there were some notable exceptions to the state of affairs described above. What he fails to emphasize is that in the period leading up to World War II the NIH extramural programs, though small by today's standards, were gradually expanding. Many NIH research scientists, whether intramural or extramural, were not conducting innovative therapy intended to benefit their families, their patients, or their neighbors. They were conducting more fundamental research intended to explore the causes of disease, the workings and interrelationships of complex organ systems, and distinctions between normal and abnormal bodily functions. Therapeutic benefit was seldom a characteristic of such research projects.

In addition to the changes in the kinds of research projects that were pursued, changes on the issue of informed consent also emerged after World War II. Prior to this time, although a few research investigators sought informed consent from subjects, most investigators gave little if any information to their subjects concerning the purposes and risks associated with research studies. Concern for the rights and welfare of research subjects was left in the hand, or more precisely, in the conscience of the research investigator. Although a handful of investigators recognized and respected the rights of research subjects, a majority of investigators were unaware of these rights and saw little difference in ethical responsibility between functioning as a physician and functioning as a research investigator.[6]

Ruth Faden and Tom Beauchamp note the following:

> "Informed consent" first appeared as an issue in American medicine in the late 1950s and early 1960s. Prior to this period, we have not been able to locate a single substantial discussion in the medical literature of consent and patient authorization. For example, from 1930 to 1956 we were able to find only nine articles published on issues of consent in American medical literature.[7]

After World War II, as Rothman notes, there was a fundamental change in medical ethics and its importance. He dates the change a little earlier than do Faden and Beauchamp, but both sources agree that a national awakening to ethical concerns in research, particularly the issue of informed consent, came after World War II. According to Rothman,

> The transforming event in the conduct of human experimentation in the United States, the moment when it lost its intimate and directly therapeutic character, was World War II. Between 1941 and 1945 practically every aspect of American research with human subjects changed.[5]

Faden and Beauchamp date the transformation later than does Rothman. They write,

> Shortly after the middle of the twentieth century a major transformation occurred. The influential forces and documents in ethics and policy began to take on *external* roots. Sometimes these external influences were greeted as an unwanted alien force on medicine; but in other quarters of medicine they were greeted with open admiration.[7]

It was against this changing backdrop—changes both in kinds of research projects and in the appreciation of ethical issues in medical research—that the new NIH Clinical Center commenced functioning in 1953. At that time, most NIH investigators conducting research involving humans still thought of themselves as medical practitioners. Clinical Center officials argued that it would be an unjustified intrusion into the doctor-patient relationship to allow any administrative body to interfere with the relationship between physician/investigators and their research subjects/patients.[3] Nevertheless, even those who held this view recognized that this argument could not be made with respect to *normal volunteers*—that is, healthy people who volunteered to serve as research subjects.

During World War II, it was customary for the NIH to enlist conscientious objectors to serve as normal controls in medical research. Many investigators regarded conscientious objectors as being equivalent to military draftees. Were it not for conscientious objection to war, these investigators reasoned, such persons would have been serving in the military anyway. And this view had implications for how investigators thought of research volunteers. As Rothman notes,

> Researchers [believed that they] were no more obliged to obtain the permission of their subjects than the selective service was to obtain the permission of civilians to become soldiers. One part of the war machine conscripted a soldier, another part conscripted an experimental subject, and the same principles held for both.[5]

Long after the war ended, this attitude on the part of principal investigators persisted. Reasons why it continued are not hard to find. In 1941, President Franklin D. Roosevelt established the Office of Scientific Research and Development (OSRD) to conduct research to address a wide variety of health issues occasioned by or pertinent to the war. OSRD in turn created the Committee on Medical Research (CMR), which selected some 600 medical research projects to be conducted at 135 institutions across the country. After the war, in a political coup that catapulted the NIH to the forefront of domestic agencies, the research portfolio of the OSRD was transferred in its entirety to the NIH. In some cases, OSRD investigators also moved to the NIH to continue their work in the intramural program. Others moved to institutions in which CMR-initiated research was now conducted with NIH funds. NIH administrators admired the accomplishments of CMR during the war, and they admired the energetic and efficient manner in which the research results were obtained, published, and applied. Many NIH administrators adopted the aggressive "can do" CMR attitude. They believed that the CMR approach to research served the country well during the war, and they were eager to use the same techniques in peacetime.

The Growth of the NIH

From 1944 until 1958, federally funded medical research expanded at a furious rate. A health lobby headed by Mary Lasker and sympathetic heads of important Senate and House Appropriation Committees (Senator Lister Hill and Representative John Fogarty), produced an ever-increasing flow of research dollars. The NIH budget rose from less than $1 million in 1944 to nearly $1 billion by the end of the 1950s. In some years, the NIH research budget increased by as much as 100% over the previous year. Frankel says that prior to World War II, medicine was viewed as the art of healing the sick and comforting the dying; after the war, medicine was viewed as the conquering of diseases and the promotion of health.[3]

In the face of unprecedented expansion of the medical research budget during the 1950s, NIH staff persons were preoccupied with locating and training research investigators to conduct research. The NIH Clinical Center operated a two-year program of training for research fellows, whose time at the NIH counted as military service, exempting them from the draft. The "doctor draft" provided training for hundreds of physician/investigators who formed the backbone of the expanding research effort throughout the country. The NIH fellowship program was supplemented by research training grants (made mostly to Ph.D. scientists) developed to match the supply of investigators to the increasing torrent of research dollars. Although training grants offered sophisticated scientific mentorship to new investigators, they provided virtually no education in research ethics.

A notable exception to the lack of research ethics policy occurred in the NIH intramural research program shortly after the Clinical Center opened in 1953. Following World War II, normal volunteers for intramural research at the NIH were recruited from small colleges located in the nearby District of Columbia, Maryland, and Virginia. Only persons judged to be in good health were accepted as normal volunteers. Exposing healthy volunteers to risks from research interventions designed to develop knowledge pertaining to conditions and diseases the volunteers did not have was a major departure from acceptable medical practice. The practice of using normal volunteers was patently inconsistent with the

Table 50.1
Development of Federal Protections for Human Subjects of Research

Date	*Event*
1798	U.S. Congress creates the Marine Hospital Service for sick and disabled seamen. Signed into law by President John Adams.
1887	Congress authorizes the conduct of medical research at the Marine Hospital. This one-room laboratory, directed by Joseph Kinyoun, will evolve into the National Institutes of Health (NIH).
1902	The Marine Hospital Laboratory is redesignated as the Public Health and Marine Hospital Service, which is reorganized into the Public Health Service (PHS) 10 years later.
1918	Chamberlain-Kahn Act expands the size of the PHS, directs it to study venereal diseases, and creates a commissioned corps under the direction of a surgeon general empowered to make grants-in-aid of research. Twenty-five institutions receive the first grants-in-aid.
1930	Congress gives the NIH broad authority and creates the National Advisory Health Council (NAHC) to advise the surgeon general on grants-in-aid (including contracts), considering both scientific opportunities and the social utility of research.
1942–45	Conscientious objectors who are exempted from the draft in World War II are required to serve as healthy "volunteers" for research at the NIH and awardee institutions.
1953	NIH opens the Clinical Center, later called the Warren G. Magnuson Clinical Center, the largest and most advanced biomedical research center in the world. The Clinical Center issues the first public policy for the protection of human research subjects, entitled *Group Consideration of Clinical Research Procedures Deviating From Accepted Medical Practice or Involving Unusual Hazards,* and requires peer oversight of research involving healthy volunteers. Philippe Cardon, deputy director of the NIH Clinical Center, is careful to explain the risk of the research and to elicit volunteers' informed consent. Although patient/subjects are often at much higher levels of risk than healthy volunteers, the oversight policy extends only to healthy volunteers.
1954–58	Saul Krugman conducts hepatitis studies in the Willowbrook State School for severely retarded children (see Chapter 7).
1956	Chester M. Southam and Emanuel Mandel conduct experiments at the Jewish Chronic Disease Hospital, injecting live cancer cells into elderly, indigent subjects without review of the research or consent from the subjects (see Chapter 6).
1959	Senator Estes Kefauver initiates hearings on the cost of products regulated by the FDA. In 1961, following reports of the thalidomide disaster in Europe and Canada, the hearings focus on protection of human subjects involved in testing of FDA-regulated products.
1961	Congress enacts the Kefauver-Harris amendments to the Food, Drug and Cosmetic Act, including a requirement for informed consent of subjects involved in the testing of FDA-regulated products.
1960–63	A three-year study by the Boston University Law-Medicine Research Institute concludes that only 16 PHS awardee institutions have policies for the protection of the rights and welfare of human research subjects, and in no case is an institutional policy satisfactory.
1963	NIH Director James Shannon creates the Robert B. Livingstone Committee to evaluate practices in institutions funded by the NIH and to recommend improvements. The Livingstone Committee reports that as research expands and becomes more complex, the risks to subjects will become greater, but it makes no formal recommendations.
1965	Shannon tells the NAHC that many research investigators confuse the role of principal investigator with the role of physician. He proposes the first federal policy for the protection of human subjects, calling for panels composed of both experts and non-experts to review research protocols for ethical integrity.
1966	In an article in the *New England Journal of Medicine,* Henry K. Beecher brands as unethical 22 research projects published in refereed journals. This article provides unexpected and powerful support for the establishment of ethics review panels, which initially are called *institutional review committees.*
1971	Donald S. Chalkley publishes the Yellow Book, an extension of the PHS policy to all research involving human subjects supported by any agency within the Department of Health Education and Welfare (DHEW).
1972	Senator Edward M. Kennedy begins a three-year series of hearings on human-subject research, including psychosurgery, whole-body radiation, forced sterilization of retarded women, a study of the contraceptive Depo-Provera in which some sexually active women were given placebo without their knowledge, and the Tuskegee Syphilis Study of the natural course of syphilis, during which treatment for the disease was withheld from impoverished black men in Alabama (see Chapter 8).
1972	NIH Director Robert Q. Marston calls for a broad study of the ethics of research involving human subjects. He appoints Ronald Lamont-Havers to create a task force to consider protections for many categories of vulnerable subjects.
1974	The National Research Act calls for the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The National Commission meets on a monthly schedule for the next four years, completing 16 studies and making about 125 recommendations for the protection of human subjects (see Chapter 14).
1981	DHEW Secretary Patricia Harris signs a federal regulation implementing virtually all the recommendations of the National Commission. Many of the recommendations are incorporated into revised regulations issued by the FDA.
1991	After a seven-year effort, 16 federal departments and agencies that conduct or support research involving human subjects adopt the Common Rule, a package of regulations virtually identical to the Department of Health and Human Services Regulations for the Protection of Human Subjects.

Hippocratic tradition. After considerable discussion, in 1953 the NIH Clinical Center issued a policy to protect the rights and well-being of normal research volunteers.

The policy, entitled Group Consideration of Clinical Research Procedures Deviating from Accepted Medical Practice or Involving Unusual Hazard,[8] required oversight of research involving normal volunteers by peers in the Clinical Center. Panels of reviewers were overseen by Philippe Cardon, deputy director of the NIH Clinical Center, who was careful to explain to the volunteers the risks of the research in which they were invited to participate, and to elicit their informed consent. Although patient/subjects were often placed at much higher levels of risk than normal volunteers, the oversight policy extended only to normal volunteers. The policy that Shannon recommended to the NAHC in 1965 borrowed and expanded the Clinical Center policy to all research subjects involved in both intramural and extramural research.

The Turbulent Decade of the 1960s

It was not until near the end of the 1950s that doubts concerning the beneficial results of research, and concern for the risks to research subjects and to society, began to surface in the public media. In 1959, Senator Estes Kefauver, chairman of the Senate Subcommittee on Antitrust and Monopoly, began a series of hearings concerned with the cost and availability of drugs. The hearings culminated in the 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act. Initially, the hearings were exclusively concerned with the economic aspects of drug production, distribution, and sale. Kefauver summoned pharmaceutical industry leaders to testify, and he demanded that pharmaceutical houses provide drugs to consumers at reasonable prices.

In 1961, while the Kefauver hearings were ongoing, the public media recognized that thalidomide—a drug administered to pregnant women in many countries as a sedative and to prevent morning sickness—was associated with limb anomalies in newborn infants. Thousands of infants whose mothers had used thalidomide were born without arms or legs. By 1961, a majority of U.S. homes had television sets, and televised images brought these tragedies into the living rooms of many thousands of Americans. Few of the birth defects occurred in the United States because the Food and Drug Administration (FDA) had not approved the drug. Nevertheless, the publicity given the tragic effects of thalidomide caused Kefauver to shift the focus of the hearings to the safety and efficacy of drugs. Senator Hubert H. Humphrey's Subcommittee on Reorganization and International Organization also held hearings on the thalidomide debacle. Frances Kelsey of the FDA was subsequently presented with a presidential medal because she had refused to grant FDA approval for marketing thalidomide in the United States. She based her refusal on the lack of animal research safety data.

Kefauver criticized the drug manufacturers' practice of providing experimental drugs to practicing physicians, who, in turn, treated their patients with the drugs. Patients were seldom informed that some of the drugs handed to them by their physicians were still experimental. Patients were unaware that they were sometimes used as de facto research subjects. The Kefauver bill was further amended to require FDA to certify that new drugs are both safe and efficacious. When the Kefauver-Harris bill was brought to the floor of the Senate, Senator Jacob Javits proposed an amendment—which became law—requiring that research subjects provide informed consent prior to their participation in any FDA-regulated study. Several years passed before the FDA learned how to implement the 1962 amendments. Nevertheless the Javits provision marked the first time that any sort of protection for human research participants was included in a federal statute.[3]

In the years following the thalidomide uproar, a cascade of alleged research abuses came to the attention of the media and the public. A number of research projects that had involved children were challenged as unethical. The most notable of these was the so-called Willowbrook State School study of the 1950s, in which severely retarded children were infected with a strain of hepatitis virus[4] (see Chapter 7). Similarly, failure by Chester Southam and Emanuel Mandel at the Sloan-Kettering Institute for Cancer Research and the Jewish Chronic Disease Hospital to obtain consent for the administration of live cancer cells to elderly, indigent patients in New York received critical newspaper headlines and eventually led to a condemnation by the New York State Board of Regents in 1965[3] (see Chapter 6).

Shannon, who had never accepted the view that regulation of research was an intrusion into the doctor-patient relationship, grew more and more restive about the absence of a policy governing the ethics of research. Although the peer review system for scientific merit was steadily growing more sophisticated, a policy for the protection of human research subjects had not even been articulated, much less implemented. It was this worry that prompted Shannon's recommendation to the NAHC that the extant NIH policy for normal volunteers be expanded to cover all subjects involved in both intramural and extramural research.

The Boston University Study

In 1960, encouraged or perhaps even directed by Shannon, the NIH made a three-year "grant" (today it would be classified as a contract) to the Boston University Law-Medicine Research Institute to conduct a study of ethical, legal, and moral issues associated with the practice of clinical research in the United States.[3] The Boston group conducted a survey that indicated that only 16 U.S. institutions used consent forms or documents, and only 2 had policy guidance for research involving humans. The group forwarded its report, including the survey, to the NIH in 1963.

Shannon acknowledged that he sought a policy to protect the rights of research subjects because he felt that failure to do so would jeopardize the medical research enterprise in the United States—an enterprise that after World War II was centered in the NIH. He believed that protection of the rights of subjects was essential to the development of the NIH mission. He was particularly upset when he learned that a U.S. surgeon, without prior consultation or approval from the NIH or anyone in his institution, transplanted a baboon's kidney into a human being. The patient died within minutes. The surgeon called his action "research."[9]

The Livingston Committee

The results of the Boston University Study, the publicity given to alleged research abuses, and discussions with the FDA—including discussions about how to implement the Javits amendment to the

Kefauver-Harris Act—prompted Shannon to appoint an NIH committee under the leadership of Robert B. Livingston to address these problems. The Livingston Report reached several conclusions:

> [A]s the number of investigators, subjects, and institutions engaged in clinical research increases, and as the nature of the risks . . . changes according to the extension of research into new areas, a mounting concern is expressed over the possible repercussions of untoward events which are increasingly likely to occur, and which may occur in an unfavorable pattern of [*sic*] context. . . . The NIH is not in a position to shape the educational foundations of medical ethics. . . . In our view, it would add to existing insecurities if the NIH were to assume an exclusive or authoritative position concerning the definitions of ethical boundaries or conditions necessary for clinical research.[10]

Shannon was in full agreement with the report's warning of increasingly frequent untoward events; but he found "wholly unsatisfactory" the report's conclusion that the NIH should set no ethical boundaries. He argued that the NIH was well within its authority to require institutions to meet ethical standards as a condition of receiving support for research involving humans. Following receipt of the Livingston report, Shannon forwarded four recommendations to the NAHC:

1. A professional group should . . . formulate a statement of principles relating to the moral and ethical aspects of clinical investigations.
2. There is a need for more factual information regarding actual research practices.
3. The NIH should consider providing advice concerning ethical problems, and risk-reducing practices.
4. Research grant documentation relating to clinical investigations using human subjects should be identified for special consideration throughout the PHS-NIH review process.[3]

Policy and Procedure Order #129, February 8, 1966

Following Shannon's presentation in September 1965, the NAHC deliberated for several months and then issued Policy and Procedure Order #129 (PPO #129) on February 8, 1966. The policy required awardee institutions to

> provide prior review of the judgment of the principal investigator . . . by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to determine informed consent, and (3) of the risks and potential medical benefits of the investigation.[3]

The slow pace of implementation of PPO #129 contrasted sharply with the energy that senior NIH officials had devoted to having it approved by the NAHC. Within months of its promulgation, Surgeon General William H. Stewart ruled that PPO #129 applied both to clinical research and to behavioral and social science research involving humans conducted or supported by any agency within the PHS. The policy was also extended to those enrolled in projects conducted under research training grants. PPO #129 required each awardee institution, domestic or foreign, to submit an Assurance of Compliance with each application for funding. These documents, at least in theory, were to be completed and signed before any PHS project involving human subjects could begin. Had the requirement of PPO #129 been strictly enforced, federal research involving humans would have slowed to a crawl or come to a standstill. Neither the PHS nor the NIH had made provision for a well-staffed office to implement the requirements of the policy.

The Role of the Institutional Relations Branch

Shannon assigned the task of administering PPO #129 to the institutional relations branch within the Division of Research Grants (DRG-IRB). This tiny office, which included only four professional employees with experience in the peer review system, had many other duties besides implementation of PPO #129. Staff members could give only part of their time to implementing the new policy. Staff from the DRG-IRB traveled to institutions and negotiated the required assurance documents with these institutions. Each assurance was tailored to accommodate the organizational framework of each institution. This process could often take up to a week. Before long it became clear that the policy would never be implemented if this snail-like process remained unchanged.

The NIH, by far the largest agency in the PHS, soon altered its interpretation of the policy. For the most part, general assurances replaced single project assurances. Thus an institution could negotiate one assurance document that covered all research involving human subjects for a period of three to five years. Model assurances were developed and the policy was clarified. Surgeon General Stewart, in the face of fierce protests by nonmedical researchers, made clear that the new policy also applied to behavioral and social science research involving human subjects. The policy was amended, clarified, and reissued in July 1966, in 1967, and again in 1969. The FDA found that it could implement the Javits amendment by "piggybacking" onto the institutional review committees (IRCs) established in accord with PPO #129.

Donald S. Chalkley, director of the DRG-IRB, said,

> To many it was an entirely new and strange concept. The PHS provided few guidelines. . . . Institutions were permitted to review proposals [protocols] any time prior to their actual acceptance. Understandably many institutions followed the practice of reviewing only after the actual awarding of a grant. While this was an administrative advantage for the institution as well as the investigator, it was a cause for concern among NIH officials.[3]

PPO #129 received unexpected support from the 1966 publication of an influential article written by Henry K. Beecher in the *New England Journal of Medicine*.[11] Beecher identified 22 studies published in refereed journals that contained serious ethical flaws. Because of Beecher's exalted reputation among his peers, the article was considered to be entirely credible. Although other criticisms of research ethics had been published, the Beecher article seemed to have greater impact than any of the others. The article was a stinging rebuke to those who still considered research to be beyond the purview of committees because such committees were an intrusion into the doctor-patient relationship.

Within the PHS, the duties of the surgeon general's office were divided. The surgeon general continued to issue annual reports on

the health of the nation and to exercise command over the Public Health Service Corps, but the line of authority from the Secretary of the Department of Health, Education, and Welfare (DHEW) to the agencies within the PHS ran through the assistant secretary for health (ASH), not through the surgeon general. In 1970 Philip Lee, a veteran health policy official, was assigned to the position of ASH. Lee quickly realized that PPO #129 needed clarification and improved implementation. He appointed Eugene A. Confrey to chair a task force to review and revise PPO #129. Among other statements, the task force issued the following recommendation:

> The primary duty of institutional committees was to protect the rights and welfare of human subjects. In doing so, the committee was to concern itself with the appropriateness and adequacy of efforts to obtain informed consent from subjects; weigh the risks to subjects against the potential benefits to subjects or the importance of the knowledge to be gained.[12]

The assertion that research could be justified by the "importance of the knowledge to be gained" constituted an important addition to PPO #129. It made possible the conduct of research that did not hold out the prospect of direct benefit to research subjects.[1]

The Yellow Book

Ernest Allen, director of the DHEW Division of Grants Administration Policy, recognized that the DHEW was supporting research involving human subjects with funds provided by agencies within the DHEW but outside the PHS. He therefore recommended that the policy be extended to cover all research involving humans conducted or supported by any agency within the DHEW. Donald S. Chalkley, special assistant to the director, DRG, was assigned to direct the DRG-IRB. In 1970, Confrey asked Chalkley to redraft the PPO #129.

In 1971, Chalkley published a DHEW-wide version of the policy in pamphlet form with a bright yellow cover. It was known thereafter as the *Yellow Book.* The document included the clearest version of the policy published up to that time. The Yellow Book also added commentary to help institutions understand and comply with each of its provisions.

The policy had matured to the point at which most awardee institutions considered it both workable and acceptable. Clinical investigators grudgingly accepted its requirements, and brought their studies into compliance. Nevertheless, implementation was far from ideal. Some institutions included ambiguous language in their assurance documents that provided enforcement loopholes. Almost all institutions understaffed the offices charged with implementing the policy, and only a few offered the staff training necessary to provide support for IRCs. Nevertheless, government staff learned by experience, and institutional staff members began to provide improved assistance to principal investigators and to IRCs. Many institutional staff members learned how to comply with the policy by networking with one another.

Chalkley wrote hundreds of longhand letters to heads of institutions urging them to comply, criticizing their shortcomings, and exhorting them to take their responsibility to protect human subjects seriously. Because Chalkley's letters often contained sarcasm and stinging criticism, Charles R. McCarthy, chief of the legislative development branch in the NIH's Division of Legislative Analysis [and author of this chapter], was assigned by Associate Director Ronald Lamont-Havers to edit Chalkley's letters.

Senate Health Subcommittee Hearings and the Tuskegee Study

In 1971, Senator Edward M. Kennedy became chairman of the Health Subcommittee of the Senate Labor and Public Welfare Committee. He initiated a series of hearings spaced at intervals of three or four months. Many of the hearings dealt with research issues. Kennedy made no secret of the fact that he was accumulating evidence for the creation of a national commission to deal with health research. Kennedy held hearings on the following: contraception research, including the Depo-Provera study in which some women were given placebo instead of contraceptives without their knowledge; psychosurgery research involving frontal lobotomy; lethal whole-body radiation experiments to treat military cancer victims; and the need for a national agency or commission to oversee research in the United States. Among these hearings was one that considered S.J. Res. 75, a bill introduced by Senator Walter Mondale calling for a national commission on health, society, and science.[1]

The centerpiece of the Senate Health Subcommittee hearings turned out to be the Tuskegee Syphilis Study[13] (see Chapter 8). The hearings brought to public attention the PHS study that for 35 years had monitored the natural course of untreated syphilis in approximately 400 African American men who resided in Macon County, Alabama. Most of the men were illiterate, and most did not know they were research subjects. The infamous study had continued within the PHS since 1932. Initially, it was thought that not treating syphilis might be better for people who had the disease than the standard treatment with the heavy metals arsenic and mercury. But the study, which deprived subjects of all treatment for their disease, continued for more than 25 years after the discovery of penicillin, the drug of choice for treatment of syphilis. It continued for five years after promulgation of PPO #129 in 1966, and after review and approval by an IRC at the Tuskegee Institute (now University). At the time of the hearings, the study had been assigned to the Center for Disease Control (CDC, now the Centers for Disease Control and Prevention).

Portions of the hearings on the Tuskegee Study were televised. Monte DuVal, who was the ASH at that time in the Nixon administration, created a citizen's commission chaired by Jay Katz of Yale University to examine the study. DuVal ordered the PHS to take a posture of "anticipation" of legislative constraints on research rather than try to defend the Tuskegee Study. Upon receiving a recommendation from the Katz Committee, DuVal terminated the study. Senators Kennedy, Javits, Humphrey, John Sparkman, and Mondale introduced legislation intended to prevent research abuses. Representatives Edward Roybal and Paul Rogers introduced similar legislation in the House of Representatives. Kennedy and Rogers continued to hold hearings on the provisions in the bills that had been introduced.

In 1972, Robert Q. Marston, who succeeded Shannon as NIH director, renamed the DRG-IRB and transferred it to the Office of the Director, NIH. The new unit, still headed by Chalkley, was called the Office for Protection from Research Risks (OPRR). In that same year, Marston delivered a major address at the University of Virginia in which he called for a broad expansion of the

DHEW policy for the protection of human subjects. He assigned Ronald Lamont-Havers, associate NIH director for extramural affairs, to chair a PHS task force made up of a number of subcommittees dealing with research involving human fetuses, children, prisoners, cognitively impaired persons, and persons who were socially deprived. These subject categories came to be known as *vulnerable subjects* categories. In 1974, DHEW Secretary Caspar Weinberger, at Marston's suggestion, created a committee chaired by Seymour Perry to make recommendations for the compensation for research subjects injured in research process.

In the spring of 1974, congressional compromises led to the introduction of two bills, one in the Senate and one in the House of Representatives. Each included features of bills that been introduced in both houses of Congress. Kennedy's bill included a provision that would create a permanent government commission, patterned after the Securities and Exchange Commission, to oversee research. Rogers' bill called for a national advisory commission to make recommendations to the DHEW secretary. After considerable negotiation, Kennedy agreed to support the commission set forth in the Rogers bill. As a condition of this agreement, Kennedy insisted that the DHEW policy for the protection of human subjects be upgraded and reissued as a federal regulation. The DHEW, preferring to deal with a temporary advisory commission rather than with a permanent oversight agency, quickly formed a drafting committee that included Charles U. Lowe, Jane Fullerton, and Charles R. McCarthy. Richard Riseberg, a young attorney in the DHEW Office of General Counsel provided legal advice concerning provisions of the Administrative Procedures Act. Because the NIH had never before issued regulations, no one on the committee had any experience in producing regulations. Nevertheless, under pressure from Kennedy, the committee hurriedly drafted regulations for the protection of human subjects based primarily on Chalkley's Yellow Book. In its rush to placate Kennedy, the DHEW waived the usual clearance requirements and the Regulations for the Protection of Human Subjects (45 CFR 46, Subpart A) were published on May 30, 1974.[14] This version of the regulations had a number of flaws, but it sufficed to advance the protection of human subjects until such time as the National Commission could complete its work and the regulations could be carefully revised in the light of the Commission's findings and recommendations.

The publication of the regulations cleared the way for Rogers and Kennedy to agree to support an advisory commission for the protection of human subjects. One of the duties of the commission would be to measure the impact of research on society, as requested by Mondale. A study of psychosurgery supported by Roybal (who called psychosurgery "murder of the mind") was included, and in response to false rumors that the NIH was conducting research on living human fetuses, Representative Angelo Roncallo added a ban on fetal research. Rogers later persuaded him to accept a temporary moratorium on fetal research until the new commission could issue recommendations. Rogers and his staff drafted a new bill that included enough features of each of these initiatives to forge a compromise. The DHEW, in response to a request from Rogers for technical assistance, directed Charles R. McCarthy to draft a list of responsibilities that would be assigned to the new commission. McCarthy's draft of duties remained unchanged in the final version of the bill. The Rogers bill used a new term—*institutional review board (IRB)*—for the first time. The term *IRB* replaced *institutional review committee (IRC)*, the term that had been in vogue since the passage of the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act in 1962.

Meanwhile, subcommittees of the Lamont-Havers task force were busy drafting pieces of what was intended to be a major report on the protection of human research subjects. Before this report could be finished, however, Congress enacted the National Research Act (PL 93–348), and President Nixon signed it into law on July 12, 1974. Title II of the Act addressed protection of human subjects. Foremost among its provisions was the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). The PHS turned over the drafts of the Lamont-Havers task force to the new commission.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Beginning in December 1974, the National Commission met for two days of each month, with rare exceptions, for the next four years. In 1975 it issued a report on fetal research that called for regulations allowing fetal research under stringent conditions.[15] In succeeding years it published reports on research involving prisoners, children, and those institutionalized as mentally infirm, as well as a report on IRBs. Perhaps its most important contribution was the report entitled *Ethical Principles and Guidelines for the Protection of Human Subjects.* This was popularly called the Belmont Report, named after the conference center in Maryland where it was conceived.[16] The Belmont Report identified and applied three overarching principles of research ethics: (1) respect for persons, (2) beneficence, and (3) justice. These principles were explained in simple but eloquent language, presented as guiding norms under which all research involving human subjects should be conducted. They provided a guide for the decisions of IRBs and a framework for the drafting of future regulations (see Chapter 14). The findings, reports, and recommendations of the National Commission were, for the most part, polished and carefully presented. Each new report was published by the OPRR in the *Federal Register.*

National Commission reports and recommendations were similar in many respects to those made by in the Lamont-Havers task force. However, National Commission reports differed in several important ways. First, they were thoroughly researched and their findings were meticulously documented. Second, they included many scholarly background documents that provided depth and credibility seldom associated with reports of federal advisory bodies. Third, because they were drafted in public hearings, they enjoyed support of the public—who were given an opportunity to testify at nearly every meeting—and of the press, which was allowed to be present for all of their deliberations.

During the four-year period when the National Commission was at work, the OPRR was also making significant progress. It finally managed to negotiate acceptable assurances with all of the research institutions that were supported by the DHEW. These assurances extended the regulations not only to subjects participating in DHEW-funded research but to all human subjects involved in research conducted within each institution.

In 1975, following the National Commission's report on fetal research, the OPRR issued Subpart B of the regulations to address

research involving pregnant women and human fetuses. In 1977 OPRR Director Chalkley suffered a major stroke and retired from federal service. In 1978 the OPRR published Subpart C, entitled "Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects." This report had been nearly completed before Chalkley retired. In September 1978, McCarthy was selected as the new director of the OPRR. He was assigned several additional duties, including staff director of the DHEW Secretary's Ethics Advisory Board and chair of the PHS drafting committee to incorporate recommendations of the National Commission into regulatory form."

The National Research Act contained what has come to be known as a *forcing clause*. This was a requirement that the DHEW secretary must either accept and implement the recommendations of the National Commission or publish in the *Federal Register* the reasons for not accepting them. Because few cabinet officers are ever willing to reject findings of a highly respected ethics commission, virtually all of the National Commission's suggestions (approximately 125) were accepted. The drafting committee worked for nearly two years to incorporate each of the commission's recommendations into a new version of 45 CFR 46 Subpart A, preparing a comprehensive regulation that would reflect the Belmont Principles and both the letter and spirit of the National Commission's work. The drafting committee considered about 1,500 public comments on the National Commission reports and proposed regulations.

In November 1980, Ronald Reagan was elected president of the United States. In the course of his campaign, Reagan had threatened to repeal all federal regulations. OPRR officials felt sure that he would not literally carry out that threat, but Reagan's transition team advised them that it might be very difficult to get regulations for the protection of human subjects published after he took office. The OPRR submitted Subpart A of the revised regulation to Health and Human Services Secretary Patricia Harris for final approval soon after the election. (The DHEW had been transformed into the Department of Health and Human Services, DHHS, earlier in 1980, when a separate Department of Education was created.) Harris's office called for a number of minor revisions and ordered a new preamble to be drafted. The regulations were returned to the OPRR for revision on January 16, 1981. The OPRR worked around the clock for several days, before it was finally able to secure approval from Harris on January 19, only a few hours before she left office.

The President's Commission and the Common Rule

After the National Commission disbanded, a new advisory body, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (President's Commission), was created. During its first year, the new commission operated on money that had been set aside for use by the Secretary's Ethics Advisory Board. Consequently, the ethics board was disbanded at the end of the Carter administration in January 1981. Much of the energy of the President's Commission was directed, not at research, but at problems in the health-care delivery system of the United States. However, the President's Commission issued two reports and one major directive concerning research involving humans. The Commission praised the DHHS "Regulations for the Protection of Human Subjects" and recommended that all federal departments and agencies that conduct or support research involving human subjects should follow a Common Rule modeled after them.

The task of persuading 16 federal departments and agencies to follow the same regulations and to coordinate their efforts with the White House Office of Science and Technology, the Office of Management and Budget, and the State Department (for research conducted outside the United States) was assigned to the OPRR. It proved to be very difficult for two reasons: (1) Departments and agencies felt that regulations should be geared to specific programs operated within each department or agency, not to general standards designed for a vast array of programs across the government; and (2) turnover in departments and agencies meant that agreements had to be renegotiated whenever new appointees assumed senior positions in the agency or department. Joan P. Porter, special assistant to the director of the OPRR, worked tirelessly under direction of the OPRR director to fulfill the commission's recommendation. It took nearly 10 years to gain simultaneous agreement from all of the affected departments and agencies. The Common Rule was promulgated June 18, 1991[17] (see Chapter 15).

After 14 years, McCarthy retired as the OPRR's director. During his tenure, he also was staff director of the DHEW Secretary's Ethics Advisory Board, serving as liaison to two national commissions and implementing their recommendations, completing the assurance process for all institutions that receive funding from the DHEW, and publishing the Common Rule. (He also chaired the committee that issued a new policy for humane care and use of laboratory animals.) McCarthy emphasized education. When he was liaising with the staff of Congressman Rogers on the legislation that became the National Research Act, he had inserted a clause in the legislation that required the DHEW to conduct education as well as enforce compliance with the regulations governing research involving human subjects. His calendars show that during his tenure, OPRR personnel participated in at least 187 educational programs concerning the protection of human research participants. He strongly encouraged a fledgling organization called Public Responsibility in Medicine and Research (PRIM&R) to conduct workshops and educational events pertaining to the protection of human subjects. PRIM&R steadily improved the quality and breadth of its programs and underwent steady growth. Gradually the research community in the United States and in other research-intensive countries came to understand and carry out their responsibilities to human research subjects under rules that had been fashioned by the DHEW and honed by the National Commission.

Gary Ellis was named director of the OPRR in the fall of 1992. He emphasized conducting site visits and inspections to assure strict compliance with the regulations. He stressed improved record keeping and he often said, "If there is not a written record, it didn't happen." Under his aggressive leadership, the OPRR suspended the assurances of compliance of more than 13 domestic research institutions between 1992 and 2000. Until the suspension of an institution's assurance document was lifted, no research involving human subjects could be undertaken in that institution. Each suspension affected large numbers of personnel in the affected institutions, and also affected many of the institutes of the NIH, the PHS, and other funding agencies.

Ellis and many others contended that because the OPRR was regulating research funded by the NIH, the location of the OPRR within the NIH constituted a potential (and occasionally an actual)

conflict of interest. He sought to have the OPRR transferred to the Office of the Secretary in order to avoid conflict or the appearance of conflict of interest. The assurance suspensions and the desire to move the OPRR to the level of the secretary, DHHS, made Ellis a controversial figure within the entire human research community.

When 45 CFR 46 was promulgated in 1981, most research projects were conducted under awards made to a single investigator in a single institution. Gradually the NIH and other funding agencies decreased the number of grants made to single institutions and increased the number of awards made multiple institutions. In the decade of the 1990s, awards often were made to a consortium of institutions conducting projects under the same protocol. Adjustments had to be made in the oversight process to avoid unnecessary duplication of review while protecting human subjects. Some institutions utilized central IRBs and commercial IRBs to address the problem.

The OPRR under Ellis's leadership moved from communication via regular mail and telephone to electronic mail, documentation, and record keeping. Guidance was published on the Internet rather than mailed to each awardee institution. New kinds of filing systems were created. Foreign institutions could communicate as swiftly and easily as domestic ones. Complex questions of how to apply the rules to institutions outside the United States involved diplomacy. Adjusting and adapting to these realities characterized Ellis' time in the OPRR.

In 2000, acting on recommendations from the National Bioethics Advisory Commission (NBAC), the DHHS moved the OPRR out of the NIH and placed it in the Office of the DHHS Secretary. The relocated office was called the Office for Human Research Protections (OHRP). In September 2000, Greg Koski, a Harvard University physician, was selected to be the new director. Koski worked closely with the Institute of Medicine within the National Academies of Science and with PRIM&R. He strongly endorsed creation of a nongovernment accrediting agency to assist research institutions to remain in full compliance with the Common Rule. He played an important role in persuading the Association of American Medical Colleges and other professional health organizations to join with PRIM&R in funding an independent, private accrediting agency to certify the adequacy of institutional research protection programs. By 2006, that organization, the Association for Accreditation of Human Research Protection Programs (AAHRPP), had announced full accreditation for approximately 43 institutions, and well over 100 institutions were seeking accreditation. Accreditation is seen as a mark of excellence and appears to be the wave of the future. Moreover, it offers institutions the opportunity to evaluate their programs from time to time, to make sure that they are in compliance with regulations and that human research participants are well protected.

In January 2003, Bernard Schwetz was named acting director of OHRP, and a year later, he was named director. Schwetz again stressed the need for education of a growing and changing research community. He emphasized the need for human research protection programs including, but extending well beyond, IRBs. Schwetz also offered the services of OHRP as an aid to institutions rather than an enforcer of regulations. He increased the number of "not for cause" site visits, in which OHRP representatives offer assistance to institutions to improve their programs rather than cite them for noncompliance. OHRP published a number of documents on the Internet to assist institutions to interpret and apply the regulations. Schwetz also created the Secretary's Advisory Committee on Human Research Protections (SACHRP) to provide outside advice on how best to provide protections for human research subjects.

In the meantime, the funding of both clinical and behavioral-social science research steadily increased. The need for protection of the rights and welfare of human subjects has grown apace. As stem cell research, genetic research, and proteomics research have expanded the traditional areas of research involving human subjects, so will the need for vigilant oversight need to change.

Growth With Continuity

From James Shannon's 1965 testimony to the National Advisory Health Council until the present time, progress has been made in protecting human research participants. The insights that Shannon presented to the NAHC found expression in PPO #129. Each expression of policy and each new regulation has included all of the best characteristics of the past. Progress in recognizing the rights and welfare of human research participants has been captured in each succeeding set of regulations. Progress in the understanding and application of sound research ethics has taken place in both domestic and the foreign settings. IRBs are established in more than 80 nations worldwide. They have become more insightful and sophisticated in conducting review and oversight of research protocols involving human subjects. Clinical investigators and behavioral and social scientists have come to know, understand, and apply the rules to their own research protocols. Administrators have come to understand that the regulations require institutions to train and oversee their personnel so that those enrolled in research will receive the protection that they are owed. Although the protection of human subjects has expanded in countless ways, IRBS continue to stand at the center of the program.

With the advent of funding for multicenter research involving humans, a single phrase in the 1981 version of the regulations has become extremely important. Section 46.111(a)(6) authorizes IRBs to make adequate provision for monitoring the data collected to ensure the safety of research participants. That clause provided for the creation of data and safety monitoring boards (DSMBs) to monitor the data collected in trials involving many sites (see Chapter 53). The DSMB has become a major and often essential tool in protecting human research participants in multicenter trials. The OHRP now faces the challenge of finding an efficient method of coordinating the work of IRBs and DSMBs.

The IRB has served the United States and many other countries well. It is here to stay. But unless it is considered to be an evolving and expanding mechanism, adapting to the problems of each period of history, it is in danger of becoming fossilized and ineffective. Administrators, research investigators, ethicists, regulators, Congress, and the general public bear the responsibility of creating mechanisms and methods for the IRB to continue to protect human research participants in a manner that is demanded by the highest principles of ethics.

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