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STRANGERS AT THE BEDSIDE

A History of How Law and Bioethics Transformed Medical Decision Making

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judgments about intended and unintended consequences are bound to be premature. The field of medicine is now buffeted by the winds of change—let one issue float up, and it is immediately blown away by yet another issue. For a time, all that anyone wanted to talk about were the new federal reimbursement formulas ("Is There Life after DRGs?" was the title of one lecture). Then the concern shifted to quality control (Can patient care and hospital budgets survive interns getting a full night's sleep?), and then focused on the treatment of AIDS (What degree of risk should a physician be required to accept? How far should AIDS patients be allowed to go in choosing their own drug regimens?). Each issue prompted the call for new rules, committees, and guidelines, and each has brought still more participants (from data retrieval specialists to AIDS activists) into medicine. Thus, it is much too early to offer final verdicts, but not too early to remember just how recently medicine and medical decision making became so central a subject in public and policy discourse. I can only hope, as do many other historians, that an analysis of the origins of a change can help us—doctors, patients, and citizens alike—to direct and enhance the change.

CHAPTER 1

The Nobility of the Material

CHANGE began with a whistle-blower and a scandal.

In June 1966, Henry Beecher, Dorr Professor of Research in Anesthesia at Harvard Medical School, published in the *New England Journal of Medicine (NEJM)* his analysis of "Ethics and Clinical Research" and thereby joined the ranks of such noted muckrakers as Harriet Beecher Stowe, Upton Sinclair, and Rachael Carson.[1] As has so often happened in the course of American history, a publication like *Uncle Tom's Cabin*, *The Jungle*, or *Silent Spring* will expose a secret—whether it be the violation of the slave family, the contamination of food, or the poisoning of the environment—so compellingly as to transform public attitudes and policy. Beecher's article fits in this tradition. Its devastating indictment of research ethics helped inspire the movement that brought a new set of rules and a new set of players to medical decision making.[2]

The piece was short, barely six double-columned pages, and the writing terse and technical, primarily aimed at a professional, not a lay, audience. Beecher tried (not altogether successfully) to maintain a tone of detachment, as though this were a scientific paper like any other. "I want to be very sure," he insisted, "that I have squeezed out of it all emotion, value judgments, and so on."[3] Even so, its publication created a furor both inside and outside the medical profession.

At its heart were capsule descriptions of twenty-two examples of

investigators who had risked "the health or the life of their subjects" without informing them of the dangers or obtaining their permission. No citations to the original publications or names of the researchers appeared. Beecher did give the editors of the *NEJM* a fully annotated copy, and they vouched for its accuracy; he steadfastly refused all subsequent requests for references. Publicly, he declared that his intention was not to single out individuals but to "call attention to widespread practices." Privately, he conceded that a colleague from the Harvard Law School had advised him that to name names might open the individuals to lawsuits or criminal prosecution.[4]

The research protocols that made up Beecher's roll of dishonor seemed flagrant in their disregard of the welfare of the human subjects. Example 2 constituted the purposeful withholding of penicillin from servicemen with streptococcal infections in order to study alternative means for preventing complications. The men were totally unaware of the fact that they were part of an experiment, let alone at risk of contracting rheumatic fever, which twenty-five of them did. Example 16 involved the feeding of live hepatitis viruses to residents of a state institution for the retarded in order to study the etiology of the disease and attempt to create a protective vaccine against it. In example 17, physicians injected live cancer cells into twenty-two elderly and senile hospitalized patients without telling them that the cells were cancerous, in order to study the body's immunological responses. Example 19 involved researchers who inserted a special needle into the left atrium of the heart of subjects, some with cardiac disease and others normal, in order to study the functioning of the heart. In example 22, researchers inserted a catheter into the bladder of twenty-six newborns less than forty-eight hours old and then took a series of X rays of the bladders filling and voiding in order to study the process. "Fortunately," noted Beecher, "no infection followed the catheterization. What the results of the extensive x-ray exposure may be, no one can yet say."

Beecher's most significant, and predictably most controversial, conclusion was that "unethical or questionably ethical procedures are not uncommon" among researchers—that is, a disregard for the rights of human subjects was widespread. Although he did not provide footnotes, Beecher declared that "the troubling practices" came from "leading medical schools, university hospitals, private hospitals, governmental military departments . . . governmental institutes (the National Institutes of Health), Veterans Administration Hospitals and industry." In short, "the basis for the charges is broad." Moreover, without attempting any numerical estimate of just how endemic the practices were among researchers, Beecher reported how dismayingly easy it had been for him to compile his list. An initial list of seventeen examples had been easily expanded to fifty (and winnowed down to twenty-two for publication). He had also examined 100 consecutive studies that were reported on in 1964 "in an excellent journal; 12 of these seemed unethical." He concluded, "If only one quarter of them is truly unethical, this still indicates the existence of a serious problem."

At a time when the media were not yet scouring medical journals for stories, Beecher's charges captured an extraordinary amount of public attention. Accounts of the *NEJM* article appeared in the leading newspapers and weeklies, which was precisely what he had intended. A circumspect whistle-blower, he had published his findings first in a medical journal without naming names; but at the same time, he had informed influential publications (including the *New York Times*, the *Wall Street Journal*, *Time*, and *Newsweek*) that his piece was forthcoming. The press reported the experiments in great detail, and reporters, readers, and public officials alike expressed dismay and incredulity as they pondered what had led respectable scientists to commit such acts. How could researchers have injected cancer cells into hospitalized senile people or fed hepatitis viruses to institutionalized retarded children? In short order, the National Institutes of Health (NIH), the major funder of research in the country, was getting letters from legislators asking what corrective actions it intended to take.[5]

Beecher, as he fully expected, infuriated many of his colleagues, and they responded angrily and defensively. Some, like Thomas Chalmers at Harvard, insisted that he had grossly exaggerated the problem, taking a few instances and magnifying them out of proportion.[6] The more popular objection (which can still be heard among investigators today) was that he had unfairly assessed 1950s practices in terms of the moral standards of a later era. To these critics, the investigators that Beecher had singled out were pioneers, working before standards were set for human investigation, before it was considered necessary to inform subjects about the research and obtain their formal consent to participa-

tion. The enterprise of human investigation was so novel that research ethics had been necessarily primitive and underdeveloped.

However popular—and, on the surface, appealing—that retort is, it not only fails to address the disjuncture between public expectations and researchers' behavior but is woefully short on historical perspective. If the activity was so new and the state of ethics so crude, why did outsiders shudder as they read about the experiments? However tempting it might be to short-circuit the history, neither human experimentation nor the ethics of it was a recent invention. Still, Beecher's critics were not altogether misguided: there was something substantially different about the post–World War II laboratories and investigators. If researchers were not as morally naïve as their defenders would suggest, they occupied a very special position in time. They had inherited a unique legacy, bequeathed to them by the World War II experience.

Thus, for many reasons, it is important that we trace, however briefly, this history, particularly in its most recent phases. In no other way can we understand how investigators could have designed and conducted the trials that made up Beecher's roster. And in no other way can we understand the gap between the investigators' behavior and public expectation, a gap that would produce not only wariness and distrust but also new mechanisms for governing clinical research. These attitudes and mechanisms spread, more quickly than might have been anticipated, from the laboratory to the examining room. A reluctance to trust researchers to protect the well-being of their subjects soon turned into an unwillingness to trust physicians to protect the well-being of their patients. In the new rules for research were the origins of the new rules for medicine.

Until World War II, the research enterprise was typically small-scale and intimate, guided by an ethic consistent with community expectations.[7] Most research was a cottage industry: a few physicians, working alone, carried out experiments on themselves, their families, and their immediate neighbors. Moreover, the research was almost always therapeutic in intent; that is, the subjects stood to benefit directly if the experiments were successful. Under these circumstances, the ethics of human investigation did not command much attention; a few scientists, like Claude Bernard and Louis Pasteur, set forth especially thoughtful

and elegant analyses. But for the most part, the small scale and potentially therapeutic character of the research seemed protection enough, and researchers were left to their own conscience, with almost no effort to police them. To be sure, not everyone's behavior matched the standard or lived up to expectations. By the 1890s, and even more frequently in the opening decades of the twentieth century, some investigators could not resist experimenting on unknown and unknowing populations, particularly inmates of orphanages and state schools for the retarded. But at least before World War II such practices were relatively infrequent.

The idea of judging the usefulness of a particular medication by actual results goes back to a school of Greek and Roman empiricists, but we know little about how they made their judgments and whether they actually conducted experiments on human beings. The medieval Arab medical treatises, building on classical texts, reflect an appreciation of the need for human experiments, but again the record is thin on practice. Scholars like the renowned Islamic scientist and philosopher Avicenna (980–1037) recommended that a drug be applied to two different cases to measure its efficacy, and he also insisted that "the experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man." However, he offered no guidance about how or on whom such experiments should be conducted.[8]

If earlier practices remain obscure, a number of ethical maxims about experimentation do survive. Maimonides (1125–1204), a noted Jewish physician and philosopher, counseled colleagues always to treat patients as ends in themselves, not as means for learning new truths. A fuller treatment of research ethics came from the English philosopher and scientist Roger Bacon (1214–1292). He excused the inconsistencies in therapeutic practices among contemporary physicians on the following grounds: "It is exceedingly difficult and dangerous to perform operations on the human body, wherefore it is more difficult to work in that science than in any other. . . . The operative and practical sciences which do their work on insensate bodies can multiply their experiments till they get rid of deficiency and errors, but a physician cannot do this because of the nobility of the material in which he works; for that body demands that no error be made in operating upon

it, and so experience [the experimental method] is so difficult in medicine."[9] To Bacon the trade-off was worth making: the human body was so noble a material that therapeutics would have to suffer deficiencies and errors.

Human experimentation made its first significant impact on medical knowledge in the eighteenth century, primarily through the work of the English physician Edward Jenner, and his research on a vaccination against smallpox exemplifies both the style and technique that would predominate for the next 150 years. Observing that farmhands who contracted the pox from swine or cows seemed to be immune to the more virulent smallpox, Jenner set out to retrieve material from their pustules, inject that into another person, and see whether the recipient could then resist challenges from small amounts of smallpox materials. In November 1789 he carried out his first experiment, inoculating his oldest son, then about a year old, with swinepox. Although the child suffered no ill effects, the smallpox material he then received did produce an irritation, indicating that he was not immune to the disease.[10]

Jenner subsequently decided to work with cowpox material. In his most famous and successful experiment, he vaccinated an eight-year-old boy with it, a week later challenged him with smallpox material, and noted that he evinced no reaction. No record exists on the interaction between Jenner and his subject save Jenner's bare account: "The more accurately to observe the progress of the infection, I selected a healthy boy, about eight years old, for the purpose of inoculation for the cow-pox. The matter . . . was inserted . . . into the arm of the boy by means of two incisions."[11] Whether the boy was a willing or unwilling subject, how much he understood of the experiment, what kind of risk–benefit calculation he might have made, or whether his parents simply ordered him to put out his arm to please Mr. Jenner remains unknown. Clearly, Jenner did the choosing, but do note the odd change in style from the active "I selected" to the passive "the matter was . . . inserted." All we can tell for certain is that the boy was from the neighborhood, that Jenner was a man of standing, that he chose the boy for the experiment, and that smallpox was a dreaded disease. Still, some degree of trust probably existed between researcher and subject, or subject's parents. This was not an interaction between strangers, and Jenner would have been accountable had anything untoward happened.

Word of Jenner's success spread quickly, and in September 1799 he received a letter from a physician in Vienna who had managed to obtain some vaccine for his own use. His first subject, he told Jenner, was "the son of a physician in this town." Then, encouraged by his initial success, he reported, "I did not hesitate to inoculate . . . my eldest boy, and ten days afterwards my second boy." In this same spirit, Dr. Benjamin Waterhouse, professor of medicine at Harvard, learned of Jenner's work and vaccinated seven of his children; then, in order to test for the efficacy of the procedure, he exposed three of them to the disease at Boston's Smallpox Hospital, with no ill effects. Here again, colleagues and family were the first to share in the risks and benefits of research.[12]

Even in the premodern era, neighbors and relations were not the only subjects of research. Legends tell of ancient and medieval rulers who tested the efficacy of poison potions on condemned prisoners and released those who survived. Much better documented is the example of Lady Mary Wortley Montagu, wife of the British ambassador to Turkey, who learned about Turkish successes in inoculating patients with small amounts of the smallpox material to provide immunity. Eager to convince English physicians to adopt the procedure, she persuaded King George I to run a trial by pardoning any condemned inmate at the Newgate Prison who agreed to the inoculation. In August 1721, six volunteers were inoculated; they developed local lesions but no serious illness, and all were released. As science went, the trial was hardly satisfactory and the ethics were no better—the choice between death or enrollment in the experiment was not a freely made one. But such ventures remained the exception.[13]

For most of the nineteenth century, research continued on a small scale, with individual physicians trying out one or another remedy or procedure on a handful of persons. Experimentation still began at home, on the body of the investigator or on neighbors or relatives. One European physician, Johann Jorg, swallowed varying doses of seventeen different drugs in order to analyze their effects; another, James Simpson, searching for an anesthesia superior to ether, inhaled chloroform and awoke to find himself lying flat on the floor.[14] In what is surely the most extraordinary moment in nineteenth-century human experiments, Dr. William Beaumont conducted his famous studies on "The

Physiology of Digestion" on the healed stomach wound of Alexis St. Martin. There was a signed agreement between them, though not so much a consent form (as some historians have suggested) as an apprenticeship contract; but even this form testified to the need for investigators to obtain the agreement of their subjects. St. Martin bound himself for a term of one year to "serve, abide, and continue with the said William Beaumont . . . [as] his covenant servant"; and in return for board, lodging, and $150 a year, he agreed "to assist and promote by all means in his power such philosophical or medical experiments as the said William shall direct or cause to be made on or in the stomach of him."[15]

The most brilliant researcher of the century, Louis Pasteur, demonstrates even more vividly just how sensitive investigators could be to the dilemmas inherent in human experimentation. As he conducted laboratory and animal research to find an antidote to rabies, he worried about the time when it would be necessary to test the results on people. In fall 1884 he wrote to a patron deeply interested in his work: "I have already several cases of dogs immunized after rabic bites. I take two dogs: I have them bitten by a mad dog. I vaccinate the one and I leave the other without treatment. The latter dies of rabies: the former withstands it." Nevertheless, Pasteur continued, "I have not yet dared to attempt anything on man, in spite of my confidence in the result. . . . I must wait first till I have got a whole crowd of successful results on animals. . . . But, however I should multiply my cases of protection of dogs, I think that my hand will shake when I have to go on to man."[16]

The fateful moment came some nine months later when there appeared at his laboratory door a mother with her nine-year-old son, Joseph Meister, who two days earlier had been bitten fourteen times by what was probably a mad dog. Pasteur agonized over the decision as to whether to conduct what would be the first human trial of his rabies inoculation; he consulted with two medical colleagues and had them examine the boy. Finally, he reported, on the grounds that "the death of the child appeared inevitable, I resolved, though not without great anxiety, to try the method which had proved consistently successful on the dogs." By all accounts, Pasteur passed several harrowing weeks as he oversaw the administration of twelve inoculations to the boy. ("Your father," Madam Pasteur wrote her children, "has had

another bad night; he is dreading the last inoculations on the child. And yet there can be no drawing back now.") By mid-August, Pasteur relaxed, "confident of the future health of Joseph Meister" and the validity of his findings.[17] The extraordinary caution with which Pasteur approached human experimentation, even when it might save a life, was a standard that not all of his successors would maintain.[18]

The most significant formulation of research ethics in the nineteenth century was the work of Claude Bernard, professor of medicine at the College of France. Bernard conducted pioneering research in physiology, discovering, among other things, the essential role of glycogen in fueling muscle movement. In addition, he composed an exceptionally astute treatise on the methods of experimentation, including the ethics of experimentation. Fully cognizant of and generally comfortable with the traditions in human experimentation—"morals do not forbid making experiments on one's neighbor or one's self"—Bernard set down the maxim that he believed should guide practices: "The principle of medical and surgical morality," he wrote in 1865, "consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others." To be sure, Bernard did allow some exceptions; he sanctioned experimentation on dying patients, including feeding a condemned woman larvae of intestinal worms without her knowledge to learn whether the worms developed in her intestines after her death. "As experiments of this kind are of great interest to science and can be conclusive only on man, they seem to be wholly permissible when they involve no suffering or harm to the subject of the experiment." But Bernard made eminently clear that scientific progress did not justify violating the well-being of any individual.[19]

Bernard's writing is so celebrated today—his maxims have undoubtedly been repeated more often in the past 20 years than in the prior 100—that it is particularly important to affirm that he was not unique among contemporaries in voicing or acting on such sentiments. Let one obscure example suffice. In 1866, J. H. Salisbury, an American professor of physiology, was eager to test a theory that linked malarial fever to vapors arising from stagnant pools, swamps, and humid low grounds. (He was correct in associating such settings with malaria; his mistake was making vapors, rather than mosquitoes, the agent that

spread the disease.) Accordingly, he filled six tin boxes with "decidedly malarious dying prairie bog, transported them to a district some five miles away from the malaria area, and placed them on the sill of an open second-story window of the bedroom of two young men." He instructed them to keep the box on the sill and the window open. On the twelfth and fourteenth days of the experiment one and then the other of the men came down with the fever; Salisbury repeated the experiment a second time with three more young men, and two of them contracted the fever. Although he wanted very much to continue, he stopped his research: "On account of . . . the difficulty of obtaining the consent of parties for experiments, I have been unable to conduct this part of the examination further." Clearly, the neighbors were convinced that the odors from his box caused malaria, and they would no longer consent to put themselves at risk—a judgment that Salisbury understood and did not attempt to subvert.[20]

In fact, by the nineteenth century, common law recognized both the vital role of human experimentation and the need for physicians to obtain patients' consent. As one English commentator explained in 1830: "By experiments we are not . . . speaking of the wild and dangerous practices of rash and ignorant practitioners . . . but of deliberate acts of men from considerable knowledge and undoubted talent, differing from those prescribed by the ordinary rules of practice, for which they have good reason . . . to believe will attend to the benefit of the patient, although the novelty of the undertaking does not leave the result altogether free of doubt." The researcher who had consent was "answerable neither in damages to the individual, nor on a criminal proceeding. But if the practitioner performs his experiment without giving such information to, and obtaining the consent of his patient, he is liable to compensate in damages any injury which may arise from his adopting a new method of treatment."[21] In short, the law distinguished carefully between quackery and innovation; and so long as the investigator had obtained the agreement of the subject, research was a legitimate, protected activity.

With the new understanding of germ theory in the 1890s and the growing professionalization of medical training and research in the 1900s, the sheer amount of human experimentation increased. Clinical trials of new therapeutic agents became much more frequent, even

before the 1935 introduction of sulfonamides. Over this period, the intimate link between investigators and subjects weakened, although the relatively small scale and essentially therapeutic character of the research continued.

Subjects were now more likely to be a group of patients in a particular hospital rather than neighbors or kin. Physicians administered a new drug to a group of sick patients and compared their rates of recovery with past rates among similar patients or with those of other patients who did not have the drug. (Random and blind clinical trials, wherein a variety of patient characteristics are carefully matched and where researchers are purposely kept ignorant of which patient receives a new drug, were still in the future.) Thus, in Germany physicians tested antidiphtheria serum on thirty hospitalized patients and reported that only six died, compared to the previous year at the same hospital when twenty-one or thirty-two died.[22] In Canada, Banting and Best experimented with insulin therapy on diabetic patients who faced imminent death, and took recovery as clear proof of the treatment's efficacy.[23] So too, Minot and Murphy tested the value of a liver preparation against pernicious anemia by administering it to forty-five patients in remission, who all remained healthy so long as they took the treatment. The normal relapse rate was one-third, and three patients who stopped treatment on their own accord relapsed.[24] It is doubtful that many of these subjects received full information about the nature of the trial or formally consented to participate. But they probably were willing subjects, ready to gamble, even if they understood neither the odds nor the nature of the game, since the research had therapeutic potential and they were in acute distress or danger.

As medicine became more scientific, some researchers did skirt the boundaries of ethical behavior in experimentation and started elevating medical progress over the subject's welfare. But often as not, hostile public reactions made clear that they were perilously close to violating the norms. Probably the most famous experiment in this zone of ambiguity was the yellow fever work of the American army surgeon Walter Reed. In some ways, he demonstrated a genuine sensitivity to the ethics of experimentation; in other ways, he anticipated all too clearly the abuses that were to follow.

Reed's goal was to identify the source of transmission of yellow fever,

which was taking a terrible toll among North and South Americans. When he began his experiments, mosquitoes had been identified as crucial to the transmission, but their precise role was still unclear. "Personally," Reed wrote from Cuba, "I feel that only can experimentation on human beings serve to clear the field for further effective work."[25] In time-honored tradition, members of the research team first subjected themselves to the mosquito bites; but it soon became apparent that larger numbers of volunteers were needed, and the team adopted a pull-them-off-the-road approach. No sooner was the decision made to use volunteers than a soldier happened by. "You still fooling with mosquitoes?" he asked one of the doctors. "Yes," the doctor replied. "Will you take a bite?" "Sure, I ain't scared of 'em," responded the man. And with this feeble effort to inform a subject about the nature of the experiment, "the first indubitable case of yellow fever . . . to be produced experimentally" occurred.[26]

As Reed's project came to rely on growing numbers of human subjects, its procedures became more formal. After two of the team's members died of yellow fever from purposeful bites, the rest, who had not yet contracted the disease, including Reed himself, decided "not to tempt fate by trying any more [infections] upon ourselves. . . . We felt we had been called upon to accomplish such work as did not justify our taking risks which then seemed really unnecessary." Instead, Reed asked American servicemen to volunteer, which some did. He also recruited Spanish workers, drawing up a contract with them: "The undersigned understands perfectly well that in the case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay on this island he prefers to take the chance of contracting it intentionally in the belief that he will receive . . . the greatest care and most skillful medical service." Volunteers received $100 in gold, and those who actually contracted yellow fever received a bonus of an additional $100, which, in the event of their death, went to their heirs.[27]

Reed's contract was traditional in its effort to justify the research by citing benefits for the subjects—better to be sick under Reed's care than left to one's own devices. But the contract was also innovative, in that intimacy gave way to a formal arrangement that provided an enticement to undertake a hazardous assignment, and the explanation in

subtle ways distorted the risks and benefits of the experiment. Yellow fever endangered life only "to a certain extent"; the likelihood that the disease might prove fatal was unmentioned. So too, the probability of contracting yellow fever outside of the experiment was presented as an absolute certainty, an exaggeration to promote subject recruitment.

Although the press had no knowledge of the contract, it did keep an eye on the research, prepared to render judgments about appropriate risks and benefits. Just how uneasy journalists were with nontherapeutic research protocols is evident from the headlines that local Cuban newspapers ran about Reed's work. "HORRIBLE IF TRUE!" declared one of them, and the accompanying story reported on "a rumor . . . so horrible" about Spanish immigrants being shut up at night in special quarters into which "are released a large number of mosquitos who have bitten individuals suffering from yellow fever. . . . If the workman is taken sick and dies the experiment has demonstrated its effectiveness." Such research, the article concluded, constituted "the most monstrous case of humanitarian . . . savagery which we have been witness to." Even more notable, after Reed and his team, but not all other investigators, were convinced that the mosquito was the agent that transmitted yellow fever, some of Reed's colleagues wanted to continue the experiments in order to identify the dangerous insect strains more precisely. An article in the *Washington Post* took them to task, urging that the human experiments be halted because it would be unconscionable to continue putting people at risk now that "all are agreed that the mosquito does the business."[28] In sum, Reed was at once candid and self-serving, and the public had little difficulty distinguishing between the two.

Some human experiments in the pre–World War II period did cross the boundaries of acceptable ethics and might well have been included on Beecher's list. A number of researchers in the United States and elsewhere could not resist using incompetent and institutionalized populations for their studies. So captive and compliant a group of people seemed ideal, from a purely experimental perspective, for testing new treatments. The Russian physician V. V. Smidovich (publishing in 1901 under the pseudonym Vikenty Veeressayev) cited more than a dozen experiments, mostly conducted in Germany, in which unknowing pa-

tients were inoculated with microorganisms of syphilis and gonorrhea.[29] When George Sternberg, the surgeon general of the United States in 1895 (and a collaborator with Walter Reed), wanted to test the efficacy of a preparation that might immunize against or treat smallpox, he ran experiments "upon unvaccinated children in some of the orphan asylums in . . . Brooklyn."[30] Dr. Joseph Stokes, of the Department of Pediatrics at the University of Pennsylvania School of Medicine, and two colleagues analyzed the effects of "intramuscular vaccination of human beings . . . with active virus of human influenza" by experimenting on the residents of two large state institutions for the retarded.[31]

The work of Hideyop Noguchi is another notable case in point. An associate member of the Rockefeller Institute for Medical Research, Noguchi investigated the ability of a substance he called "luetin," an extract from the causative agent of syphilis, to diagnose syphilis. Just as Clemens von Pirquet had demonstrated in 1907 that the injection of a small amount of tuberculin into the skin could indicate a tubercular condition, Noguchi hoped to prove that an injection of a small amount of luetin could indicate a syphilitic condition. After carrying out animal experiments that demonstrated to his satisfaction that luetin could not transmit the disease, he moved to human experimentation. With the cooperation of fifteen New York physicians, Noguchi tested some 400 subjects, mostly inmates in mental hospitals and orphan asylums and patients in public hospitals. Two hundred fifty-four of them were syphilitic; the remainder, his "various controls," included 456 normal children and 190 adults and children suffering from such diseases as tuberculosis and pneumonia. Before administering luetin to these subjects, Noguchi and some of the physicians did first test the material on themselves, with no ill effects. But no one, including Noguchi, informed the subjects about the experiment or obtained their permission to do the tests.[32]

Noguchi did have his justifications: First, the test was safe, as shown by his own participation. Second, it ostensibly was therapeutic, in that it might detect hidden cases of syphilis among the subjects. But the arguments were patently weak and certainly did not ward off a strong outcry, at least from some quarters of the public. The antivivisectionists, in particular, saw in this research a confirmation of their fear that

a disregard for the welfare of animals would inevitably engender a disregard for the welfare of humans. Under the title "What Vivisection Invariably Leads To," one pamphleteer asked, "Are the helpless people in our hospitals and asylums to be treated as so much material for scientific experimentation, irrespective of age or consent?" And if the research was so risk-free, asked a leader of the movement, "might not the Rockefeller Institute have secured any number of volunteers by the offer of a gratuity of twenty or thirty dollars?" The press soon joined in. The *New York Times* ran the story under the banner, "THIS OUTRAGE SHOULD BE PUNISHED"; and the president of the Society for the Prevention of Cruelty to Children wanted to see criminal charges brought against Noguchi. U.S. Senator Jacob Gallinger of New Hampshire, an antivivisectionist sympathizer, called for a commission to investigate practices in New York hospitals and to enact legislation that would punish investigators who conducted such experiments. So too, the Committee on Protection of Medical Research of the American Medical Association asked editors of medical journals to examine papers submitted for publication, imploring them, "In any case of diagnosis or treatment when the procedure is novel or might be objected to, let the fact be stated that the patient or his family were fully aware of and consented to the plan."[33]

In the end, neither Noguchi's research nor the other experiments on the retarded or the mentally ill produced prosecutions, corrective legislation, or new professional review policies. Violations were too few; nontherapeutic research on captive populations was still the exception. And when the public learned about such incidents, objections quickly arose, reflecting a widely shared sense of what was fair and unfair in human experimentation. Had these norms held sway even as the methods of research changed, Beecher might not have been compelled to write his article.

CHAPTER 2

Research at War

THE transforming event in the conduct of human experimentation in the United States, the moment when it lost its intimate and directly therapeutic character, was World War II. Between 1941 and 1945 practically every aspect of American research with human subjects changed. For one, a cottage industry turned into a national program. What were once occasional, ad hoc efforts by individual practitioners now became well-coordinated, extensive, federally funded team ventures. For another, medical experiments that once had the aim of benefiting their subjects were now frequently superceded by experiments designed to benefit others—specifically, soldiers on the battlefront. For still another, researchers and subjects were more likely to be strangers to each other, with no necessary sense of shared purpose or objective. Finally, and perhaps most important, the common understanding that experimentation required the agreement of the subjects—however casual the request or general the approval—was often superceded by a sense of urgency that overrode the issue of consent.

The fact that all these characteristics first appeared in wartime, as a critical part in the battle against totalitarianism, helped ensure that they would not provoke public opposition. Neither the growing distance between researcher and subject nor the inattention to principles of consent sparked critiques or expressions of distrust. To the contrary, all these characteristics were viewed as a necessary and admirable ele-

ment in the home-front effort. Later we will discuss the impact of the German atrocities, but well into the 1960s, the American research community considered the Nuremberg findings, and the Nuremberg Code, irrelevant to its own work.

In the summer of 1941, President Franklin Roosevelt created the Office of Scientific Research and Development (OSRD) to oversee the work of two parallel committees, one devoted to weapons research, the other to medical research. The need for a Committee on Medical Research (CMR) had been apparent for well over a year. The government had been sponsoring weapons research through a central agency that coordinated the work of researchers all over the country, but the chiefs of the military services could not agree on how to organize the medical research wing and lacked guiding precedents. They finally decided to establish one master agency to supervise the two activities, and thus began what Dr. Chester Keefer, one of the mainstays of the CMR, later described as "a novel experiment in American medicine, for planned and coordinated medical research had never been essayed on such a scale."[1]

Over the course of World War II the CMR recommended some 600 research proposals, many of them involving human subjects, to the OSRD for funding. The OSRD, in turn, contracted with investigators at some 135 universities, hospitals, research institutes, and industrial firms to conduct the investigations. The accomplishments of the CMR effort required two volumes to summarize (the title, *Advances in Military Medicine*, does not do justice to the scope of the investigations), and the list of publications that resulted from its grants takes up seventy-five pages. All told, the CMR expended some $25 million (a sum that pales in comparison to what the National Institutes of Health eventually spent in the 1960s), but at the time it was extraordinary.[2] In fact, the work of the CMR was so important that it supplied not only the organizational model but the intellectual justification for creating in the postwar period the National Institutes of Health. The CMR came to represent the promise of what coordinated, well-funded efforts could accomplish for scientific progress—what medical research could do for the betterment of humanity.

The health problems that confronted American soldiers and threat-

ened to undermine their combat efficiency (and combat efficiency was the criterion) were obvious to the CMR staff, who sought quick, effective solutions. They wanted not so much to support basic research but to achieve immediate clinical payoffs. The major concerns were dysentery, influenza, malaria (in the Pacific theater), wounds, venereal diseases, and physical hardships (for example, sleep deprivation, exposure to frigid temperatures). Creating effective antidotes required skill, luck, and numerous trials with human subjects, and the CMR staff oversaw the effort with extraordinary diligence. Because it was wartime, the agency underwrote protocols that in a later day (and an earlier one as well) would have produced considerable protest. But its directors deftly managed the problem. Knowing just when to proceed aggressively or cautiously, they enhanced both the scientific and social reputation of medical research.

One primary CMR target was dysentery. Battlefront conditions did not allow for standard hygienic procedures against contaminated water and food or contagion from other carriers, and dysentery was especially debilitating to a fighting corps. No effective inoculations or antidotes existed, and the CMR wanted researchers to move ahead vigorously on both fronts. Outbreaks of the disease in so many different environments made it likely that a variety of bacteria caused the infection, and hence a vaccine would have to be effective against a great number of potentially dangerous organisms. To make matters still worse, the organisms themselves were known to be highly toxic. This meant, noted one researcher, that "inoculation . . . in adequate amounts [to create immunity] may induce such severe local and general reactions as to make general application among troops impractical."[3]

Even before facing up to these formidable problems, investigators had to find a research site. Since animal experiments would yield only limited information, sooner or later the researchers would need a setting in which to test a vaccine or an antidote on humans. The obvious location was the least satisfactory—drugs could not be evaluated in the field, on soldiers at the battlefront. The preparations might be too toxic, and besides, side effects and efficacy could not be measured under gunfire. A substitute setting would have to be found, and it did not take researchers long to identify one. Stuart Mudd, one of the leading researchers on this project for the CMR, suggested the order

of things: First, "specific prophylactis by properly chosen antigenic fractions should be thoroughly explored in the laboratory." Then the agents should be tested in "institutions such as asylums," where dysentery was often rampant. This was precisely the order followed—research first on animals, then on orphans in asylums and on the retarded in institutions.[4]

No researcher and no one at CMR ever commented on the irony that to simulate the filth and lack of hygiene at the battlefront one only had to go to caretaker institutions. Rather, the fact was accepted and reported matter-of-factly: "In certain civilian institutions," noted the CMR summary volume, "where outbreaks of dysentery are not uncommon, opportunities have been furnished to observe the effect of the vaccines under approximately field conditions." Indeed, researchers scored points with the CMR for being able to get into institutions. Thus, a CMR official praised one investigator because "he has . . . access to various state institutions where facilities for study of dysentery are unexcelled."[5]

Among the most important subjects for the dysentery research were boys and girls between the ages of thirteen and seventeen in the Ohio Soldiers and Sailors Orphanage. CMR contract 293 went to doctors Merlin Cooper and B. K. Rachford of the Cincinnati Children's Hospital to attempt to immunize the children against dysentery with "killed suspensions of various types of shigella group of bacteria." The team injected different suspensions in different ways, some subcutaneously, some intramuscularly, and some intravenously; it also mixed the dysentery vaccine with the standard typhoid vaccine to learn whether the combination enhanced efficacy. All the experiments carried serious side effects, with the intravenous injections causing the most severe reactions. On 12 March 1943, ten boys were injected with ten million dysentery bacteria: "The systematic reaction," reported the team, "was profound and began within less than 30 minutes. It was essentially the same in all of the boys. The skin was pale and ashy grey in color. The blood pressure was not altered but the temperature sky-rocketed to 105°F and up in spite of measures to counteract the rise. Severe pounding headache and a constricting type of backache were almost universal complaints. The bulbar conjunctivae were hyperemic. Rapidly, nausea, vomiting and watery diarrhea ensued. Fever persisted for 24 hours and

when it subsided the subjects were exhausted. By the second day all had recovered." The ten boys had an average maximum temperature of 104.6 degrees.[6]

Although the boys did appear to have built up an immunity against dysentery (measured not by direct challenge but by laboratory tests on their blood), the severity of their reaction ruled out the vaccine. The researchers then considered whether substituting subcutaneous for intravenous injections would, in their language, "hit the target." They experimented with injecting enough inoculant to give the subjects a very sore arm, "with the thought that an inflammatory reaction might break a barrier and permit a little antigen to trickle through the blood stream toward the target." To this end, they took several boys in whom "the dosage was increased cautiously until it appeared that systematic reaction, local reaction, or both were limiting factors."[7] Then, with the dose level established, they inoculated another group of ten boys subcutaneously with the vaccine, but the subjects still averaged fevers of 102 degrees, which was too severe a reaction to permit general use.

The team also tested a potential vaccine by injecting it subcutaneously in a group of girls at the Home. They experienced less swelling on their arms than did the boys, but their systemic responses were just as extreme: "Nausea, abdominal pain, headache, vomiting and on one occasion, diarrhea were observed. In one girl the reaction was unusually severe. . . . This subject became nauseated 3 hours after the injection and vomited repeatedly during the ensuing 17 hours." Although the project could not produce a safe vaccine, the researchers remained optimistic, noting that they had used very high dosages in order to make certain that they were getting substantial responses. Their final report explained that among the children at the asylum "many reactions should be classified as severe. However, there is no evidence to warrant the inference that successful immunization of human beings cannot be accomplished with dosages of vaccine too low to yield severe reactions. In these experiments dosage was purposefully raised as high as was considered safe in order to facilitate technically the measurements of heterologous immunity."[8] In other words, they had elevated the dosages to demonstrate the potency of the agent, whatever the side effects on the children.

Residents at other custodial institutions, particularly for the mentally

retarded, also served as subjects for dysentery vaccine experimentation. Researchers considered them less-than-ideal candidates, not because they were incapable of giving consent but because the researchers did not know whether the condition of retardation altered reactions to the vaccine. Nevertheless, CMR-sponsored dysentery projects were conducted at the Dixon (Illinois) Institution for the Retarded and at the New Jersey State Colony for the Feeble-Minded.[9] So too, investigators evaluated the efficacy of sulfonamide preparations against dysentery by using ward patients at public hospitals for their subjects, with no information conveyed or consents obtained. Once again, the research carried significant dangers to the subjects, for the drugs under investigation could cause extensive kidney damage.[10] Indeed, James Watt, of the U.S. Public Health Service, and Sam Cumins, a resident in medicine and pathology at the Shreveport (Louisiana) Charity Hospital, published (in the widely read *Public Health Reports*) findings that included 6 deaths among 238 cases of sulfonamide-treated patients in their protocols. Although the death rate appeared lower among treated than nontreated populations, there is no indication that the subjects or their relatives had any idea that they were part of an experiment—and a risky one at that. Here is but one example:

> *Case 3*— Twenty-month-old colored female admitted with a history of severe diarrhea. The culture was positive. . . . The patient was treated with sulfamethazine and 3 days later the temperature and clinical findings showed definite improvement. However, at the end of this time the temperature began to rise. Sulfonamide was discontinued as urinary findings indicated definite kidney damage. The patient's fever remained at a high level. Progressive toxicity ensued with oliguria. The patient died on the eighth hospital day. Death due to toxic nephritis presumably resulting from the sulfonamide used. The colon showed healing ulcerations of the mucosa.[11]

This research project, like the others, did not produce an effective vaccine or antidote. The preparations were either too potent or too weak to do any good. That most of the subjects were the institutionalized retarded or that consent was ignored did not seem to create

problems, at least to judge by the silence both in the CMR and in the press. The overarching consideration was that dysentery was such a peril to the fighting soldiers that researchers on the home front had to do everything to eradicate it.

Probably the most pressing medical problem that the CMR faced right after Pearl Harbor was malaria, "an enemy even more to be feared than the Japanese."[12] Not only was the disease debilitating and deadly, but the Japanese controlled the supply of quinine, one of the few known effective antidotes. Chemists had discovered the antimalarial actions of pentaquine, but the complications, including stomach pains and diminished mental competence, were unacceptable. The CMR leaders hoped that further research would establish an effective dosage with fewer side effects or that researchers might uncover new and less toxic therapeutic agents.

Malaria, unlike dysentery, seldom occurred in the United States, so researchers had no ready sites for drug trials. After testing antidotes on animals, they would next have to transmit the disease to human subjects and then measure the efficacy of their interventions. But where were they to find subjects to participate in such protocols? The answer, with no one dissenting, was the state mental hospitals and prisons.

Dr. Alf Alving of the University of Chicago, under CMR grant 450, organized a sixty-bed clinical unit for drug testing at the Manteno (Illinois) State Hospital. The subjects were psychotic, back-ward patients whom researchers purposely infected with malaria through blood transfusions and then gave experimental antimalarial therapies. Alving's reports made no mention of any effort to obtain their consent, but the very choice of psychotic inmates demonstrates how irrelevant such concerns were. He did hire a psychiatrist to spend "between four and six hours a week discussing the psychiatric aspects of the patients we deal with at Manteno." But the assignment was to explain the subjects to the researchers, not to interpret the experiment for the subjects.[13]

Dr. Alving and other investigators relied still more heavily on prisoners to meet their research needs. Through the cooperation of the commissioner of corrections of Illinois and the warden at the Stateville penitentiary (better known as Joliet), reported Dr. Alving, "one entire floor of the prison hospital and a portion of a second floor have been

turned over to the University of Chicago to carry out malarial research. Approximately 500 inmates have volunteered to act as subjects." Some were infected via mosquito bites (a mode of transmission that was more dangerous than blood transfusion) and then given pentaquine, a "promising" drug regimen. Researchers then correlated the severity of the malaria challenge (moderate, severe, extraordinarily severe), with the drug regimen, relapse rate, and side effects, which included nausea, vomiting, changes in the heartbeat rhythm (depression of T waves), fever, and blackouts. In the course of these trials, one prisoner died, suffering a heart attack after several bouts of high fever. The researchers insisted the death was unrelated to the malaria experiments, but worried about attracting other volunteers. However, the incident had no adverse impact. "We heard through the grapevine," Dr. Alving reported to Washington, "that there was considerable argument for a day or two. The end result, however, was quite astonishing. We have had quite a number of new volunteers who were converted to the worth-whileness of experimental work."[14]

Whether these prisoners were truly capable of volunteering for the experiments was not broached by the researchers, the CMR, prison officials, or the press. Almost all the commentary was congratulatory, praising the wonderful contributions that the inmates were making to the war effort. Press releases from Washington lauded the inmates' willingness to volunteer and without a promise of reward, "accept full responsibility for any ill effects, aware of the risk and discomfort . . . and knowing, too, that . . . there is a real hazard involved." Furthermore, they said, "these one-time enemies to society appreciate to the fullest extent just how completely this is everybody's war."[15]

The CMR also supported a major research effort to create a vaccine against influenza. Although not as threatening as malaria, respiratory ailments were "the cause of the greatest amount of disability" among soldiers, and of all the infections, influenza was the most feared. It not only had the highest mortality rate, but could again reach the catastrophic epidemic levels of 1919. As the CMR reported, the "memory of the great pandemic of influenza that occurred toward the end of World War I and realization of its disastrous effects stimulated, at the very beginning of mobilization, the investigation of all possible methods for the control of this disease."[16]

One team, under the direction of Dr. Werner Henle of the University of Pennsylvania Medical School and Philadelphia's Children's Hospital, conducted extensive research on vaccines against influenza A and B. His bimonthly reports to the CMR described his progress in preparing the inoculant and the arrangements made to test them on several hundred residents both at the nearby state facility for the retarded (Pennhurst) and the correctional center for young offenders. The protocols typically involved administering the vaccine to the residents and then three or six months later purposely infecting them with influenza (by fitting an aviation oxygen mask over their face and having them inhale a preparation of the virus for four minutes). The team also infected control groups with the virus, but not the vaccine, in order to compare the different rates of infection. As was to be expected with influenza, those who contracted the disease suffered fever (up to 104 degrees), aches, and pains.[17] Although the vaccines often did provide protection, they were not always free of side effects. As with the malaria preparations, researchers experimented with different preparations. One group of women residents at Pennhurst were injected with an influenza vaccine in a mineral oil base, and many of them developed nodules at the injection site that persisted for six to eighteen months; one had such a severe abscess as to require surgery.[18]

A second team working on influenza vaccines was led by Dr. Jonas Salk, who would later develop the first antipolio vaccine. This group took its human subjects from among the residents of Michigan's Ypsilanti State Hospital and followed essentially the same design as the Henle team: inoculate a group (for example, the "102 male residents of a single ward . . . [who] ranged in age from 20 to 70 years") with the vaccine and later challenge them with the virus; select a comparable group of residents for controls and infect them with the virus without the benefit of the vaccine.[19] The reports from the Salk team, published in such prestigious publications as the *Journal of Clinical Investigation*, accurately identified the subjects, and the researchers fully described the findings: "In the unvaccinated group, 11, or 41%, . . . had temperatures of 100 or more and 6, or 22%, had temperatures of 101 or above. In the 69 vaccinated individuals, 7, or 10%, had temperatures between 100 and 100.9."[20]

Pleased with these preliminary results, Salk and his team turned the

entire Ypsilanti Hospital, with its 2,000 residents, into a research site, adding as well the 5,700 patients at the nearby Eloise Hospital and Infirmary. Half received the vaccine, and the other half a placebo. Blood analysis indicated immunities among the inoculated, but the best evidence of efficacy came a year later when, by chance, an epidemic of influenza broke out at Ypsilanti. To the researchers' satisfaction, those inoculated had a significantly lower incidence of the disease.

After these successes, the Office of the Surgeon General of the U.S. Army arranged for the vaccine to be tested on enrollees in the Army Specialized Training Program at eight universities and a ninth unit made up of students from five New York medical and dental colleges. "With the approval of the appropriate authorities," but with no mention of what the subjects were told about the experiment, the teams inoculated 6,263 men and injected 6,211 others with a placebo. Able to keep close track of them for follow-up studies, the researchers learned that 7 percent of the controls, as compared to only 2 percent of the inoculated, had contracted influenza within a year. The research begun on the institutionalized mentally ill and continued on recruits and students produced the desired result: an effective influenza vaccine.[21]

It was not just the success or failure of any single experiment, however, that gave CMR in particular and medical research in general such a favorable standing with the public during World War II. Closely associated with these enterprises were the efficient production and distribution of penicillin (many people mistakenly credited the war effort with the discovery of penicillin), and the CMR deserves much of the praise. Its staff helped develop and allocate the "miracle drug," promoting not only cures but morale on the war front and the home front.

It was the CMR that met the challenge posed by the renowned British pathologist Howard Florey during his visit to the United States in the summer of 1941 and his demonstration on the antibacterial properties of the penicillin mold. The problem was how to produce sufficient penicillin without sacrificing its potency. Under CMR superintendence, private drug companies began the cumbersome manufacturing process. By December 1942 enough of the drug was available to test it on 90 cases, and by December 1943, 700 cases. Thus, what might have been the most devastating medical problem confronting the armed services—death from wound infections—turned out to be altogether man-

ageable. By June 1944 enough penicillin was available to treat all the wounded in the Normandy invasion.

The system devised by the CMR between 1942 and 1944 was successful in meeting military needs and collecting data on efficacy. Most of the drug went to ten general and military hospitals where a specially trained medical officer supervised its use and reported on outcomes. Lesser amounts went to twelve hospitals to test for efficacy against gonorrhea. (This was probably the source of the widely repeated but apocryphal tale of a medical officer who administered his only vial of penicillin to the soldier who was "wounded" in the brothel, not to the one wounded in the battlefield, because the brothel victim would return sooner to the front lines). Although the CMR records are silent on what, if anything, patients were told before receiving penicillin, the early trials typically involved the gravely ill who had failed on other therapies. Thus, in April 1943 a small group of battle casualties who had contracted osteomyelitis were being cared for without success at the Bushnell General Hospital in Brigham, Utah. A bacteriologist at the hospital wrote Chester Keefer about his own futile attempts to make enough penicillin to treat the men; Keefer then arranged to send him a limited supply of the drug from his own stores. The soldiers underwent a "remarkable" recovery, and the efficacy of penicillin against this type of infection was established.[22]

The CMR also kept some reserves of the drug to dispense on a case-by-case basis for civilian use. Any physician who believed that his patient required penicillin was to send full details of the case to the CMR, and Keefer then evaluated the request. His criterion was straightforward: he allotted the drug to patients with a deadly disease who demonstrated no satisfactory response to alternative therapies and for whom there was reason to believe penicillin might prove effective. Thus, patients with staphylococcal meningitis or puerperal fever received the drug, whereas those with tuberculosis or leukemia did not. Word of pencillin's effectiveness spread, and newspaper stories all over the country heralded the miracles that the drug performed—in one town it saved a dying child, in another, an almost moribund woman who had just given birth. Medical research became identified with miracles, and medical researchers with miracle makers.

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Whenever the wartime research goals raised issues that might have aroused public opposition, the CMR directors handled the situation skillfully and delicately. They recognized the limits of CMR's maneuverability, thereby maintaining an almost perfect record of support. Two examples amply demonstrate their techniques, one involving research into the effects of hardship conditions on combatants, the other involving efforts to find a cure for gonorrhea.

Of all the research that the CMR supported, none fit more closely with wartime needs than survival under hardship conditions. The Nazi investigations produced some of the most horrific experiments conducted on concentration camp inmates and testified to at Nuremberg. The CMR, in this instance, did not violate the dignity or the rights of subjects. Where one might have expected the greatest disparity between war goals and protection of human subjects, none occurred.

The medical issues were as obvious as they were unexplored: If a group of sailors were shipwrecked and ended up on a raft with a limited supply of water, ought they to supplement their supply by drinking some amount of salt water? What ration kit would provide soldiers in very hot (or cold) climates with an optimum nutritional balance? How did heat (or cold or altitude) affect the performance of physical tasks? The subjects for CMR-sponsored research on such topics came from the ranks of conscientious objectors (COs) who believed that by enrolling as subjects, they were not primarily serving the military machine but humanity, that they were contributing to an effort not to destroy but to save lives. For this research, investigators did not use inmates of mental hospitals or institutions for the retarded, probably not for ethical reasons but because the experiments required competent and cooperative subjects. Since the measure of the effects of heat and nutrition would be performance, they wanted subjects capable of carrying out routine tasks under normal conditions.

The COs were formally under the jurisdiction of the Selective Service Administration, which in 1943 decided to allow them to volunteer for research work, either as subjects or as laboratory assistants. COs were also affiliated with a national service organization, generally, the American Friends (Quakers), the Mennonites, or the National Service Board for Religious Objectors. Hence, an investigator who wanted to use a CO in his research first had to approach the CMR and then contact

both the Selective Service Administration and the CO's particular service organization. He had to compose two very different letters, one to the CMR explaining how the research would further the war effort and another to the CO's organization explaining how it would promote the well-being of humanity—and most researchers proved adept at fulfilling the dual assignment. The process was cumbersome but well worth the bother. With trained personnel so scarce, well-educated and diligent COs not only contributed to the project as cooperative subjects but as skilled assistants and administrators. The net effect of all these procedures was to put the survival research under the closest scrutiny, with government agencies, private organizations, and the subjects themselves fully informed about the experiments. The process also protected the COs from coercion, for a request for assistance went to the service organization, not directly to the individual, and the CO had to come forward and express his willingness to volunteer.

Those who did volunteer drank various mixtures of saltwater and fresh water and then had their weight checked and urine analyzed. (The findings confirmed the Ancient Mariner's view that sea water was of no benefit.) They subsisted on 500 grams a day, some with water alone, others with different foodstuffs. (Here the lesson was to stock lifeboat kits not with the standard chocolate and biscuits but with more easily digested glucose and fat.) Others sat on rooftops exposed to wind and frigid temperatures and then had their physiological responses measured; or sat in sweltering rooms, became dehydrated, and then performed simple tasks to test their efficiency; or sat in low-pressure chambers, simulating conditions at different altitudes and then underwent psychological and physiological testing. The research proceeded smoothly: the investigators pleaded for more COs, the Selective Service sought assurances that the COs were not getting off too lightly, and the COs completed their assignments and even remained with the teams afterward, satisfied that they had respected their scruples and served their nation.[23]

With even greater attention to the potential for public opposition, the CMR researchers sought a prevention and cure for gonorrhea. However intense the pressure for results, the CMR would not risk a scandal. It conducted a remarkably thorough and sensitive discussion of the ethics of research and adopted procedures that satisfied the

principles of voluntary and informed consent. Indeed, the gonorrhea protocols contradict blanket assertions that in the 1940s and 1950s investigators were working in an ethical vacuum.

Everyone in the CMR and in the Surgeon General's Office recognized the threat of gonorrhea to military efficiency. In February 1943, Dr. J. Earle Moore, the chairman of the Subcommittee on Venereal Diseases for the National Research Council, informed the CMR that each year 350,000 military personnel were likely to contract fresh infections of gonorrhea. He noted, "Assuming an average loss of time of 20 days per infected man (the actual figure for Army in recent years to 1941 was 35–45 days, for Navy 10–15 days), this will account for 7,000,000 lost man days per year, the equivalent of putting out of action for a full year the entire strength of two full armored divisions or of ten aircraft carriers." Thomas Parran, the surgeon general, noted that gonorrhea not only weakened the armed services but also "represented a serious threat to the health and efficiency of our defense workers."[24] The problem, in short, was nothing to smirk about.

Nor was the problem easy to resolve. As of 1942 no one had been able to induce gonorrhea in animals, and therefore all the testing of preventives and cures would require human subjects. (That penicillin was soon to resolve the issue could not, of course, be known.) Investigators were eager to tackle the assignment but questioned the ethical, legal, and political implications. In October 1942, Dr. Moore informed Dr. Richards, the chairman of the CMR, that he had recently received a letter from Dr. Charles Carpenter, of the University of Rochester School of Medicine, who wanted to "work out a human experiment on the chemical prophylaxis of gonorrhea. He has asked me to supply him with a statement that in my opinion such human experimentation is desirable. . . . I have pointed out to Dr. Carpenter that I could not make such a statement without the approval of higher authority. May I ask you to supply me with the attitude of the Committee on Medical Research toward human experimentation in general, and toward the particular problem of human experimentation in the chemical prophylaxis of gonorrhea."[25]

Richards promised to bring the question immediately to the full committee: "In the meantime I have confidence that the Committee will support me in the statement that human experimentation is not

only desirable, but necessary in the study of many of the problems of war medicine which confront us. When any risks are involved, volunteers only should be utilized as subjects, and these only after the risks have been fully explained and after signed statements have been obtained which shall prove that the volunteer offered his services with full knowledge and that claims for damages will be waived. An accurate record should be kept of the terms in which the risks involved were described." As for gonorrhea research, the CMR would have to rely on "the judgment of the Responsible Investigator, supplemented by the judgment of the committee in whose field the investigator is proceeding." Three weeks later Richards informed Moore that the CMR fully endorsed his position on human experimentation; all legal responsibility for damages rested with the investigator and his institution, but "arrangements can be made whereby both he and the Institution can be protected by insurance."[26]

Thus encouraged, Dr. Carpenter, and several other investigators as well, submitted grants to the CMR for gonorrhea research on human subjects. The protocols were elaborate and sophisticated both in terms of scientific method and protection of human subjects. In order to study the efficacy of oral and topical preventive treatments, Carpenter intended to divide volunteers into three categories: one group would take sulfonamide compounds by mouth and then be exposed to the infection; a second would be exposed to the infection, after which topical agents would be applied to the genital tract; a third would serve as controls, infected but not given any oral or topical protection. Carpenter proposed to conduct the research on prisoners, for they offered the advantage of being under complete control during the necessary observation period and out of contact with women. He informed the CMR that negotiations were already under way with prison officials in Georgia.

The CMR carefully reviewed the proposal in and out of house. The referees approved of the science and many, like Dr. R. E. Dyer, the director of the National Institutes of Health, expressly approved of the ethics: "The outline of methods to be employed seems adequate to insure a definite answer and to safeguard the volunteers."[27] But some reviewers were apprehensive about possible legal repercussions. The

head of the American Medical Association (AMA), for example, was concerned that an unscrupulous lawyer might learn about the project, bring suit, and try to discredit all medical research. Taking such possibilities seriously, the CMR heads set out to make certain that every contingency had been considered and to marshal full support.

To these ends, it sponsored a day-long meeting on 29 December 1942 that brought together representatives from the military services, state health departments, and interested researchers. The group not only reviewed the protocols and explored potential legal liabilities (for example, might a state law against maiming oneself be invoked against the volunteers?) but also scrutinized a "Proposed Plan of Procedure in the Study of Chemical Prophylaxis in Human Volunteers among Prison Inmates," which was to guide all the researchers.

The proposed plan specified precisely which prisoners would be ineligible to volunteer (for instance, those who were chronically ill, had a history of rheumatic fever, or had negative reactions to sulfonamides). It also specified the protocol for transmitting the infection: a nonsulfonamide-resistant strain with a low thermal death point was to be applied for five minutes. The proposed plan also included a two-page, single-spaced "Statement of Explanation of the Experiment and Its Risks to Tentative Volunteers"—in effect, a consent form:[28]

> The study which we plan to carry on here, and for which we have asked your cooperation, is concerned with gonorrhea. You may also know this disease as the 'clap,' 'strain,' or the 'running ranges.' Some of you have had the infection at some time in the past and you know it did not make you seriously sick. Recently a simple, dependable treatment has been discovered which consists of a drug taken in the form of pills.
>
> What we propose to try now is to develop certain methods of *preventing* the disease. . . . Gonorrhea causes a great loss of time in the Army and Navy. . . . It is not possible to use animals for this purpose because they are not susceptible to gonorrhea. Therefore, we are calling on you for your cooperation. This is one way in which you can specifically help in the war effort. The benefits will not be limited to the armed forces . . . and it is very likely that you and your families might later profit from them.

In the first place, I want to assure you that so far as we are able to discover, there is no reason to expect any injury from this treatment, but one cannot predict with positiveness that the result in all cases will be the same. . . .

Most patients with gonorrhea can be cured within 5 to 10 days with modern treatment without experiencing discomforts or complications. A few patients with gonorrhea do not respond to modern treatment methods (probably less than 1 in 10). These patients can usually be cured by older methods, which, however, require more time to get results. A few of the patients who are treated by these older methods develop certain complications in the lower genital tract which, in most instances, are ultimately cured. In very rare instances patients treated by the older methods develop complications which involve the joints, the eyes, and other organs.

A very small percentage of patients treated by modern methods experience discomfort while taking the medication. This may consist of a tired sensation or a slight headache, but these symptoms never become serious if the patient is observed daily by the physician. Fever, skin rash, nausea, and vomiting rarely occur but do disappear rapidly when the treatment is stopped. Other reactions have been reported which involved the blood, joints, kidneys, liver, and nervous system, but these reactions have been so rare that the possibility of their occurrence is extremely remote.

Before we can accept you as part of our group, it is necessary to obtain written permission from you.

Although the document exaggerated the potential benefit of the research to the subjects and too blatantly tried to persuade them to make their contribution to the war effort, it noted the potential complications and accurately assessed the research risks. In all, it satisfied the need to inform and protect human subjects.

The CMR staff continued to move circumspectly, reviewing the proposed research with city and state health officers, prison officials, heads of major research organizations, and legal advisors. Overwhelming support for the investigations emerged, and the consensus was that using prisoners was the only feasible and acceptable option. As Dr. Moore told Dr. Richards, civilians would not have submitted to the sexual isolation and medical supervision for the necessary six months, military

personnel could not have been kept from active duty for so long, and "inmates of institutions for the feeble-minded or insane" could not have been used because it would have been "clearly undesirable to subject to any experimental procedure persons incapable of providing voluntary consent."[29] A few reviewers, like Frank Jewett, the president of the National Academy of Science, questioned whether prisoners were capable of giving voluntary consent to an experiment, but most others were persuaded that the benefits of the research outweighed whatever doubts anyone might have.[30] Thomas Parran summed up the prevailing view: "The utilization of human subjects who voluntarily submit themselves to experimentation may properly be compared to the research which enabled Doctor Walter Reed and his co-workers to discover the method of transmission of yellow fever."[31]

The aftermath of these deliberations was not as interesting as the deliberations themselves. The CMR staff voted to support the research; but then, to be certain that the protocols violated no state laws, they proposed using prisoners in federal penitentiaries. James Bennett, the director of the federal system, was eager to cooperate and to help enroll subjects. "We cannot obligate the government," he informed Dr. Moore, "insofar as reduction of sentence for those who volunteer is concerned. It is believed, however, that the U.S. Board of Parole would be willing to give each subject . . . due credit and consideration for his willingness to serve his country in this manner when he becomes eligible for parole." The administrative hurdles cleared, a major project began at the U.S. penitentiary at Terre Haute, Indiana, but the investigators soon terminated it because "not any of the exposure techniques employed proved capable of producing disease with a consistency considered to be adequate for a study of experimental prophylaxis."[32] Shortly thereafter, the curative role of penicillin was established, obviating the need for additional research.

At first glance, the record of human experimentation during World War II constitutes a curious mixture of high-handedness and forethought. The research into dysentery, malaria, and influenza revealed a pervasive disregard of the rights of subjects—a willingness to experiment on the mentally retarded, the mentally ill, prisoners, ward patients, soldiers, and medical students without concern for obtain-

ing consent. Yet, research into survival under hardship conditions and into gonorrhea was marked by formal and carefully considered protocols that informed potential subjects about the risks of participation.

Behind these differences lies the evaluation of the CMR administrators and researchers about the likely response to specific investigations. When they sensed the possibility of an adverse public reaction, they behaved cautiously. Giving gonorrhea to prisoners might have raised a storm of protest from a variety of sources, some objecting to prisoners injuring themselves, others objecting to efforts to protect the promiscuous from the consequences of their immorality; since the protocol might, therefore, have ended up on the front page of a newspaper or in a courtroom, the CMR directors were scrupulous about building a scientific consensus on the importance of the project and protecting the rights of the volunteers. As a result of these calculations and actions, the research community secured public acceptance of a new kind of medical research and human experimentation.

Most of the time, however, the CMR and the research community were confident that their work would not be questioned—that their research on dysentery, malaria, and influenza using incompetent and incarcerated subjects would pass community scrutiny. Why, then, did officials who understood the need to make subjects' participation informed and voluntary in occasional cases find it so easy to disregard the requirements in most other cases? How could they say in the case of gonorrhea that it was "clearly undesirable to subject to any experimental procedures persons incapable of providing voluntary consent," and then go ahead and do precisely that in the case of dysentery and malaria?

The answer begins with an appreciation of the fact that the first widespread use of human subjects in medical research occurred under wartime conditions. First, a sense of urgency pervaded the laboratories. Time was of the essence when combat soldiers were under the immediate threat of disease. A campaign mentality inevitably affected not only the theaters of war but the theaters of research, justifying every shortcut or elimination of time-consuming procedures. The presumption was full speed ahead, *except* where negative fallout was most likely.

But why were informing a subject about an experiment and obtaining consent defined as time-consuming, instead of necessary, measures? Because, in the second instance, wartime conditions brought a reliance on such procedures as the draft, forced military duty, and assignment to combat—and these new facts of life inevitably affected the mind-set of researchers. Every day thousands of men were forced to face death, whether or not they understood the campaign, the strategy, or the cause. Since these investigations were integral to the military effort, the rules of the battlefield seemed to apply to the laboratory. Researchers were no more obliged to obtain the permission of their subjects than the Selective Service was to obtain the permission of civilians to become soldiers. One part of the war machine conscripted a soldier, another part conscripted an experimental subject, and the same principles held for both.

Moreover, the use of mentally incompetent people as research subjects seemed to be in accord with popular expectations of sacrifices to be made on the home front. All citizens were—or were supposed to be—contributing to the war effort, even at great personal cost and inconvenience. By this standard, it was reasonable to expect the mentally ill and retarded to make their contributions too, albeit involuntary ones. It was ever so easy to believe that if these handicapped individuals could somehow have understood the nature of the request, if they could have had a momentary flash of competence and been asked whether they wished to join the experiment and further the war effort, they would have agreed. Hence, to enroll them in research was not to violate their rights but to exercise a substituted judgment: Were they competent, they would have volunteered for the project.

It requires little historical imagination to recognize the appeal of this line of argument in a society mobilized for war. Since the mentally ill and retarded had the same stake as all other citizens in an Allied victory, it seemed altogether appropriate that they be called on to perform whatever services they could. And at a time when the social value attached to consent had so frequently to give way before the necessity of conscription and obedience to orders, there was little reason for medical researchers to worry about using incompetent human subjects. Some people were ordered to face bullets and storm a hill; others were

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.

CHAPTER 3

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