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STRANGERS AT THE BEDSIDE

*A History of How Law and
Bioethics Transformed Medical
Decision Making*

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told to take an injection and test a vaccine. No one ever said that war was fair, or that it should be fairer for the incompetent than the competent.

To make this same point in traditional philosophical terms, wartime inevitably promotes teleological, as opposed to deontological, positions. The greatest good for the greatest number is the most compelling precept to justify sending some men to be killed so that others may live—and this ethic has little difficulty in defending the use of the institutionalized retarded or mentally ill for experimentation. Of course, the investigations were to be scientifically sound, and to have passed all the appropriate animal tests; but these criteria met, it appeared acceptable to test the interventions on humans, including those unable to give consent.

In sum, the lessons that the medical researchers learned in their first extensive use of human subjects was that ends certainly did justify means; that in wartime the effort to conquer disease entitled them to choose the martyrs to scientific progress. They learned, too, that the public would accept such decisions, and that so long as the researchers were attentive to potential areas of dispute, the support for research was considerable. All of this constituted an intellectual legacy that researchers would not forget, even when peacetime conditions returned.

The Gilded Age of Research

THE twenty years between the close of World War II and the appearance of Henry Beecher's exposé witnessed an extraordinary expansion of human experimentation in medical research. Long after peace returned, many of the investigators continued to follow wartime rules. Utilitarian justifications that had flourished under conditions of combat and conscription persisted, and principles of consent and voluntary participation were often disregarded. This was, to borrow a phrase from American political history, the Gilded Age of research, the triumph of laissez-faire in the laboratory. Yet between 1945 and 1965 very few investigators or their funders took note of the changed circumstances. The thrust of public policy was not to check the discretion of the experimenter but to free up the resources that would expand the scope and opportunity for research.

The driving force in post-World War II research, including both intellectual direction and financial support, was provided by the National Institutes of Health. Created in 1930 as an outgrowth of the research laboratory of the U.S. Public Health Service, the NIH did not assume its extraordinary prominence until 1946.¹ When the Committee on Medical Research, along with the other wartime organizations, was about to be phased out, many scientists and political leaders (but not all) found the prospect of the federal government abdicating its

research role simply unthinkable.² So vital an activity could not be permitted to regress to the prewar condition of limited and haphazard support by private foundations and universities.³

It was not difficult to make the case for transforming the NIH into the peacetime CMR. In the fall of 1945, Vannevar Bush, the director of the Office of Scientific Research and Development, laid out plans for a Program for Postwar Scientific Research in a report entitled "Science, the Endless Frontier." Bush first listed the achievements of medical research over the past two hundred years and then noted the "spectacular" record during World War II. He recounted the victories over smallpox, typhoid, tetanus, yellow fever, and infectious diseases, noting first the discovery of the sulfa drugs and then, of course, penicillin. Medicine, he insisted, was on the verge of its most heroic explorations, and at such a moment it would be foolhardy to close off the "frontiers" of science by ending federal support.

To judge by congressional reactions as well as press comments, Bush's appeal struck a responsive chord. Although disputes broke out about the appropriate division of authority between the government and the investigator, and among the various federal agencies, there was significant agreement on the need for a federal investment in research.⁴ "World medicine," noted one editorial, "appears to be approaching the threshold of a brilliant new era of discovery in which some of mankind's most dreaded diseases may be wiped out." And the proof of the assertion was in the "miracle drug"—penicillin. It unleashed the imagination of both the general public and the research community, so that no prediction of progress, however grandiose, seemed fanciful. In the fall of 1945, Alexander Fleming, who had discovered the antibacterial properties of the penicillin-producing mold, toured the United States, received a hero's welcome, and delivered the same exhilarating message: "We are only at the beginning of this great study. . . . We can certainly expect to do much toward reducing the sum total of human suffering."⁵ Political figures echoed his refrain: "We have found the cause of a number of epidemic diseases and have practically conquered them," declared Louisiana's Senator Joseph Ransdell. "May we not expect the same kind of success against the so-called degenerative diseases if we work hard enough?"⁶ And his heady optimism bore directly on the prospects for a strengthened NIH, for Ransdell was one

of the Senate's strongest supporters of the new program. The press, too, invoked the wartime experience and the benefits of penicillin to buttress the case for an expanded NIH. "This seems to be the golden age of chemotherapy," commented the *New York Times*. "It is sad to realize that had it not been for the war, penicillin might not yet have been placed in the hands of physicians, and that we need something more than the natural curiosity of the research scientist to speed discovery that means so much to mankind."⁷

If the general well-being of humanity was not reason enough to justify federal support of research, then national self-interest was. In 1945, unlike 1919, there was little sense that the Allies had won a war to end all wars; hence, those concerned with defense strategies, like Secretary of the Navy James Forrestal, strongly endorsed expansion of the NIH. The United States, he argued, had been foolish not to fund medical research between the two wars and dared not repeat the error.⁸ "A future aggressor," concurred editorial writers, "will move even more swiftly than Hitler did. Two oceans will not give us time to establish another OSRD. Continuous systematic research is an evident necessity. It may be regarded as a kind of military insurance."⁹

Thus, in 1945, the lesson learned from both the battlefield and the laboratory was to reorganize the NIH along the lines of the CMR and fund it generously—in effect, involve an army of investigators from universities and hospitals in the war against disease and await the impressive results. With World War II just behind and with medical research so closely linked to national security, discussions about federal research policy inevitably invoked war metaphors: Given the high stakes, the campaign was to be an all-out battle against disease. Researchers reinforced and reflected this attitude: With the potential for incredible breakthroughs so great, all—and one means *all*—methods of investigation were legitimate.

The results of this mandate were apparent first in the spectacular growth of the NIH. Congress gave the NIH not only the responsibility but the budgetary resources to expand on the work of the CMR. In 1945 the appropriation to NIH was approximately \$700,000. By 1955 the figure had climbed to \$36 million; by 1965, \$436 million; and by 1970, \$1.5 billion, a sum that allowed it to award some 11,000 grants,

about one-third requiring experiments on humans. As a result of this largess, NIH was able both to run an extramural program like the CMR had done, making grants to outside investigators, and to administer an internal, intramural research program of its own. In 1953, NIH opened its Clinical Research Center, in which investigators appointed to its own staff coordinated patient treatment with medical research. Those who worked at the Bethesda site during the "halcyon days" of the 1950s, to quote the NIH deputy director during that period, J. D. Rall, were overwhelmed by the "awesome immensity of the place and diversity of research interests."¹⁰ Indeed, the scope and significance of NIH operations were such that through the 1980s, practically every chairman of a basic science department in major American medical schools was at some point in his career an NIH fellow or NIH grant recipient.

The Clinical Center was a 500-bed research hospital that admitted patients on referral when their disease fit with the particular investigatory interests of one of the seven NIH institutes. The focus was mainly, but not exclusively, on chronic diseases, including arteriosclerosis, rheumatoid arthritis, leukemia, and schizophrenia. Every patient admitted was part of a formal research study—a research subject—but the NIH, at least before 1965, never put the matter quite so baldly. Instead, it blurred the lines between research and therapy. The Clinical Center, as its patient brochures and handbooks explained, would "benefit all people by adding to our storehouse of knowledge . . . [and] at the same time . . . provide the best possible medical and nursing care." The center's "team of experts [was] working for your better health and for new knowledge." The facility also admitted a group of volunteers drawn from religious and service organizations to serve as normal controls in some of the projects. The NIH materials hastened to assure them, as they did the patients, that their well-being came first: "The normal control is not 'experimented upon' without regard to his individual welfare. . . . The welfare of the patient takes precedence over every other consideration."¹¹

The Clinical Center, however, instituted almost no formal procedures or mechanisms to ensure that patients' best interests were not sacrificed to the researchers' own agendas. The center did not, in the first instance, educate patients to be alert to possible conflicts of inter-

est or to question the researcher closely about the protocol. The material that specifically addressed "The Patient's Part in Research at the Clinical Center" invoked the ethos of the traditional doctor-patient therapeutic relationship and essentially asked the patient to trust the researcher: "Just like the family doctor, the physician in the Clinical Center has a professional and moral obligation to do everything possible to benefit the patient. . . . The primary purpose of the Clinical Center is medical research in the interest of humanity, and this purpose is achieved at no sacrifice of benefit to the individual." That an NIH researcher was many things but assuredly *not* a family physician, or that the well-being of humanity and the well-being of a patient might diverge, were issues the NIH would not confront.

The Clinical Center set neither formal requirements to protect human subjects nor clear standards for its investigators to follow in making certain that subjects were well informed about the research protocols. As a result, the hallmark of the investigator-subject relationship was its casualness, with disclosure of risks and benefits, side effects and possible complications, even basic information on what procedures would be performed, left completely to the discretion of the individual investigator.¹² Thus, patients at the National Heart Institute were asked to sign a general consent form before undergoing surgery; but, as its director, Donald Fredrickson, later observed, explaining the procedures to the patients was "by no means universal." One reason for the omission, Fredrickson explained, was that researchers were convinced their protocols involved no significant risk to the patient; in their view, since the experiments did not depart markedly from standard practice and represented only a minor variant on major therapeutic or diagnostic interventions, the details were too trivial to justify disclosure. But Fredrickson added a second consideration, without noting the inherent contradiction between the two points: the investigators feared that discussing the research aspects in detail would "unduly alarm the patient and hinder his reasonable evaluation of procedures important to his welfare." Thus, the cardiac surgery service had its patients sign only a standard surgical consent form, even though, as Fredrickson conceded, the procedures might be anything but standard. For example, "during the surgery, research procedures are sometimes performed, such as . . . application of tiny metal clips to the heart for

post-operative measurements, etc." So too, on the diagnostic cardiology unit: "Neither the details of all measurements or procedures carried out during catheterization nor a complete recital of each specific hazard is given the average patient."¹³ The conclusion seems inescapable that it was not so much the subjects' well-being but the researchers' needs that kept the communication between them to a minimum.

Moreover, NIH investigators were not obliged by internal rules or their own sense of propriety to consult with colleagues in order to make certain that their evaluation of risks was not biased by an eagerness to do the research. They were not required to obtain another investigator's opinion, let alone approval, on whether the protocol was truly nothing more than a minor deviation from standard practice. To be sure, NIH did have a Medical Board Committee composed of representatives of each of the institutes and the Clinical Center staff, and NIH officials maintained that "any nonstandard, potentially hazardous procedure, or any involving normal subjects receives appropriate group consideration before it is undertaken." However, as one deputy director explained, "It is not necessary to present each project to any single central group." Investigators who wanted a consultation on whether their protocol involved "potential hazard to the life or well-being of the patient" had the option of seeking the advice of the Medical Board Committee; but if the investigators believed that their protocols were not hazardous, they were free to proceed. The choice was the investigator's alone and so, not surprisingly, the board was rarely consulted. Nor were informal consultations a regular practice. The Heart Institute, for example, had been without a director from 1953 to 1961. The result, according to Fredrickson, was "a sense of 'hopelessness' on the part of the Clinical Associates and some lack of dispassionate review of the conduct of some of the more routine aspects of research and clinical care."¹⁴

Researchers at the other NIH institutes were equally casual. Patients might receive a general description of the protocols, but the specifics were not often spelled out. Some investigators asked for a signature on a general release form; others noted in the chart that they had discussed the issues with the patient. NIH, however, had no fixed methods or requirements to make certain that the subject received an explanation of the procedures, indicated an understanding of them, and voluntarily consented to participate. Dr. Robert Cohen, the director of clinical

investigations for the National Institute of Mental Health, reported that "in only a small percentage" of cases did patients sign a specific consent form, and even then, "the negative aspects of therapy" were not usually stipulated and recorded on the forms. His counterpart at the National Cancer Institute noted that some colleagues followed a formal procedure and others an informal one, and that they could not agree among themselves about either the style or the substance of the investigator-subject communication.¹⁵ Thus, the Cancer Institute had no uniform policy about consent other than a general understanding that the researcher should somehow obtain it.

Peer review of NIH research protocols followed this same pattern. Officially, patient care at the Clinical Center was the joint responsibility of clinicians and researchers, and institute directors contended that consultations between them at the bedside or in committees ensured high-quality medical care and research. Ostensibly, colleagues were judging the scientific value and ethical soundness of each other's work. However, no regulations existed to ensure a timely or effective implementation. In some institutes, group consideration of research proposals took place at ward rounds conducted by the chief of service; in others, the branch chiefs and the scientific director of the institute met to discuss a particular project. But such sessions were unscheduled and infrequent, and in the absence of a formal system, everyone conceded that some research could slip through the cracks. When the clinical director of the Cancer Institute was asked, "Is it possible for a physician on the staff to do a procedure that is essentially new or different before it has been reviewed either by group consideration or by the service head?" he responded "that it is possible, that it is unlikely, and that it is assumed that senior investigators will discuss continually with their immediate superiors their current research efforts."¹⁶ NIH officials in the 1950s clearly were unready to acknowledge that assumptions and practice might well diverge, or that explicit guidelines and procedures might seal the cracks. Left to themselves, they were ready to let the researchers handle decision making.

This policy reflected, first, a faith at the Clinical Center that the researcher-subject relationship was identical to the doctor-patient relationship.¹⁷ In medical investigations, as in medical therapy, the well-being of patients (even if they were now subjects), was paramount.

Holding to such a premise, the Clinical Center directors unhesitatingly transferred the discretion that the physician enjoyed in the examining room directly to the investigator in the laboratory. In fact, the only time that NIH required formal review and approval of a human experimentation protocol by its Medical Board Committee was with research involving normal volunteers. NIH treated normal subjects differently precisely because they did not fit into the traditional doctor-patient relationship. Since the subjects were not sick, the researcher could not invoke a clinical model of responsibility, and NIH here—but only here—thought it necessary to go beyond a trust in the investigator's judgment.

Second, the Clinical Center assumed that researchers who were concerned about the ethics of a particular protocol would on their own initiative consult with colleagues. Peer review, however ad hoc, would provide the necessary checks; professionals would be self-regulating. The alternative—to insist on precise explanations to patients and to obtain their formal consent—seemed but an empty ritual to the NIH research community. Laypeople had neither the scientific knowledge nor emotional capability, especially when they were acutely ill, to understand protocols. "The usual patient," as one of the directors put it, wants "to avoid the necessity of grappling with painful facts related to his own welfare. He prefers (and in a real sense he has no other choice) to depend on an overriding faith that the physician and institution will safeguard his interests above any other consideration." At the Clinical Center particularly, he continued, "patients feel that they have . . . gained an opportunity that is open to relatively few."¹⁸ These patients were not about to question or oppose the physician's judgment. The patient was to trust the physician, whether in the guise of researcher or therapist, and that was the sum of the matter.

At least some NIH chiefs recognized that other, very different considerations accounted for the softness of the procedures—namely, an enormous intellectual and emotional investment in research and the shared conviction that the laboratory would yield up answers to the great mysteries of disease. Since the researcher, not the clinician, controlled the NIH structure and occupied the positions of leadership in its hierarchy, the absence of regulations reflected researchers' prefer-

ences to keep their laboratory work unfettered. "At NIH," observed Dr. Phillippe Cardon (a psychiatrist, not a bench researcher), "taking care of patients is not by and large considered to be as challenging, important, or rewarding as is doing a clinical experiment. . . . If we were more interested in taking care of patients than in research, we wouldn't be here. It is unrealistic to expect most very good investigators also to be very good physicians (or vice versa)." Cardon himself was not overly concerned about the implications of this fact, for he, at least, trusted the researcher to "judge the relative values of right and wrong" and abide by the appropriate limits in "putting patients 'in jeopardy' for the public good." Still, he asked, "In clinical research, is the means utilized justified by the ends?"¹⁹ His own answer seemed to be a qualified yes, provided that the peril was not too great and the potential public benefit considerable.

Raising the issue as Cardon did at once enlightened and troubled some of his NIH colleagues. "We are on the defensive," responded one of them, "because, whether we like it or not, we have in some senses utilized the concept of the end justifies the means." Each of us here, observed another, knows that "it is easy to get carried away with the importance of one's own research." Still others conceded that researchers had a "special angle of vision" (others might say a self-interest) that could lead them to minimize the risks of an experiment to the subject when the benefits to humanity seemed extraordinary. These worries, however, did not dictate NIH policy. Rather, a confidence in the ultimate value of research fostered and justified a hands-off policy that left investigators with the sole discretion to determine risks and benefits. The final word went to one institute director who concluded: "Society would be in peril if we did not do clinical research."²⁰

The NIH was so committed to this position that it would not devise procedures or guidelines to govern the extensive extramural research that it supported. By 1965 the NIH extramural program was the single most important source of research grants for universities and medical schools, by NIH estimates supporting "between 1,500 and 2,000 research projects which, by their titles, indicate presumptive experimentation involving man." Nevertheless, grant provisions included no stipulations about the conduct of human experimentation, and NIH

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internal memoranda noted that it treated applications "for clinical research the same as for other research." NIH staff did find that many investigators, "without formal requirements for such information . . . may describe . . . local practices concerning the provision for informed consent, and other matters relating to professional ethical considerations." Reviewers, too, on their own initiative would "often deliberate ethical questions in relation to grants." However, such submissions were voluntary and the discussions random. "There is little attempt," NIH officials reported, "to develop consensus as to what clinical research practices should be, or even to define what is the nature of the ethical issues at stake."²¹

The universities made little effort to fill the gap. In 1960, Dr. Louis Welt, of the University of North Carolina School of Medicine, one of the handful of people then interested in the ethics of human experimentation, asked some eighty university departments of medicine about their practices and guidelines. He reported that of the sixty-six responding departments "only eight have a procedural document and only 24 have or favor a committee to review problems in human experimentation."²² Shortly thereafter, a newly established Law-Medicine Research Institute at Boston University conducted a similar survey and confirmed Welt's findings. Only nine of fifty-two departments of medicine had a formal procedure for approving research involving human subjects, and only five more indicated that they favored this approach or planned to institute such procedures. Twenty-two departments did have a peer-review committee, but with merely an advisory role.²³

Both of these surveys revealed a widespread conviction that ethical considerations in research were best left to the judgment of the investigators. They were in the best position to calculate the risks and benefits to the subjects, to share information they thought appropriate, and ultimately to decide whether the subjects were voluntarily and knowingly agreeing to participate in the experiment. The medical research community, noted the Boston University survey, has "a general skepticism toward the development of ethical guidelines, codes, or sets of procedures concerning the conduct of research." Welt not only reached the same conclusion but agreed with it: "A committee cannot take responsibility. . . . This must always be in the hands of the individual investigators." Consultations with colleagues could be useful,

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but "responsibilities return to their rightful place in the minds and hearts of the investigators."²⁴

Granted, no profession invites regulation, and individuals, whether they work at the bench or the desk, prefer to be left alone on the assumption that they will behave ethically. Medical researchers and their institutions (from the NIH to almost all university medical schools and teaching hospitals), however, viewed the investigator's prerogative as sacrosanct, and that fact requires explanation. Perhaps any highly motivated group would have reacted in this same fashion, magnifying the importance of their own work so as to minimize the sacrifices that others would have to make for it, but few commentators called them to task. No less puzzling, in the immediate postwar decades, this delegation of authority to the researcher did not spark significant opposition or debate from outside medicine. Neither Congress nor the academy nor the media urged that human experimentation be subjected to the oversight of committees or be responsive to formal principles and codes defining the rights of subjects.²⁵

The response to human experimentation might well have been otherwise. After all, the Nuremberg tribunal in 1945 and 1946 cast a shadow over the entire field of human experimentation. Revelations about the atrocities that the Nazis committed—for instance, putting subjects to death through prolonged immersion in subfreezing water to learn the limits of bodily endurance or castrating them in order to study the effects of X rays on the genitals—might have sparked a commitment in the United States to a more rigorous regulation of research. So too, the American research effort during the war may have raised questions and spurred closer oversight. Some might have suggested that Americans had come close to following the dictum, proclaimed by Hitler in 1942, that "as a matter of principle, if it is in the interest of the state, human experiments were to be permitted," that it was unacceptable for "someone in a concentration camp or prison to be totally untouched by the war, while German soldiers had to suffer the unbearable." This was, in fact, the line of argument that the defense attorney for the Nazi doctors pursued at the Nuremberg trial. With the research on American prisoners at question, he asked that the court "not overlook the fact that particularly during the last years, even outside Germany, medical experiments were performed

on human beings who undoubtedly did not volunteer for these experiments."²⁶

The Nuremberg Code, the set of standards on ethical research that emerged from the tribunal, might have served as a model, even if a slightly flawed one, for American guidelines. Its provisions certainly were relevant to some types of medical research that had been (and still were) under way in the United States. The opening provision of the Nuremberg Code declared: "The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent." By this principle, the mentally disabled were not suitable subjects for research—a principle that American researchers did not follow. Moreover, the Code insisted that the research subject "should be so situated as to be able to exercise free power of choice," which rendered questionable the American practice of using prisoners as research subjects. The Nuremberg Code also declared that human subjects "should have sufficient knowledge and comprehension of the elements of the subject matter involved as to make an understanding and enlightened decision." Thus, American practices notwithstanding, persons mentally disabled by illness or retardation were not to be enrolled.

Yet, with a few exceptions, none of these issues received sustained analysis in the United States in the immediate postwar period. Neither the horrors described at the Nuremberg trial nor the ethical principles that emerged from it had a significant impact on the American research establishment. The trial itself did not receive extensive press coverage. Over 1945 and 1946 fewer than a dozen articles appeared in the *New York Times* on the Nazi research; the indictment of forty-two doctors in the fall of 1946 was a page-five story and the opening of the trial, a page-nine story.²⁷ (The announcement of the guilty verdict in August 1947 was a front-page story, but the execution of seven of the defendants a year later was again relegated to the back pages.) Over the next fifteen years only a handful of articles in either medical or popular journals took up Nuremberg.

In part, this silence may have represented a postwar eagerness to repress the memory of the atrocities. But more important, the events described at Nuremberg were not perceived by researchers or commentators to be directly relevant to the American scene. The violations

had been the work of Nazis, not doctors; the guilty parties were Hitler's henchmen, not scientists. Francis Moore, a professor of surgery at Harvard Medical School and a pioneer in kidney transplantation, was especially sensitive to ethical issues in experimentation and was ahead of most of his colleagues in recognizing the dilemmas in human experimentation. But even as he decried the German atrocities, he distanced science and non-Germans from them. The "horrible nightmares of Dachau and Belsen will ever stand in the conscience of all men," he told a symposium on drug research in 1960. But the lesson had to remain "most especially in the conscience of Germans"; further, "the tragedy of this intentional suffering and torture can never be erased, but one of the ironic tragedies of the human experimentation by the German 'scientists' was that no good science of any sort came from any of this work."²⁸

Madness, not medicine, was implicated at Nuremberg. Few people noticed that many of the German perpetrators were university-trained and university-appointed researchers or that many of them possessed first-rate medical credentials and had pursued notable careers. Instead, the prevailing view was that they were Nazis first and last; by definition, nothing they did, and no code drawn up in response to them, was relevant to the United States.²⁹

Other articles that addressed the Nuremberg trial drew from it not the lesson that the state should regulate experimentation but quite the reverse—that the state should not interfere with medicine. Nuremberg became a stick with which to beat the idea of "socialized medicine," not the occasion to oversee research.³⁰ The logic of the argument was that the atrocities were the result of government interference in the conduct of research (and here, the distinction between the Nazi government and all other governments was lost). Science was pure—it was politics that was corrupting. Hence, state control over medicine through regulations that intruded in the private relationship between doctor and patient or investigator and subject were likely to pervert medicine.

Even an incident notorious enough to capture headlines and expose the unregulated character of human experimentation had a minimal impact on the mood of benign neglect. In 1962, when Senator Estes Kefauver was winding up a long and only modestly successful campaign to regulate drug company prices, the thalidomide scandal broke.

The drug, widely prescribed in Europe for pregnant women at risk for spontaneous abortion or premature delivery, was in the process of being evaluated for safety by the Food and Drug Administration (FDA). One official, Francis Kelsey, dissatisfied with the quality of the European test results, delayed approval, and in the interim the link between thalidomide and birth defects (typically, warped or missing limbs) became established. Although a major catastrophe had been averted, some 20,000 Americans, of whom 3,750 were of childbearing age and 624 were reported as pregnant, had already taken thalidomide on an experimental basis, that is, as part of the drug company protocols. However, the precise number of recipients was unknown and their identification incomplete, mostly because the companies and the prescribing physicians who were conducting the trials kept very sloppy records. Kefauver took full advantage of the scandal to clinch the case for greater regulation, and as a direct result, Congress empowered the FDA to test drugs not only for safety (an authority it had held since 1938) but for efficacy as well.

In the course of the hearings and debates on the bill, the senators learned, to the amazement of some of them, that patients who had received experimental drugs in these clinical trials did not always know that they were participating in an experiment. Many of the subjects who had taken thalidomide had had no idea that they were part of drug trial and had not given their consent. New York's Senator Jacob Javits, profoundly disturbed by this situation, proposed an amendment to the Kefauver bill that would have compelled the secretary of Health, Education and Welfare (HEW) to issue regulations that "no such [experimental] drug may be administered to any human being in any clinical investigation unless . . . that human being has been appropriately advised that such drug has not been determined to be safe in use for human beings."³¹ One might have thought that the desirability and fairness of such a regulation were indisputable; surely subjects in an experiment should be told that a drug is not demonstrably safe and asked whether they wish to take it. Yet the debates that followed were anything but mild, and the Javits amendment did not survive for long in its original form. As late as 1962, even so elementary a protection of human subjects could not win approval, and the reasons clarify why regulating medical research appeared unacceptable.

Javits cogently argued his case. He assured colleagues that he was not opposed to human experimentation and fully appreciated its critical role in medical progress ("I feel deeply that some risks must be assumed"). Nevertheless, "experimentation must not be conducted in a blind way, without people giving their consent. . . . [Otherwise,] where is the dignity, the responsibility, and the freedom of the individual?" These arguments notwithstanding, Javits recognized that the amendment was running into trouble, and attempted to salvage it by changing the language from the secretary "shall" to the secretary "may" issue such regulations; in its weakened form, intervention became discretionary, not obligatory, and allowed for as many exceptions as the secretary might wish. Javits also made clear that his proposal would affect only the administration of drugs whose safety was not known; he was not asking that patients be informed about all drugs physicians prescribed for them.³²

Nevertheless, Javits could not persuade his colleagues to impose so elementary a requirement on researchers. First, the senators responded with extreme caution because they consistently confused experimentation with therapy and the investigator with the physician. And just as this blurring of the lines committed the NIH to a hands-off policy, so it undercut a regulatory response from Congress. Senators feared that compelling physicians to inform a patient about an experimental drug would also compel them to inform a patient about a diagnosis that was fatal; in order to get patients to take the new drug, the doctor would have to tell them that they were suffering from a life-threatening illness. For example, Colorado's Senator John Carroll, claimed to be generally sympathetic to the Javits amendment: "I believe that under normal circumstances, when a man . . . goes to a doctor, that man has a right to know if he is to be given untested medicine. . . . I firmly believe every human being has a right to know whether he is being treated with experimental medicine . . . that he is to be used as a guinea pig." Why, then, oppose the amendment? Because with a "strict, mandatory, prenotification requirement, we might prevent the doctor from helping his patients in times of extreme emergency." Or as Mississippi's Senator James Eastland insisted: "It might be an experimental drug, a single injection of which would provide him with a chance to live." The debate even slipped over into the case of the coma patient, in the

process revealing the senators' inability to distinguish between the competent and the incompetent patient, and between an emergency and a nonemergency situation. Thus, one senator objected to the proposal because it would keep a comatose patient from getting potentially life-saving drugs: "How could he be notified that an experimental drug is being used?"³³

In the Senate, as in the Clinical Center and countless university hospitals as well, the ethos of the examining room cloaked the activities of the laboratory, and the trust accorded the physician encompassed the researcher. Lawmakers were no more able than NIH officials to distinguish the human subject from the patient, so that efforts to regulate experimentation—however reasonable—were translated into attempts to regulate therapy, which were still considered unnecessary and intrusive. For any change to occur, it would first be necessary to differentiate the researcher from the doctor and the laboratory from the examining room.

Moreover, the confusion of experimentation with therapy reflected an extraordinary optimism about the prospects of innovation. The hearings may have been deeply affected by thalidomide, but when it came to regulating research, the senators saw every new drug as a potential penicillin. They hesitated to intervene in research because they assumed that experiments were likely to prove successful and the drugs under investigation would turn out to be therapeutic wonders. Through the course of the debate the senators frequently posed their hypothetical cases about experimental drugs in terms of the new, miraculous injection, the life-saving pill, the prescription that would revive the near-dead. They measured the impact of regulation not by calculating risks but by exaggerating benefits. Fantasies, not nightmare cases, ruled: the researcher who had a miracle cure for a deadly disease or who could awaken the comatose patient ought not to be burdened or bridled with administrative regulations.

Starting from such premises, it is small wonder that Congress proved unwilling to say cleanly and simply that researchers must obtain the permission of their subjects before conducting drug experiments. The Javits amendment finally emerged in the legislation as a request to the secretary of HEW to promulgate regulations so that investigators dispensing experimental drugs would obtain the consent of their sub-

jects "except where they deem it not feasible or, in their best professional judgment, contrary to the best interests of such human beings."³⁴ The qualifications took the heart out of the resolution, granting investigators broad discretion to decide when such vague considerations as feasibility or best interest were being served.

Between 1945 and 1965 an occasional academic conference or organization attempted a sophisticated analysis of the issues in human experimentation—the deliberations of the Law-Medicine Research Institute at Boston University are one such example. The more typical approach, however, is exemplified by the National Society for Medical Research (NSMR). Founded to counter the campaigns of antivivisectionists, the NSMR, in 1959, for the first time devoted a conference to "Clinical Research—Legal and Ethical Aspects." Persuaded that "the law has not kept pace with modern medical developments," the conference attendees produced several useful analyses, including one on the weaknesses of the Nuremberg Code and another on the value of peer review in human experimentation. But the most notable characteristic of the 1959 conference—indeed, of much of the literature on ethics and human experimentation between 1945 and 1965—was its calmness. The discussions made the problems seem more conceptual than actual, more academically interesting than pressing. There was no sense of crisis, of lives at stake, or of trusts violated, and no hint of scandal. When Dr. Louis Welt discussed the difficulty of obtaining a noncoerced consent, the group he focused on was medical students, not prisoners or the mentally disabled. When a colleague reviewed human experimentation at the NIH Clinical Center, he found its guiding principles altogether adequate (requiring "only slight modification in light of experience") and made no comment about actual practices.³⁵

When discussants glimpsed a conflict of interest between the researcher and the subject, or between the principle of the greatest good for the greatest number and the rights of the individual, they grew distinctly uncomfortable and moved either to smooth over differences or to make certain that the research enterprise was not seriously hampered. Thus, the NSMR's 1959 conference report made the ordering of priorities clear: "The standards for health research on human subjects should recognize the imperative need for testing new procedures,

materials and drugs on human subjects as essential to the public interest. The protection of personal rights of individuals . . . can co-exist with the public necessity to use people—sick or well—as subjects for health research.” The primary goal was testing new procedures, and the rights of individuals would coexist with it. The conference report did declare that experiments on minors or on the incompetent should have the approval of parents or guardians and should “also significantly benefit or may reasonably benefit the individual.” But, probably aware of how far World War II practices had departed from this standard, the authors added a critical qualification: “There may perhaps be justification in the absence of this requirement in a national emergency or for an experiment of utmost importance. Here, the availability of certain persons, not able to consent personally, may constitute a strategic resource in terms of time or location not otherwise obtainable.” Although the report conceded that “the Nazis hid behind this rationalization . . . [and] such justifications should not even be considered except in the most dire circumstances,” still it gave retrospective approval to the wartime researchers and prospective approval to investigators on the brink of findings of “utmost importance.”³⁶

In this same spirit, several international medical organizations in the postwar decades published guidelines for human experimentation, expanding on the Nuremberg Code. Most of these efforts, however, did not involve American groups; and with the exception of a few researchers who made this a field of special study, the codes captured little attention in the United States and had minimal impact on institutional practices.³⁷ The American Medical Association (AMA), which spoke for the interests of general practitioners, rather than specialists or medical investigators, did frame a research code, but the stipulations were vague and lacked any reference to means of enforcement. The code required the voluntary consent of the human subject but said nothing about what information researchers should impart; who, if anyone, should monitor the process; or what the ethics were of conducting research on incompetent subjects, such as the institutionalized mentally disabled. The code did condemn experiments on prisoners, expressing explicit “disapproval of the participation in scientific experiments of persons convicted of murder, rape, arson, kidnapping, treason or other heinous crimes.”³⁸ But its aim was to protect public safety, not inmates’

rights. The AMA believed that parole boards were treating prisoner-volunteers too generously, giving them early release as a reward for assuming medical risks, and thus returning hardened criminals to the streets too quickly.³⁹

In all, American researchers in the immediate post-World War II period ran their laboratories free of external constraints. The autonomy they enjoyed in conducting human experiments was limited only by their individual consciences, not by their colleagues, their funders, their universities, or any other private or public body. How the investigators exercised this discretion, the record they compiled, became the focus of Henry Beecher’s analysis. What we find there is a case study of the dangers of leaving medical science on its own.

CHAPTER 4

The Doctor as Whistle-blower

THE career of Henry Beecher provided few clues that he would be the one to expose in most compelling fashion how the researchers in the post-World War II decades abused their discretion. Unlike many whistle-blowers, Beecher stood at the top of his profession. Although the family name is a famous one in American history—his kin included Harriet Beecher Stowe, the “little lady” that Lincoln credited with bringing on the Civil War, and Henry Ward Beecher, the minister who was exceptionally influential until being disgraced by an adulterous affair—Henry’s branch had not prospered. He grew up in Kansas in very modest circumstances and graduated from the University of Kansas. Talented and ambitious, he worked his way through Harvard Medical School, trained in general medicine, and then joined the Harvard faculty and the staff of the Massachusetts General Hospital (MGH). Beecher was so highly regarded that when in the late 1930s Harvard and the MGH sought to professionalize the field of anesthesiology, they gave him the assignment. He did a masterful job, coming to hold the Dorr Professorship of Research in Anesthesia and to chair the department.¹

What prompted Beecher to analyze the conduct of human experiments and to go public with his findings? Anesthesiologists do have a reputation for being the fifth column within medicine. Beecher belonged to the specialty that daily watches colleagues perform in the operating room and then discusses their relative strengths and weak-

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nesses. He was also something of a maverick who delighted in controversy and conflict. In 1954, for example, he was senior author of “A Study of the Deaths Associated with Anesthesia and Surgery,” a paper framed in highly judgmental terms. Its purpose was to determine “the extent of the responsibility which must be borne by anesthesia for failure in the total care of the surgical patient.” Others would have called this an investigation of comparative mortality with anesthetic agents. The major finding was that the use of the new and very popular anesthetic agent curare was associated with a significantly higher death rate, and Beecher hoped, again in contentious fashion, that “the study itself, by directing attention to these matters, would lead to sharper criticism of existing practices with improvement in them,” which it did.²

Beecher’s concern for research ethics also drew on his personal experiences. He was both a committed investigator and one who was fully prepared to use his laboratory skills to promote societal ends. His major interest in the 1940s and 1950s was the effects of drugs on pain, performance, and perceptions, a field which he pioneered. Given the obvious military relevance of the subject, Beecher worked closely with the U.S. Army during World War II and continued the collaboration into the opening years of the cold war. He explored such questions as which narcotic was best administered to wounded soldiers in combat, and he also alerted the military to the importance of what he called “the second great power of anesthesia,” that is, its potential as a truth-telling serum. In short, Beecher learned firsthand about research in the service of society and in the process may have become sensitive to how slippery a slope he was on.

The most important consideration, however, was Beecher’s commitment to good science, that is, to well-designed and properly constructed research protocols. He was among the first to insist on the need for controls in drug experiments, convinced that in no other way could the investigator eliminate the placebo effect and accurately measure the efficacy of a new drug. Beecher’s most lasting contribution as a researcher was to establish how the very act of taking a drug, whatever its potency, led some patients to improve; he calculated that “of the average pain relief produced by a large dose of morphine treating severe pain, nearly half must be attributed to a placebo.” Hence, if the outcomes for one group taking a medication were not compared to

outcomes for a similar group taking a placebo, the efficacy of a drug could not be known. "The scientist as well as the physician," insisted Beecher in 1959, "is confronted with a bewildering array of new agents launched with claims sometimes too eagerly accepted by a compassionate physician trying to help a patient in trouble. The properly controlled, quantitative approach holds the only real hope for dealing with the oncoming flood of new drugs."³ Thus, Beecher's sharpest fear was that research of dubious ethicality might impugn the legitimacy of experimentation, discrediting the prime force bringing progress to medicine. Bad ethics would undercut the pursuit of good science, and the result would be widespread ignorance and old-fashioned quackery.⁴

When Beecher first addressed research ethics in the late 1950s, only a handful of others shared his concern, and not until the mid-1960s did his ideas capture widespread attention. The breakthrough occurred in March 1965 at a conference on drug research at Brook Lodge, Wisconsin, sponsored by the Upjohn pharmaceutical company. Beecher delivered a paper on the ethics of clinical research, which went beyond discussions of general principles to cite specific cases. Although he did not name individual investigators, he discussed specific research protocols, all published, whose ethics disturbed him. His use of real cases caught the media's attention, and both the *New York Times* and the *Wall Street Journal* ran lengthy accounts of his talk.⁵ Colleagues, too, evinced an unusual interest in his remarks, by no means all of it friendly or favorable. "I really was subjected to a most humiliating experience," Beecher told a friend about the aftermath of the Brook Lodge meeting. In particular, he reported, Dr. Thomas Chalmers and Dr. David Rutstein, both colleagues at the Harvard Medical School, "called a press conference to refute what I said without finding out whether or not I could be present. They made prepared statements and the meeting was terminated before I had an opportunity to do so. Chalmers charged me with being an irresponsible exaggerator. Rutstein stood up there with him and did not dissent."⁶ Beecher seemed somewhat surprised by so agitated a response, but he immediately moved to defend his position and, judging by the way he threw himself into the task, relished the opportunity.

Beecher's strategy was to turn the Brook Lodge presentation into a professional journal article that documented the ethical dilemmas in

human experimentation by describing actual research protocols. He had no trouble accumulating some fifty examples of what he considered investigations of dubious ethicality, and in August 1965, he submitted the article (again without footnotes to the cases) to the *Journal of the American Medical Association (JAMA)*. In a covering letter he told the editor, John Talbott, that the manuscript represented "about ten years of as careful thought as I am capable of doing. It has been read by a great many individuals, including the president of the Massachusetts Medical Society, who, though appalled by the information, agree that it should be published, and the sooner the better. I do hope you will find this suitable for publication in the Journal . . . the finest place for it to appear, in my view. It is rather long. I do not believe it can be shortened significantly and carry the same message, which so urgently needs to be disseminated." After Talbott responded that he was sending it out for review, Beecher wrote again to emphasize how important it was that *JAMA* publish the piece: "Last year I gave an oral presentation at a closed medical meeting and the reverberations from that are still continuing. . . . Unquestionably the shoe pinched a lot of feet."⁷

In October, Talbott rejected the article, informing Beecher that neither of two reviewers favored publication. One insisted that "the story could be told in twenty-five per cent of the space, illustrated by ten items with references rather than forty-eight items without references." The other found it so "poorly organized [that] frankly, I was surprised that a thoughtful physician of Doctor Beecher's stature expected you to review this manuscript. Should the decision be to revise, I would be interested in seeing the revision provided it is well prepared and eliminates nine-tenths of the examples." Apparently not eager to get involved in publishing so controversial a piece, Talbott noted that Beecher had twice expressed an unwillingness to make substantial deletions and did not give Beecher the option of changing his mind or making revisions. He thought it best to have Beecher "start afresh with another editorial board."⁸

Beecher then turned to the *New England Journal of Medicine (NEJM)*. He submitted a slightly revised and fully annotated copy, and Dr. Joseph Garland and two of his assistants (the "brain trust," he called them) reviewed it case by case; they recommended omitting about half the protocols, apparently not so much for reasons of space but because

they did not find all the examples equally compelling. Some author-editor give-and-take went on, but Beecher accepted their recommendations and was not unhappy to have the piece, in his view, "understate the problem."⁹

Conscious that the *NEJM* did not enjoy the *JAMA*'s circulation, Beecher notified the press about its forthcoming publication and at the same time warned John Knowles, the head of the MGH, that "a considerable amount of controversy" might ensue. "I have no doubt that I shall come in for some very heavy criticism. For the sake of the Hospital, I have tried to make certain that the material is as thoughtful, as accurate and as unexaggerated as possible."¹⁰

Beecher's indictment was powerful, arousing, as classic exposés do, a sense of disbelief that such practices had continued for so long without either scrutiny or sanction. A sample of three conveys the style of the twenty-two.

Example 16. This study was directed toward determining the period of infectivity of infectious hepatitis. Artificial induction of hepatitis was carried out in an institution for mentally defective children in which a mild form of hepatitis was endemic. . . . A resolution adopted by the World Medical Association states explicitly: "Under no circumstances is a doctor permitted to do anything which would weaken the physical or mental resistance of a human being except from strictly therapeutic or prophylactic indications imposed in the interest of the patient." There is no right to risk an injury to 1 person for the benefit of others.

Example 17. Live cancer cells were injected into 22 human subjects as part of a study of immunity to cancer. According to a recent review, the subjects (hospitalized patients) were "merely told they would be receiving 'some cells'— . . . the word cancer was entirely omitted."

Example 19. During bronchoscopy a special needle was inserted through a bronchus into the left atrium of the heart. This was done in an unspecified number of subjects, both with cardiac disease and with normal hearts. The technique was a new approach whose hazards were at the beginning quite unknown. The subjects with normal hearts were used, not for their possible benefit but for that of patients in general.¹¹

The investigations that made up Beecher's roster of dishonor differed in methods and goals. The researchers in some explored physiologic responses (as in example 19); in others, they attempted to learn more about a disease (examples 16 and 17); in still others, they tested new drugs (example 4) or withheld a drug of known efficacy to test an alternative (example 1). All the examples, however, endangered the health and well-being of subjects without their knowledge or approval. Only two of the original fifty protocols, Beecher reported, so much as mentioned obtaining consent, and he doubted that even they had gone very far in that direction: "Ordinary patients will not knowingly risk their health or their life for the sake of 'science.' Every experienced clinician knows this. When such risks are taken and a considerable number of patients are involved, it may be assumed that informed consent has not been obtained in all cases." Perhaps, he was later asked, the investigators had actually obtained consent but neglected to mention it in their publications? Beecher found it fanciful to believe (as in example 1) that a group of soldiers with strep throat would knowingly participate in an experiment in which they would be denied penicillin and face the risk of contracting rheumatic fever: "I have worked on the ward of a large hospital for 35 years, [and] I know perfectly well that ward patients will not . . . volunteer for any such use of themselves for experimental purposes when the hazard may be permanent injury or death."¹²

Beecher's cases did not represent only a few bizarre examples; rather, his catalogue described how mainstream investigators in the period from 1945 to 1965 exercised their broad discretion. This fact emerges from a review of the original publications from which Beecher took his twenty-two examples—the first such review since the *NEJM* editors accepted the article for publication. (See Appendix A for complete citations to the twenty-two cases.)

Comparing the original twenty-two articles with Beecher's published account makes clear in the first instance that the strength of Beecher's indictment does not emanate from its methodological sophistication or scientific character. The selection was impressionistic, even arbitrary, not part of a random survey or systematic inquiry. Beecher himself considered the cases to be no more than apt examples, protocols that he knew about or had discovered as he read the *Journal of Clinical*

Investigation or the *NEJM*. Not surprisingly, then, the list of twenty-two has many idiosyncrasies: fully half of the studies involved research into cardiovascular physiology (examples 6 through 13 and 19 through 21), and two of the studies (examples 15 and 19) were carried out in England. But however haphazard the selection process, Beecher was singling out mainstream science—indeed, science on the frontier. To judge by such criteria as each researcher's professional affiliation, the sources of funding, and the journal of publication, these were typically protocols from leading investigators in leading institutions, working on some of the most important questions in medicine. Beecher was describing the clinical ethics of elite researchers, those already in or destined to be in positions of authority.

Beecher's twenty-two examples were current, all drawn from the immediate postwar period. One of the papers appeared in 1948, thirteen appeared between 1950 and 1959, and eight between 1960 and 1965. The journals were prestigious: six of the papers appeared in the *NEJM* (examples 1, 4 through 6, 14, and 16), five in the *Journal of Clinical Investigation* (examples 8, 10, 13, 15, 20), two in the *JAMA* (examples 2 and 9), and two in *Circulation* (examples 19 and 20). The funders of the research (which numbered more than twenty-two, since some projects received multiple support) included the U.S. military (the surgeon general's office or the Armed Forces Epidemiology Board), five projects; the National Institutes of Health, five projects; drug companies (including Merck and Parke, Davis and Company), three projects; private foundations, eight projects; and other federal offices (including the U.S. Public Health Service and the Atomic Energy Commission), three projects. Clearly, this was not research in tiny labs carried out by eccentric physicians.

Perhaps most telling were the auspices under which the research projects were conducted. Thirteen of the twenty-two examples came from university medical school clinics and laboratories: Case Western Reserve University (examples 1 and 2); the University of California Center for Health Sciences, Los Angeles (example 5); Harvard Medical School and its affiliated hospitals, including Peter Bent Brigham Hospital and Children's Hospital (examples 6, 9, 13, and 19); the University of Pennsylvania (example 7); Georgetown and George Washington Universities (example 8); Ohio State University (example 12); New

York University (example 16); Northwestern University (example 18); and Emory and Duke Universities (example 21). Three of the projects were conducted at the Clinical Center of the NIH (examples 10, 11, and 20).

The credentials of the principal investigators were one more indication of their importance. The younger ones were often research fellows, some in medicine (Case Western Reserve, example 1), others in surgery (Harvard, example 6); or postdoctoral or exchange fellows (NIH, examples 7 and 14). In two cases the more senior people were professors (NYU, example 16; Cornell, example 17). Among the junior researchers, a number were beginning to make their mark in the world of research and later went on to illustrious careers, becoming national leaders in medicine, chairmen of major departments, and winners of major awards, often for the very research that Beecher had cited.

Dr. Saul Krugman conducted the research described in Beecher's example 16, the purposeful infection with hepatitis of residents at the Willowbrook State School for the Retarded. After his Willowbrook investigations of 1956 through 1972, Dr. Krugman became the chairman of the pediatrics department at New York University and the winner, in 1972, of the Markle Foundation's John Russell Award. The citation praised Krugman for demonstrating how clinical research ought to be done. In 1983, Dr. Krugman also won the Lasker Prize, probably the highest award given for research in this country, just a notch below the Nobel Prize.

Dr. Chester Southam was the investigator in Beecher's example 17. An associate professor of medicine at the Cornell University Medical School and the chief of the section on clinical virology at the Sloan-Kettering Institute for Cancer Research, he was in charge of the research involving the injection of cancer cells into elderly and senile patients. In 1967, Dr. Southam was elected vice-president of the American Association for Cancer Research, and in 1968 he became its president.¹³

Examples 10 and 11, studies in heart physiology on patients at the NIH Clinical Center, involving "a mercury-filled resistance gauge sutured to the surface of the left ventricle" and "simultaneous catheterization of both ventricles," were conducted in 1957 and 1960 by Dr. Eugene Braunwald, then a researcher in cardiology at the NIH. (Dr.

Braunwald's is the only name to appear three times on the Beecher roll—principal investigator in these two cases, and one of the four authors of the paper in example 20.) In 1967, Dr. Braunwald won the Outstanding Service Award of the Public Health Service and in 1972, the Research Achievement Award of the American Heart Association. In 1972 he became Hersey Professor and chairman of the Department of Medicine at Peter Bent Brigham Hospital, Harvard Medical School, and he later headed the Department of Medicine at Beth Israel Hospital as well.

How is the behavior of these investigators to be understood? It will not suffice to claim that they were simply less moral or trustworthy than their colleagues. They were too well supported, too integral to the research establishment, and, ultimately, too much honored to characterize as aberrant or deviant. The idea that these particular experiments raised complicated ethical issues beyond the state of the field is no more persuasive. In practically every one of the twenty-two cases, it was self-evident that the subjects would not benefit directly from the research and might even be harmed. Neither Krugman's retarded subjects nor Southam's senile ones nor Braunwald's cardiac ones would have been better off for having participated in the protocols.

It also seems too narrow an explanation to place all the blame on raw personal ambition—the desire to get grants, win promotions, capture the prize. Undoubtedly, these considerations motivated some of the researchers, and Beecher himself, although he did not address the question directly, suggested this motivation. He stressed in particular the new and massive infusion of research funds through the NIH and the intensified research ethos in the postwar period. "Medical schools and university hospitals are increasingly dominated by investigators," he observed. "Every young man knows that he will never be promoted to a tenure post . . . unless he has proved himself as an investigator," and this at a time when "medical science has shown how valuable human experimentation can be in solving problems of disease and its treatment."¹⁴ However valid his point, it does not explain why the research community evinced no difficulty with these protocols, why no scientist who read Krugman's publications in the 1950s protested, and

why no department that reviewed the work of these researchers withheld promotion on the grounds of unethical behavior.

A better entry point for understanding how investigators and their colleagues justified these protocols is the impact of the World War II experience, because the exceptional protocol of the pre-1940 period became normative. Clinical research had come of age when medical progress, measured by antidotes against malaria, dysentery, and influenza, was the prime consideration, and traditional ethical notions about consent and voluntary participation in experimentation seemed far less relevant. A generation of researchers were trained to perform, accomplish, and deliver cures—to be heroes in the laboratory, like soldiers on the battlefield. If researchers created effective vaccines, diagnostic tests, or miracle drugs like penicillin, no one would question their methods or techniques.

This orientation survived into the postwar years, not simply because a license granted is not easily revoked, but because the laboratory achievements were so remarkable. Having been given extraordinary leeway, the researchers delivered extraordinary products: an array of antibiotics, including a cure for tuberculosis; a variety of drugs for treating cardiac abnormalities; a new understanding of hepatitis. Given this record, who would want to rein in such talent and creativity, to intrude and regulate behavior inside the laboratory? Surely not a senate committee that was investigating a drug scandal, let alone the NIH, whose extramural grants were funding the research. How much wiser to trust to the researcher and await one breakthrough after another.

Most of the researchers in Beecher's protocols were the heirs to this wartime tradition, although they had not actually participated in the war effort or held Committee on Medical Research (CMR) contracts. Of the thirty-two American investigators, only eight had been born before 1920 (of whom four had seen military service); of the twenty-four others, seventeen were born between 1921 and 1929, and seven between 1931 and 1934. They were, in other words, the products of medical and scientific training in the immediate postwar period, trained to think in utilitarian terms and ready to achieve the greatest good for the greatest number.

It is no coincidence that this cohort of investigators took as their

research subjects persons who were in one sense or another devalued and marginal: they were either retarded, institutionalized, senile, alcoholic, or poor, or they were military recruits, cannon fodder for battles in a war against disease. These social characteristics at once reflected and promoted a utilitarian calculus among researchers, encouraging them to make the same judgments in the 1950s and early 1960s as their predecessors had made in the 1940s.

Beecher had relied on the logic of the situation—the patients' presumed unwillingness to put themselves at jeopardy—to argue that the researchers had not actually obtained consent from their subjects. Had he scrutinized the types of patients enrolled in the protocols more closely, he could have clinched his point, for in practically every instance, they lacked either the opportunity or the ability to exercise choice. The research subjects in examples 1 and 2 were soldiers in the armed forces; in example 3, charity patients; in examples 4 and 16, the mentally retarded; in examples 6 and 22, children or newborns; in examples 9 and 17, the very elderly; in example 12, the terminally ill; in examples 13 and 15, chronic alcoholics with advanced cases of cirrhosis. The subjects in examples 8, 10, 11, and 20 were patients in the Clinical Center, where, as we have noted, patients were generally not informed about the research procedures that accompanied treatment interventions. In fact, these four examples (involving catheterization and strain-gauge studies) were the very ones that Donald Fredrickson had cited, when he headed the Clinical Center's Heart Institute, to demonstrate that NIH patients were kept ignorant of protocols.

The incompetence of many of these subjects had enabled the researchers to assert all the more confidently their right to exercise discretion and to substitute their own judgment. Because the subjects could not understand the intricacies of a scientific protocol, the investigators felt justified in taking matters into their own hands. To Chester Southam, it was unnecessary to offer explanations to elderly and senile patients about injections of cancer cells because they would become frightened and because he knew, supposedly, that no danger existed. Some of this calculation may have reflected the laboratory version of the old clinical saw that a minor operation is an operation being performed on someone else. But Southam and other investigators were

convinced that their procedures, however daring or invasive, actually carried little risk. (Little risk, but some: When Southam was later asked why, if the procedure was so harmless, had he not injected the cancer cells into his own skin, he replied that there were too few skilled cancer researchers around.) So too, Eugene Braunwald may have reasoned that it was unnecessary to obtain the permission of Clinical Center patients to insert a strain gauge on cardiac vessels or to measure cardiac functioning with a catheter because he reckoned the risks to be minimal.¹⁵ And in this spirit, Saul Krugman reasoned that feeding live hepatitis viruses to Willowbrook residents was acceptable not only because the disease was already endemic there but because he considered the Willowbrook strain of the virus to be mild, posing no threat to the well-being of the children.¹⁶

After minimizing the question of risks, the researchers confidently asserted that the potential benefits were enormous. Southam conducted his experiments in the belief that the reactions of an already debilitated patient to foreign cancer cells would cast new light on the immunological system and bring him close to a cure for cancer. Was Southam an unethical researcher? Hardly, in his view. He aimed to become one of humanity's great benefactors. Behind Krugman's Willowbrook research was a conviction that he could do more good for more people if he could conquer hepatitis. Was Krugman taking advantage of the institutionalized retarded? Hardly. Whatever vaccines he produced would protect them against a disease to which they were particularly exposed. So too, Braunwald was undoubtedly convinced that his studies would be of enormous gain to all heart patients, which turned out to be correct. Was Braunwald ignoring the rights of the desperately sick at the Clinical Center? No, for the more he learned about cardiovascular functioning, the better those patients would be served.

A powerful exposé is often more able to identify a problem than to propose effective or imaginative solutions, and Beecher's contribution was no exception. He was too committed a researcher to so much as dally with the thought of abolishing human experimentation and was even reluctant to regulate it in ways that might hamper its operation. He was exceptionally ambivalent about the implications of his own findings and, at least initially, very reluctant to use them as basis for

new departures. First, Beecher doubted the ability of a formal code of ethics to shape researchers' behavior. He did not believe "that very many 'rules' can be laid down to govern experimentation in man. In most cases these are more likely to do harm than good. Rules are not going to curb the unscrupulous."¹⁷ Second, he was skeptical of the value of making the consent process itself more elaborate and trusting informed patients to look after their own best interest. After all, patients were too inclined to accede to physicians' requests, with or without well-intentioned explanations.

At the same time, however, Beecher, as much as any single figure, undercut the assumptions that were so critical to the hands-off policy at NIH and elsewhere: that the physician and the investigator were one and the same, and that the trust patients afforded to doctors should be extended to researchers. In one of his first major discussions of research ethics, an article in *JAMA* in 1959 on "Experimentation in Man," Beecher painstakingly differentiated between the two roles, subverting the idea that the ethical tradition in medicine was sufficient to produce ethical behavior in research. The two activities were "different in their procedures, in their aims, and in their immediate ends." The physician's exclusive concern was with the well-being of one particular patient; his ethical obligations were clear and uncomplicated (or at least relatively so): to do all in his power to advance the well-being of the patient. The investigator, on the other hand, was in a much more complicated position. His aim was to advance knowledge that would benefit society; his overriding allegiance was to his protocol, to a class of patients, if you will, not to the individual subjects in his protocol.

Beecher feared that a commitment to the general good as against the individual good might easily legitimate ethically dubious research, and he feared such a prospect especially because of the lessons of Nuremberg, which he was among the first to explicate. Perhaps he was conscious of the atrocities because of his earlier work with the army; in his papers are copies of then-classified German research reports, mostly dealing with the effects of exposure, which he may have evaluated, at the army's request, for their scientific value. Whatever the reason, he insisted: "Any classification of human experimentation as 'for the good of society' is to be viewed with distaste, even alarm. Undoubtedly all sound work has this as its ultimate aim, but such high-flown expres-

sions . . . have been used within recent memory as cover for outrageous acts. . . . There is no justification here for risking an injury to an individual for the possible benefit to other people. . . . Such a rule would open the door wide to perversions of practice, even such as were inflicted by Nazi doctors on concentration-camp prisoners. . . . The individual must not be subordinated to the community. The community exists for man."¹⁸

On a less profound level, Beecher also distinguished the researcher from the physician by outlook and ambition. Doctors might let monetary concerns guide their actions, making treatment decisions in order to increase their incomes, but such behavior was immediately recognized as patently unethical. Investigators, however, were caught up in a system of promotions and grant getting that so emphasized research results as to obfuscate research ethics. The physician who lined his pockets at his patients' expense was condemned, whereas the researcher who produced new findings by disregarding the rights of his subjects might well win scientific prizes. Researchers knew they had to publish in order not to perish by being denied academic advancement and government funding; everyone recognized that tenure came only to those who proved themselves superb investigators, whatever their ethics. This environment nullified a concept of identity of interest between researcher and subject.

Yet the power of this critique notwithstanding, Beecher wavered, reluctant to recommend new rules or methods of regulation. He did have a short list of dos and don'ts for investigators: no use of prisoners of war for research, extreme caution about conducting research on laboratory personnel or medical students (who might feel obliged to consent because of their positions), but an allowance to do research on prisoners and volunteers if they gave consent. Beecher was also prepared to implement some type of "group decision supported by a proper consultive body," although he offered no details on how it might be organized or administered. But his final word on the researchers who conducted the twenty-two protocols was a variation on the theme of "they knew not what they did." He noted, with more rhetorical flourish than evidence or accuracy, that their "thoughtlessness and carelessness, not a willful disregard of the patient's rights, account for most of the cases encountered." Armed with such a formulation, he

comfortably asserted that "calling attention . . . will help to correct abuses present." He maintained such an old-fashioned faith in the integrity of the individual researcher that, after weighing all the alternatives, he concluded: "The more reliable safeguard [is] provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator."¹⁹

In the end, Beecher's responses highlight the strengths and weaknesses of the insider's exposé. Without his courage, the movement to set new rules for human experimentation would have proceeded on a much slower track. Few others had the scientific knowledge and ethical sensibilities to call into question medical researchers' ethics. But at the same time, with such knowledge and sensibility came both forgiveness (investigators know not what they do) and paternalism (subjects can never understand what investigators do). Left to Beecher, the reaction to the scandals would have been an appeal to professional trust and responsibility, as though consciousness-raising could solve the problem.

New Rules for the Laboratory

EVEN the most sensational exposé will not necessarily spark fundamental alterations in public attitudes or policy. Media attention is fickle and the competition for front-page coverage or a few minutes on the evening news so intense that even egregious scandals may fade from attention. Further, countless ways exist for those in authority to explain problems away, from blaming a few bad apples to assuring everyone that the deficiencies have already been corrected. But not all exposés disappear without a trace. They may affect those so high in power as to generate critical changes (Watergate) or reveal conditions so substandard as to shock the conscience (a hellhole of an institution for the retarded), or describe conditions so frightening in their implications as to rivet attention (images of a silent spring). Human experimentation had elements in common with all of these, helping to ensure that its scandals would produce structural change.

A number of investigators certainly attempted to minimize the problem. Some insisted, as we have seen, that Henry Beecher's cases were aberrations; although no one dared to make the point so bluntly, other researchers undoubtedly believed it proper to trade off the rights of highly marginal groups for the sake of scientific progress, to keep the World War II model operational and out of mothballs. After all, strictly utilitarian principles could justify the experiments of a Saul Krugman; the retarded, it could be argued, did not have all that much to lose

when compared to the societal gains if the research produced a vaccine against hepatitis. And Beecher himself exemplified how difficult it was to break out of an older, hands-off model of maintaining a faith in the integrity of the investigator and minimizing the implications of a conflict of interest with the subject. Nevertheless, the scandals deeply affected public attitudes and brought an unprecedented degree of regulation and oversight to the laboratory.

The exposés had an especially critical impact on the leadership of the National Institutes of Health (NIH), by far the most important source of funds for clinical research, and the Food and Drug Administration (FDA), responsible for overseeing the testing and licensure of all new drugs. These agencies were exquisitely alert to congressional pressures: let public opinion be mobilized, and they might be hauled in to testify at hearings, criticized and embarrassed for failures to keep investigators in check, and left to suffer the consequences of budget cuts. Calculating in a most self-protective and painstaking manner the repercussions that would follow when public officials read articles about abuses in human experimentation and editorial writers questioned the wisdom of a continued trust in the individual researcher, they moved quickly to contain the crisis. Given the potential negative fallout, the price of inaction was unacceptably high. Thus, the fact that authority was centralized in bodies that were at once subordinate to Congress and superordinate to the research community assured that the scandals would alter practice. Indeed, this circumstance explains why the regulation of human experimentation came first and most extensively to the United States, rather than other industrialized countries.

To be sure, the leaders of the NIH and (to a lesser, but still important, degree) the FDA were integral to the medical research community. These were not outsiders or newcomers to clinical research, and they were not likely to adopt either far-reaching or consistently intrusive measures. Nevertheless, their need to act meant that this exposé would not capture headlines in today's newspaper and be forgotten tomorrow.

The NIH leaders initially concerned themselves with research ethics after the Kefauver hearings in 1962 disclosed that physicians were administering experimental drugs without informing patients. James

Shannon, then the head of the NIH, immediately requested Robert B. Livingston, the associate chief of the Division of Research Facilities and Resources, to investigate the "moral and ethical aspects of clinical investigation." Since the overwhelming sentiment in the Senate debate on the resolutions proposed by Kefauver and Javits was to leave research unfettered, the Livingston Report, delivered in November 1964, was under little external pressure to recommend a change in the laissez-faire policy. The authors of the report recognized that "there is no generally accepted professional code relating to the conduct of clinical research" and expressed "a mounting concern . . . over the possible repercussions of untoward events . . . [because] highly consequential risks are being taken by individuals and institutions as well as NIH." But they did not urge the adoption of stricter regulations. "There was strong resistance," recalled one of the participants, "on attempting to set forth any guidelines or restraints or policies in this area." The report's framers concluded that "whatever the NIH might do by way of designing a code or stipulating standards for acceptable clinical research would be likely to inhibit, delay, or distort the carrying out of clinical research," rendering any such efforts unacceptable.¹

The Livingston Report was not to be the last word, for even before Beecher's article, disturbing incidents had continued to surface. The case that received the greatest publicity and most disturbed the NIH was Chester Southam's cancer research on senile and demented patients, begun in 1963. The attention was so great that within two years the research was the object not only of extensive press coverage but of a lawsuit and a disciplinary hearing for Southam before the New York State Board of Regents. Almost all the publicity was hostile, and none of it was lost on the NIH. "It made all of us aware," one official confessed, "of the inadequacy of our guidelines and procedures and it clearly brought to the fore the basic issue that in the setting in which the patient is involved in an experimental effort, the judgment of the investigator is not sufficient as a basis for reaching a conclusion concerning the ethical and moral set of questions in that relationship."²

Just as the ripple effects of Southam's research were being felt, Beecher's well-publicized 1965 lecture and then his 1966 *NEJM* article revealed that Southam's insensitivity to the ethics of experimentation was not idiosyncratic. Again, the NIH had to consider the implications

of this publicity for its own functioning. At least one congressman asked NIH officials how they intended to respond to Beecher's charges, and the associate director for the extramural programs hastened to assure him that the findings "as might be expected have aroused considerable interest, alarm, and apprehension." Although "there are instances in the article which are either cited out of context, incomplete, or with certain mitigating circumstances omitted," still at NIH "constructive steps have already been taken to prevent such occurrences in research supported by the Public Health Service."³

However, a congressman's letter was only the most visible sign of NIH's vulnerability (or sensitivity) to political and legal pressure. Any Washington official who hoped to survive in office understood the need to react defensively—to have a policy prepared so that when criticism mounted, he or she would be able to say that yes, a problem had existed, but procedures were already in place to resolve it. The NIH director, James Shannon, readily conceded that one of his responsibilities, even if only a minor one, was "keeping the Government out of trouble." And his advisors concurred. It would be nothing less than suicidal to believe, as one of them put it, that "what a scientist does within his own institution is of no concern to the PHS." An ad hoc group appointed by Shannon to consider NIH policies reported back to him that if cases involving researchers' disregard of subjects' welfare came to court, the service "would look pretty bad by not having any system or any procedure whereby we could be even aware of whether there was a problem of this kind being created by the use of our funds."⁴

More than bureaucratic survival was at stake, though. The NIH response represented not just self-protection against potential legal and political repercussions but a reckoning with the substantive issues involved, an understanding of the causes behind the behavior of the individual researchers. By the mid-1960s it had become apparent to the NIH leadership that an incident like Chester Southam's protocol could be multiplied to twenty-two (to read Beecher) or to an even larger number by those familiar with the state of research at its own Clinical Center or other leading university and hospital laboratories. As a result of the exposés, the NIH leadership, as well as a number of individual researchers, also came to believe that a conflict of interest marked the interaction of investigator and subject: what was in the best interests

of the one was not in the best interests of the other. The bedrock principle of medical ethics—that the physician acted only to promote the well-being of the patient—did not hold in the laboratory. (Later we will trace the implications of the discovery that this principle no longer held in the examining room either.) The doctor-patient relationship could no longer serve as the model for the investigator-subject relationship.

This conclusion moved Shannon and others at the NIH to alter its policies. Clinical research, they now recognized, "departs from the conventional patient-physician relationship, where the patient's good has been substituted for by the need to develop new knowledge, that 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 a wholly objective assessment of the moral nature or the ethical nature of the act which he proposes to perform."⁵ The researchers' aims, in other words, will distort their ethical judgments. The intrinsic nature of their quest renders them morally suspect. This postulate accepted, in February 1966 and then in revised form in July 1966, the NIH promulgated, through its parent body, the U.S. Public Health Service (PHS), guidelines covering all federally funded research involving human experimentation.

The regulators moved very carefully, aware that they were in unexplored and dangerous territory. "This policy," explained Dr. William Stewart, the surgeon general, "seeks to avoid the danger of direct Federal intervention, case by case, on the one hand, and the dangers inherent in decisions by an individual scientist on the other." The 1 July 1966 order decentralized the regulatory apparatus, assigning "responsibility to the institution receiving the grant for obtaining and keeping documentary evidence of informed patient consent." It then mandated "review of the judgment of the investigator by a committee of institutional associates not directly associated with the project"; and finally, it defined (albeit quite broadly) the standards that were to guide the committee: "This review must address itself to the rights and welfare of the individual, the methods used to obtain informed consent, and the risks and potential benefits of the investigation." As Stewart explained: "What we wanted was an assurance from [the grant-receiving institutions] that they had a mechanism set up that reviewed the potential benefit and risk of the investigation to be undertaken, and that

reviewed the method that was used to obtain informed consent. And we thought that this should be done by somebody besides the investigator himself—a group. We thought this group might consist of a variety of people, and left it up to the institutions to decide.” Stewart proudly stated: “We have resisted the temptation toward rigidity; for example, we have not prescribed the composition of the review groups nor tried to develop detailed procedures applicable to all situations. . . . Certainly this is not a perfect instrument. But . . . this action has introduced an important element of public policy review in the biomedical research process.”⁶

Thus, for the first time and in direct response to the abuses of discretion, decisions that had traditionally been left to the individual conscience of physicians were brought under collective surveillance. Federal regulations, a compulsory system of peer review, assurances by universities and hospitals that they were monitoring the research, specific criteria that investigators had to satisfy, and a list of proscribed activities replaced the reliance on the researchers’ goodwill and ethical sensibilities.

The new rules were neither as intrusive as some investigators feared nor as protective as some advocates preferred. At their core was the superintendence of the peer-review committee, known as the institutional review board (IRB), through which fellow researchers approved the investigator’s procedures. With the creation of the IRB, clinical investigators could no longer decide unilaterally on the ethics of their research, but had to answer formally to colleagues operating under federal guidelines. Thus, the events in and around 1966 accomplished what the Nuremberg tribunal had not: to move medical experimentation into the public domain and to make apparent the consequences of leaving decisions about clinical research exclusively to the individual investigator.

For all the novelty of the response, policy changes designed and implemented by insiders had distinct limitations. For one, the NIH leadership did not at first insist on including in the collective decision-making process those who were outsiders to the world of research. The agency’s 1966 policies still allowed scientists to review scientists to determine whether human subjects were adequately informed and protected. Given the NIH views on conflict of interest, the regulations did require that members of the review committee should have “no vested

interest in the specific project involved.” But they were vague about other criteria, stipulating that members should have “not only the scientific competence to comprehend the scientific content . . . but also other competencies pertinent to the judgments that need to be made.” Accordingly, through the 1960s, most institutions restricted membership on the IRB to fellow investigators, and only a few included outsiders (most of whom were lawyers and clergymen) on the committee.

Second, and even more important, the NIH response focused more on the review process than the consent process. The agency did recognize the importance of the principle of consent, changing the title of its Clinical Center manual from *Group Consideration of Clinical Research Procedures* (1953) to *Group Consideration and Informed Consent in Clinical Research* (1967). And it did set forth guidelines for the researcher that cited the need to obtain “informed consent.” But the NIH retained an investigator’s skepticism about the ultimate value of the procedure, a position that was widely shared in the research community. As a Harvard colleague of Beecher’s put it in responding to an early draft of his article: “Should informed consent be required? No! For the simple reason that it is not possible. Should any consent be required? Yes! Any teaching and research hospital must clearly identify itself as such . . . to the patient upon admission. . . . The fact that the patient is requesting admission to this hospital represents tacit consent. How do we interpret tacit consent? Not as a license but as a *trust*. This adds, not subtracts, responsibility.”⁷

In keeping with this orientation, the internal memorandum enclosed with the new NIH Clinical Center manual read: “While there is general agreement that informed consent must be obtained, there is also the reservation that it is not possible to convey all the information to the subject or patient upon which he can make an intelligent decision. There is a strong feeling that the protection of the subject is best achieved by group consideration and peer judgment.” Moreover, the NIH was not yet prepared or able to be very specific about what phrases like “informed consent” meant in practice. “Many of these key terms,” conceded Eugene Confrey, the NIH director of research grants, “lack rigorous definition or are incompletely defined for purposes of general application.” But the root of the difficulty was that NIH officials had trouble grasping the full implications of what it meant to

obtain consent. The NIH publication explaining to "normal volunteers" at the Clinical Center that participation in the research was truly voluntary, declared: "You will be asked to sign a statement in which you indicate that you understand the project and agree to participate in it. If you find your assigned project to be intolerable, you may withdraw from it." Suggesting that the only grounds for withdrawal was the intolerability of the project was hardly the way to educate subjects to their freedom of choice.⁸

In effect, the NIH leadership was unwilling to abandon altogether the notion that doctors should protect patients and to substitute instead a thoroughgoing commitment to the idea of subjects protecting themselves. The 1966 guidelines were innovative, but only to a point. The NIH heads still looked to the professional to ensure the well-being of the layperson, and forced to reckon with the inadequacy of trusting to one professional, they opted to empower a group of professionals. The goal was to insure that harm was not done to the subjects, not to see that the subjects were given every opportunity and incentive to express their own wishes.⁹

FDA officials were also forced to grapple with the problems raised by human experimentation in clinical research. With a self-definition that included a commitment not only to sound scientific research (like the NIH) but to consumer protection as well, the FDA leadership did attempt to expand the prerogatives of the consumer—in this context, the human subject. Rather than emulate the NIH precedent and invigorate peer review, they looked to give new meaning and import to the process of consent.

In the immediate aftermath of the 1962 Kefauver hearings and the passage of the watered-down version of the Javits amendment, the FDA required investigators to obtain the consent of patients taking experimental drugs, but for the next several years, the precise nature of the obligation was unclear. By statute, investigators were not required to obtain consent when they found it "not feasible" or "not in the best interest of the subject"; and despite a number of efforts to have the FDA clarify the meaning of these terms (including an effort by Beecher), the agency steadfastly refused. Francis Kelsey, celebrated for holding back approval on thalidomide and now chief of the FDA Investigation Drug Branch, was prepared to say publicly that these clauses

were meant to be applied narrowly for truly exceptional circumstances. But when Beecher, in 1965, asked the FDA's commissioner to confirm this position, he would only say: "The basic rule is that patient consent must be obtained except where a conscientious professional judgment is made that this is not feasible or is contrary to the best interest of the patient. It is my present opinion that it is not possible to go beyond this generalization at this time."¹⁰

In 1966, however, in the wake of the reactions set off by Beecher's article and the publicity given particularly to the cancer research of Chester Southam, the FDA shifted positions. On 30 August 1966, FDA officials issued a "Statement on Policy Concerning Consent for the Use of Investigational New Drugs on Humans," not only defining all the terms in the 1962 law but setting down what William Curran, one of the most astute students of NIH and FDA policies, described as "comprehensive rules regarding patient consent in clinical drug trials."

In the first instance, the FDA moved to close, albeit not eliminate, the loopholes. Distinguishing between therapeutic and nontherapeutic research (in accord with various international codes like the 1964 Helsinki Declaration and the arguments of critics like Beecher), it now prohibited all nontherapeutic research except where the subjects gave consent. When the research involved "patients under treatment" and had therapeutic potential, consent was to be obtained, except in what the FDA policymakers now frankly labeled the "exceptional cases," where consent was not feasible or in the patient's best interest. The FDA staff tried to define these terms more exactly. "Not feasible" meant that the doctor could not communicate with the patient (the example was a comatose patient) and "not in the best interest" meant that consent would "seriously affect the patient's disease status" (the example was the physician not wanting to divulge a diagnosis of cancer). In addition, the FDA, unlike the NIH, spelled out the meaning of *consent*. To give consent, the person had to have the ability to exercise choice and had to receive a "fair explanation" of the procedure, including an understanding of the experiment's purpose and duration, "all inconveniences and hazards reasonably to be expected," the nature of a controlled trial (and the possibility of going on a placebo), and any existing alternative forms of therapy available.¹¹

The FDA regulations unquestionably represent a new stage in the balance of authority between researcher and subject. The blanket insistence on consent for all nontherapeutic research would have not only prohibited many of the World War II experiments but also eliminated most of the cases on Beecher's roll. The FDA's definitions of consent went well beyond the vague NIH stipulations, imparting real significance to the process. Nevertheless, ambiguities and irresolution remained. The FDA still confused research and treatment, and its clauses governing therapeutic investigations left a good deal of discretion to the doctor-researcher. Despite the insistence that consent was to be waived only in exceptional cases, the FDA allowed investigators to determine which cases these were. It was still up to them to determine the course of action for the incompetent patient or to decide when to withhold a diagnosis from the competent patient.

All these qualifications notwithstanding, the rules for human experimentation had changed, and the movement would continue and accelerate, with authority shifting from inside to outside the profession, from physicians to a very different group of actors. The NIH directors glimpsed this future. As they revised the agency's regulations, they predicted that the principles governing human experimentation (and, we may add, eventually all of medicine) were about to take new directions, the "consequence of increased attention to the problem by lawyers, physicians, psychologists, sociologists, and philosophers."¹²

Human experimentation did attract the critical attention of these professionals, almost all of whom rejected outright the utilitarian calculus adopted by the researchers. But the reasons for this rejection are not self-evident; indeed, it is easier to account for the investigators' pursuit of truth and fame than to understand why the others took so different an approach, why they did not accept the investigators' explanations and welcome the sacrifices made by a marginal, and by definition unprotesting, minority. But this was not the position adopted. Outsiders crossed over into medicine to correct what they perceived as wrongs, unwilling to accept the potential social benefit and trade off the individual interest. In short, they found harm where investigators perceived the opportunity for progress. Understanding the many reasons underlying this essential difference in outlook takes us through

the rest of the book, for attitudes toward human experimentation were intertwined with attitudes toward physicians and hospitals—and then became inseparable from attitudes toward new medical procedures and technologies. Nevertheless, several points warrant immediate exploration.

First, the recognition by Beecher, as well as Shannon and others at NIH, that the traditional ethics of medicine no longer held in the laboratory and that a fundamental conflict of interest characterized the relationship between the researcher and the subject had an extraordinary impact on those outside of medicine. In fact, an appreciation of these very postulates brought philosophers, lawyers, and social scientists to a concern with medicine. Because the traditional precepts of medical ethics seemed inadequate to the problems posed by human experimentation, and because the hallowed maxims of "do no harm" and "act only in the interest of the patient," borne of a therapeutic context, did not appear to protect the subject in an experimental context, it became necessary to look to a different tradition and source for guiding principles. And this is precisely what the nonphysicians began to do, at first hesitantly and with apparent humility, later, in a more aggressive and confrontational style.

Two examples give the full flavor of the change. The topic of human experimentation initially brought to medicine Princeton University's professor Paul Ramsey, a philosopher who would exert a powerful influence over the development of the field of bioethics. In his own terms, Ramsey applied Christian ethics to contemporary issues, as evidenced in his previous books, *Christian Ethics and the Sit-In* and *War and the Christian Conscience: How Shall Modern War Be Conducted Justly?* Invited to lecture at the Yale Divinity School on medical ethics in 1968–69, he prepared for the assignment by spending a year at the Georgetown Medical School. As he later explained in *The Patient as Person*, the book that emerged from the lectures, the assignment was intimidating: "When first I had the temerity to undertake some study of ethical issues in medical practice, my resolve was to venture no comment at all—relevant or irrelevant—upon these matters until I informed myself concerning how physicians and medical investigators themselves discuss and analyze the decisions they face." He found their discussions "remarkable," convinced that no other profession "comes

close to medicine in its concern to inculcate, transmit, and keep in constant repair its standards governing the conduct of its members."¹³

Nevertheless, Ramsey did not keep silent for very long, for he concluded that medicine could not be left to its own devices. Ethical problems in medicine, he declared, "are by no means technical problems on which only the expert (in this case the physician) can have an opinion," and his first case in point was human experimentation. Having read Beecher closely and having studied some of the protocols (particularly Krugman's hepatitis research), he was persuaded that the principle of the sanctity and dignity of human life was now under challenge. Raise this principle at a gathering of physicians, Ramsey observed, and one would be greeted by a counterprinciple: "It is immoral not to do research (or this experiment must be done despite its necessary deception of human beings)." His fear was that "the next step may be for someone to say that medical advancement is hampered because our 'society' makes an absolute of the inviolability of the individual. This raises the specter of a medical and scientific community freed from the shackles of that cultural norm, and proceeding on a basis of an ethos all its own."¹⁴

The force that drove medicine down this path was the investigators' thirst for more information, a thirst so overwhelming that it could violate the sanctity of the person. "I do not believe," insisted Ramsey, "that either the codes of medical ethics or the physicians who have undertaken to comment on them . . . will suffice to withstand the omnivorous appetite of scientific research . . . that has momentum and a life of its own."¹⁵ In effect, Ramsey perceived, as others were starting to as well, an unavoidable conflict of interest. The goals of the researcher did not coincide with the well-being of the subject; human experimentation pitted the interests of society against the interests of the individual. In essence, the utilitarian calculus put every human (subject) at risk.

How was this threat to be countered? Ramsey had two general strategies. The first was to bring medicine directly into the public arena. We can no longer "go on assuming that what can be done has to be done or should be, without uncovering the ethical principles we mean to abide by. These questions are now completely in the public forum, no longer the province of scientific experts alone." Second, and more specifically, Ramsey embraced the idea of consent. It was to human ex-

perimentation what a system of checks and balances was to executive authority, that is, the necessary limitation on the exercise of power: "Man's capacity to become joint adventurers in a common cause makes the consensual relationship possible; man's propensity to overreach his joint adventurer even in a good cause makes consent necessary." Thus, Ramsey concluded: "The medical profession should no longer believe that the personal integrity of physicians alone is enough. . . . No man is good enough to experiment upon another without his consent."¹⁶ In short, human subjects, not investigators, would have to define and protect their own interests.

These same concerns sparked the interest of other outsiders to medicine. In November 1967 and September 1968, *Daedalus* ran conferences devoted to the "Ethical Aspects of Experimentation with Human Subjects," the first time this broadly interdisciplinary publication had explored a medical matter in such depth.¹⁷ Of the fifteen contributors to the issue that emerged from these meetings, six came from the health sciences (including Henry Beecher); the others represented a variety of specialties: five from law (including Guido Calabresi and Paul Freund) and one each from anthropology (Margaret Mead), sociology (Talcott Parsons), philosophy (Hans Jonas), and law and psychiatry (Jay Katz). Of course, some of these authors had already demonstrated a keen interest in bringing their disciplinary insights to medicine (most notably Talcott Parsons and Jay Katz). But most were just entering a field in which they would do outstanding work (Paul Freund, Guido Calabresi, and Hans Jonas, for example).

It was disconcerting to be among the first to cross over from one's home discipline to medicine; and it is doubtful, now that the route has been so well laid out, that anyone today would be as circumspect as Hans Jonas, a professor of philosophy at the New School for Social Research, was in describing his initiation. Reporting "a state of great humility," he declared: "When I was first asked to comment 'philosophically' on the subject of human experimentation, I had all the hesitation natural to a layman in the face of matters on which experts of the highest competence have had their say."¹⁸ But he, like Ramsey, was convinced that the issues were intriguing and disturbing enough to require sustained philosophical analysis and, ultimately, new first principles.

Jonas's starting point was the inherent conflict between the noble

purpose of gaining knowledge and the moral obligation to the subjects themselves. He, too, contrasted the social good with the personal good—or in the language of the laboratory, the need for an adequate sample size and the degradation implicit in making a person “a passive thing merely to be acted on,” against the welfare of the individual. Rejecting the notion that society could command the subject’s “sacrifice” under the terms of the social contract, and not completely satisfied with any method for resolving the conflict (“We have to live with the ambiguity, the treacherous impurity of everything human”), Jonas joined the ranks of those coming to rely primarily on the process of consent. Indeed, for him consent served not only as the justification of an individual’s participation in an experiment but as a method for ranking those who should be asked to become research subjects. Those most capable of giving consent—the best educated with the greatest degree of choice—should be the first asked; hence, on Jonas’s list, research scientists were at the top and prisoners at the bottom. He conceded that this principle of “descending order” might hamper experimentation and slow progress, but the danger to society from a disease was less than the danger of “the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.”¹⁹ Thus, Jonas and Ramsey arrived at the same conclusion: the only escape, however incomplete, from the dilemmas in experimentation was through a revitalization of the principle of consent. Human subjects had to become their own protectors.

The approach drawn from philosophers’ first principles fit neatly with the approach emerging from reformers’ social principles. In this coincidence of vision one finds some of the reasons why, beginning in the 1960s, the public identified not with researchers and the triumphs they might bring forth from their laboratories (as had been true during the 1940s and 1950s), but with the subjects of the experiments and the harms they might suffer in the laboratory. The change in perspective mirrored a grander reorientation in social thought, one that now looked more to securing personal rights than communal goods, to enhancing the prerogatives of the individual, not the collective. The political culture of the 1960s fostered an extraordinary identification

with the underdog and the minority, as evidenced by the fact that the tactics of the civil rights movement became the model for others to emulate. Just as these activists used a language of rights to counter discrimination, so too did advocates for women, children, gays, and students. It may not have been apparent or even correct to think that all of these groups actually constituted minorities (were women really a minority?) or in any conventional meaning of the term possessed rights (in what sense does a child have a right against a parent?). But those were quibbles that could not be allowed to interfere with the goal of reform. This same mind-set framed the experience of subjects in clinical research. As Beecher’s protocols amply demonstrated, the subjects were drawn disproportionately from among the poor, the physically or mentally handicapped, the elderly, and the incarcerated. The result was an identification with the retarded and the senile in their vulnerability to exploitation, not with the investigators and the prospect for a vaccine against hepatitis or a cure for cancer.

This orientation fostered a distrust of constituted authorities and medical researchers became one group among many to feel the impact of the new skepticism toward the exercise of paternalism and the loss of trust in discretionary authority. “The list of those who have suffered this loss,” I had occasion to write in the 1970s, “is as lengthy as it is revealing: college presidents and deans, high school principals and teachers, husbands and parents, psychiatrists, doctors, research scientists, and obviously, prison wardens, social workers, hospital superintendents, and mental hospital superintendents.”²⁰ The momentum of change did not, however, merely consume one institution after another. *Research scientists* appeared on the list because of specific, powerful reasons for curbing the authority of the investigator—reasons that Beecher, Shannon, Ramsey, and Jonas, each in his own way, had supplied. The original purpose behind the grant of discretion, which had emerged in the Progressive Era, was that it would allow professionals, and others like parents and husbands, the opportunity to fulfill benevolent designs, to substitute their greater knowledge for that of their patients, students, children, or spouses. But now it seemed that discretion served self-interest—that deans acted in the best interests of the university, not its students; that husbands furthered their own needs, not those of their wives; that wardens looked to the needs of

the prison, not the inmates. In this same fashion, investigators pursued their own goals—career advancement, discovery, prizes, and fame—while disregarding the risks to their subjects. It was a zero-sum game in or out of the laboratory. If the investigator was to win, the subject might well have to lose.

Moreover, the scandals and the way they were interpreted in terms of conflict of interest made it vital not only to import a language of rights into medicine but to bring formality and clearcut guidelines to procedures that had been casual and open-ended. In the realm of social welfare, it seemed best to define entitlements precisely rather than have the welfare mother trust to the discretion of the social worker; in treating juvenile delinquents, it seemed best to expand procedural protections instead of relying on the benevolence of a juvenile court judge or warden. And in this same spirit, in human experimentation it seemed best to establish an exacting review mechanism and a formal consent process rather than rely for protection on the conscience of the individual researcher. In sum, all these movements presumed a warfare between "them" and "us," in which self-serving motives were cloaked in the language of benevolence, and majorities took every occasion to exploit minorities. In such a combative world, one had to depend on rules, not sentiment, to secure fairness.

One last consideration helps tie all these movements together: the importance of events that converged in 1966 and signaled the heightened level of social conflict. This year witnessed the transformation of the civil rights movement from one that could dream, in Martin Luther King's eloquent words, about "a beautiful symphony of brotherhood" in which all of God's children joined hands to celebrate freedom, to one that designated "black power" as the only way to wrest control from an oppressive white ruling class. This year also witnessed the first defeat that the civil rights movement suffered in Congress, a defeat on a socially far-reaching question, relevant nationwide: open housing. And 1966 was the year that Beecher's *NEJM* article appeared and set off its many repercussions. Social change is too gradual a process to fit neatly onto a calendar (and social historians are prone to talk about generations and eras, not days and weeks), but 1966 has a special relevance to this story and makes connections among the various parts all the more secure.

Bedside Ethics

HOWEVER appropriate it appeared to restructure the relationship between medical researchers and human subjects, to reduce the discretionary authority of the investigator by expanding the formal authority of peers (through institutional review board oversight) and the role of the subjects themselves (through a new emphasis on informed consent), it was by no means obvious that such changes were relevant to the doctor-patient relationship. Although exposés had revealed the conflict of interest between investigators and subjects and undermined the sense of trust between them, the therapeutic encounter, at least on the face of it, entailed none of these problems. The treating physician seemingly had no concern apart from the care and cure of the patient; even as NIH officials and other critics of research practices came to recognize that the bedrock principle of medical ethics—the doctor as advocate for his or her patients—did not fit with human experimentation, they did not doubt that it held in medicine itself. The physician was different from the researcher, Hans Jonas insisted: "He is not the agent of society, nor of the interests of medical science . . . or future sufferers from the same disease."¹ The doctor's only agenda was the patient's well-being.

In fact, physicians shared a powerful tradition of ethical discourse that went back to Hippocrates and continued through modern times. It was at once high-minded, generous, and even heroic, yet remarkably

23. On the COs' experience, see Records of the OSRD, CMR, box 18. Contracts 206 and 483 provide typical examples, as does the correspondence of E. F. Adolph (University of Rochester) with E. C. Andrus, 14 December 1943 and 6 April 1944. See also Administrative Document 18, Camp Operations Division, 1 October 1943. The seawater experiments are reported in Contract 180, PI Allan Butler, 14 September 1942. Records of the OSRD, CMR, "Human Experiments," box 36.
24. Records of the OSRD, CMR, General Correspondence, "Human Experiments—Venereal Disease" (hereafter cited as Records of the OSRD, CMR, "Human Experiments"), box 39, Moore to Richards, 1 February 1943. Parran to Richards, 9 February 1943.
25. J. E. Moore to A. N. Richards, 6 October 1942. Richards to Moore, 9 October 1942.
26. Richards to Moore, *Ibid.*, 31 October 1942, box 39.
27. R. E. Dyer to Richards, 18 January 1943.
28. Records of the OSRD, CMR, General Correspondence, "Statement of Explanation of the Experiment and Its Risks to Tentative Volunteers," Minutes of a Conference on Human Experimentation in Gonorrhoea, filed with Subcommittee of Venereal Disease of the Committee of Medicine, box 39, 29 December 1942. The document may have exaggerated the efficacy of sulfanilamide treatment; there was much dispute about the actual cure rate, and recurrence was noted to be a problem, as was the existence of resistant strains. Indeed, this uncertainty was one of the reasons for the CMR research.
29. Records of the OSRD, CMR, "Human Experiments," box 39, Moore to Richards, 1 February 1943.
30. *Ibid.*, Frank Jewett and Ross Harrison to Vannevar Bush, 5 March 1943.
31. *Ibid.*, Thomas Parran to A. N. Richards, 9 February 1943.
32. James Bennet to J. E. Moore, 26 February 1943; Contractor Records, M3169, Report L7, 7 September 1945–50, pp. 45–50.

Chapter 3

1. For an overview of this history, see Donald C. Swain, "The Rise of a Research Empire: NIH, 1930 to 1950," *Science* 138 (1962): 1233–37; V. A. Harden, *Inventing the NIH: Federal Biomedical Research Policy, 1887–1937* (Baltimore, Md.: 1986), esp. pp. 179–91; Stephen P. Strickland, *Politics, Science, and Dread Disease* (Cambridge: 1972).
2. For a detailed analysis of the transfer of authority from the CMR to the NIH, see Daniel M. Fox, "The Politics of the NIH Extramural Program, 1937–1950," *Journal of the History of Medicine and Allied Sciences* 42 (1987): 447–66. As he makes clear, the transfer was easiest at the ideological level and far more complicated at the contract-grant level.

3. George Rosen, "Patterns of Health Research in the United States, 1900–1960," *Bulletin of the History of Medicine* 39 (1965): 220.
4. Vannevar Bush, "Science, the Endless Frontier: Report to the President on a Program for Scientific Research," (1945): esp. pp. 46–47, 53. In addition to Fox, "The Politics of the NIH," see also *New York Times*, 21 July 1945, 13 August 1945.
5. *New York Times*, 4 July 1945, p. 13.
6. "The National Institutes of Health: A Concerted Effort to Investigate and Study the Many Unconquered Diseases which Afflict Mankind," distributed by the Chemical Foundation, New York (n.d.), pp. 18–19, quoting from the *Congressional Record*.
7. *New York Times*, 6 February 1945, p. 18.
8. *Ibid.*, 12 September 1944, p. 12.
9. *Ibid.*, 21 November 1944, p. 24; see also 29 October 1945, sec. 4, 9.
10. J. E. Rall, epilogue, in *NIH: An Account of Research in Its Laboratories and Clinics*, ed. Dewitt Stetten, Jr., and W. T. Carrigan (New York: 1984), p. 527.
11. "Handbook for Patients at the Clinical Center," Public Health Service (PHS) Publication 315 (1953), esp. p. 2; "Clinical Center: National Institutes of Health," PHS Publication 316 (1956), esp. p. 13; "The Patient's Part in Research at the Clinical Center," PHS Publication (n.d.), pp. 2–3.
12. Minutes, Ad Hoc Committee on Clinical Research Procedures, 28 May 1965, NIH Files, Bethesda, MD., p. 1 (hereafter cited as Minutes, NIH Ad Hoc Committee). "In only a small percentage of instances do patients sign a specific consent."
13. Minutes, NIH Ad Hoc Committee, 19 March 1965, pp. 1–5. The committee was brought together to revise the 1950 publication entitled "Group Consideration of Clinical Research Procedures Deviating from Acceptable Medical Practice or Involving Unusual Hazards." Under the chairmanship of Nathaniel Berlin, the committee members reviewed past procedures in order to make recommendations, which were approved in 1966.
14. Minutes, NIH Ad Hoc Committee, 16 February 1965, p.2.
15. *Ibid.*, 28 May 1965, pp.1–3.
16. *Ibid.*, 22 January 1965, p. 2.
17. *Ibid.*, 19 March 1965, p. 4.
18. *Ibid.*, p.3; 23 April 1965, p.4
19. *Ibid.*, 2 June 1965, pp. 1–2.
20. *Ibid.*, 2 June 1965, pp. 1–3.
21. Mark S. Frankel, *The Public Health Guidelines Governing Research Involving Human Subjects*, George Washington University Program of Policy Studies in Science and Technology Monograph no. 10 (Washington, D.C.: 1972), pp. 6–12.
22. L. G. Welt, "Reflections on the Problems of Human Experimentation," *Connecticut Medicine* 25 (1961): 75–78.

23. Law-Medicine Research Institute of Boston University, Report to the U.S. Public Health Service; Frankel, *Guidelines Governing Research*, p.18
24. Welt, "Human Experimentation," pp. 78; Law-Medicine Institute, "Report." See also chapter 5, note 10.
25. The most useful and accessible compendium of relevant articles and codes is Irving Ladimer and Roger Newman, *Clinical Investigation in Medicine: Legal, Ethical, and Moral Aspects* (Boston: Law-Medicine Institute of Boston University, 1963). Ladimer and Newman were both on the staff of the Boston University Law-Medicine Institute. There was sufficient commentary on the history, ethics, and practice of human experimentation to enable the editors to assemble a 500-page book and a bibliography of 500 references. But several points must be made, quite aside from the tone of the articles and the limits of public action. First, the institute was altogether accurate in describing itself as "a program unique in the United States," and the importance of its own work should not be exaggerated. Second, the great majority of articles reprinted were from physicians—lawyers were second, Ph.D.s in other disciplines a distant third (the most notable were Renee Fox and Margaret Mead). Medical ethics and the ethics of human experimentation were still the province of physicians (see chapter 6), with lawyers making forays into this particular area.
26. *U.S. v. Karl Brandt*, Nuremberg Tribunal, Trials of War Criminals, vol. 2, pp. 71-73.
27. *New York Times*, 4 November 1945, p. 29.
28. Francis D. Moore as quoted in *Clinical Investigation in Medicine*, ed. Ladimer and Newman, p. 433.
29. On the realities of the matter, see the outstanding study by Robert N. Proctor, *Racial Hygiene: Medicine under the Nazis* (Cambridge: 1988). See also Robert Jay Lifton, *The Nazi Doctors* (New York: 1986). Note how recent these two studies are, reflective of how late the turn of attention to these issues has been.
30. See, for example, Cortez Enlow, "The German Medical War Crimes: Their Nature and Significance," *JAMA* 139 (1947): 801-5.
31. "Drug Industry Act of 1962," *Congressional Record*, 23 August 1962, p. 17391.
32. *Ibid.*, pp. 17395, 17397.
33. *Ibid.*, pp. 17398-99, 17401, 17404.
34. *Ibid.*, p. 17400.
35. See National Society for Medical Research, *Report on the National Conference on the Legal Environment of Medical Science*, Chicago, 27-28 May 1959, pp. 5-90; Welt, "Human Experimentation," pp. 75-78; Stuart Sessions, "Guiding Principles in Medical Research Involving Humans, National Institutes of Health," *Hospitals* 32 (1958): 44-64. Even to read A. C. Ivy, who was so intimately involved with the prosecution at Nuremberg, is to feel this tone;

- see, for example, "The History and Ethics of the Use of Human Subjects in Medical Experiments," *Science* 108 (1948): 1-5.
36. National Society for Medical Research, *Report on the Conference*, pp. 81-89. Otto Guttentag, a physician writing in *Science*, did describe the ultimate dilemma posed by human experimentation as "tragic in the classical sense," and he suggested a division of authority between the "physician-friend" and the "physician-experimenter." But his recommendation captured little attention in the literature and had no influence on practice. See Guttentag's commentary on Michael Shimkin, "The Problem of Experimentation on Human Beings: The Physician's Point of View," *Science* 117 (1953): 205-10.
 37. Ladimer and Newman, in their *Clinical Investigation in Medicine*, list only four American codes: those of the American Medical Association (AMA), the NIH Clinical Center, the American Psychological Association, and the Catholic Hospital Association.
 38. "Requirements for Experiments on Human Beings," Report of the Judicial Council, adopted by the House of Delegates of the AMA, December 1946, *JAMA* 132 (1946): 1090.
 39. AMA, *Digest of Official Actions* (Adopted December 1952) (Chicago: Author, 1959), pp. 617-18.

Chapter 4

1. In the absence of any biography or scholarly articles about Beecher, one must turn to obituaries and the like. See, for example, the *New England Journal of Medicine* 295 (1976): 730.
2. Henry K. Beecher and Donald P. Todd, "A Study of the Deaths . . .," *Annals of Surgery* 140 (1954): 2, 5, 17.
3. For Beecher's wartime experience, see his letters to Edward Mallinkrot, 22 December 1943 and 19 June 1945, Henry Beecher manuscripts, Francis A. Countway Library of Medicine, Harvard University (hereafter cited as Beecher MSS). See also his notes to a lecture delivered in Sanders Theater, 16 October 1946, "The Emergence of Anesthesia's Second Power." In his papers there is also an undated memorandum describing the research he wished to carry out: "We have been asked by the Army to study the compounds that have . . . in common: they give access to the subconscious. The Army has a further interest as well: It can be indicated in the question: Can one individual obtain from another, with the aid of these drugs, willfully suppressed information? If we undertake the study this latter question will not be mentioned in the contract application. We request that it not be referred to outside this room." Beecher's rationalization for carrying out the study fit perfectly with the researchers' orientation discussed in chapter 2: "In time of war, at least, the importance of the other [army] purpose hardly appears

- debatable." Henry K. Beecher, *Measurement of Subjective Responses* (New York: 1959), esp. pp. viii, 65-72.
4. The link for Beecher between placebo trials and the ethics of experimentation is most clearly made in his editorial, "Ethics and Experimental Therapy," *Journal of the American Medical Association* 186 (1963): 858-59 (hereafter cited as *JAMA*).
 5. *New York Times*, 24 March 1965; *Wall Street Journal*, 10 June 1965.
 6. Beecher to George Burch, 27 June 1966, Beecher MSS.
 7. Beecher to John Talbott, 20 August 1965, 30 August 1965, and Talbott to Beecher, 25 August 1965, Beecher MSS.
 8. Talbott to Beecher, 25 October 1965, Beecher MSS.
 9. Joseph Garland to Beecher, 30 March 1966, 7 April 1966, and Beecher to Garland, 1 April 1966, Beecher MSS.
 10. Beecher to John Knowles, 10 June 1966, Beecher MSS.
 11. Henry K. Beecher, "Ethics and Clinical Research," *NEJM* 274 (1966): 1354-60.
 12. Beecher to Joseph Sadusk, 7 June 1965, Beecher MSS. Sadusk was the medical director of the FDA. See also Beecher to Geoffrey Edsall, 3 August 1966, Beecher MSS.
 13. An excellent compilation of materials in the Southam case can be found in *Experimentation with Human Beings*, ed. Jay Katz (New York: 1972), pp. 9-65.
 14. Beecher, "Ethics of Clinical Research," pp. 1354-55.
 15. In a personal interview (April 19, 1988), Dr. Braunwald said that he did seek the permission of the patients but did not then or later supply evidence for the assertion. Note the comments of Donald Fredrickson in chapter 3 on these experiments as well. When I asked Dr. Braunwald why he never entered a protest against Beecher's statements about him, he declared (in a point that strengthens my general arguments about the state of research ethics in the period) that no one ever queried him about it. Despite the absence of footnotes in the Beecher article, there could be little doubt about who was doing such research.
 16. David J. Rothman and Sheila M. Rothman, *The Willowbrook Wars* (New York: 1984), chap. 11.
 17. Henry K. Beecher, "Experimentation in Man," *JAMA* 169 (1959): 461-78.
 18. *Ibid.*
 19. Beecher, "Ethics of Clinical Research," p. 1360. This was also the position of his contemporary, Louis Welt; see "Reflections on the Problem of Human Experimentation," *Connecticut Magazine* 25 (1961): 78.

Chapter 5

1. Mark S. Frankel, *The Public Health Service Guidelines Governing Research Involving Human Subjects*, George Washington University Program of Policy Studies

- in Science and Technology Monograph no. 10 (Washington, D.C.: 1972), pp. 20-21.
2. *Ibid.*, pp. 23-24.
3. John Sherman to Roman Pucinski, 1 July 1966, National Institutes of Health Files, Bethesda, Md.
4. Frankel, *Guidelines Governing Research*, pp. 23, 31.
5. *Ibid.*, p. 30.
6. Committee on Government Operations report to the Senate Subcommittee on Government Research, *Hearings on the National Commission on Health Science and Society*, 90th Cong., 2d sess., 1968, pp. 211, 212 (hereafter cited as *Hearings on Health*).
7. Henrik Bendixen to Henry Beecher, March 1966, Henry Beecher Manuscripts, Francis A. Countway Library of Medicine, Harvard University (hereafter cited as Beecher MSS).
8. *Handbook on the Normal Volunteer Patient Program of the Clinical Center*, March 1967, NIH Files, Bethesda, Md., p. 15.
9. In May 1969, PHS-NIH officials did provide a more specific definition of consent; see Frankel, *Guidelines Governing Research*, pp. 38-39. See also Ruth R. Faden and Tom L. Beauchamp, *A History and Theory of Informed Consent* (New York: 1986), pp. 205-15, for a more positive view of the 1966 document as well as the 1969 revisions.
10. The most acute analysis of the FDA regulations in human experimentation remains William J. Curran's "Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," *Daedalus* 98 (1969): 542-94; I have relied on it in the paragraphs that follow.
11. Curran, "Governmental Regulation," pp. 558-69.
12. *Hearings on Health*, pp. 211-12.
13. Paul Ramsey, *The Patient as Person* (New Haven, Conn.: 1970), p. 1.
14. *Ibid.*, p. xiv.
15. *Ibid.*, p. xv.
16. *Ibid.*, pp. xvi, 5-7, xvii.
17. The resulting publication, *Ethical Aspects of Experimentation with Human Subjects*, appeared as vol. 98, Spring 1969.
18. Hans Jonas, "Philosophical Reflections on Experimenting with Human Subjects," *Daedalus* 98 (1969): 219.
19. Jonas, "Philosophical Reflections," p. 245.
20. David J. Rothman, "The State as Parent," in *Doing Good*, ed. Willard Gaylin, Steven Marcus, David J. Rothman, and Ira Glasser (New York: 1978), pp. 84-85.