Part I

Scandals and Tragedies of Research with Human Participants

Nuremberg, the Jewish Chronic Disease Hospital, Beecher, and Tuskegee

The ethical issues raised by medical experimentation with humans hinge on one question: How can the rights of individual persons be reconciled with the demands of the scientific enterprise? That the goal of all medical research is to improve human well-being only intensifies the dilemma. Medical research with humans is justifiable because it seeks knowledge that not only is of theoretical interest but also will benefit many people and society as a whole. The question is whether such a laudable collective goal can be pursued with full protection of the rights and dignity of individuals.

Medical research has increased the well-being of humans in much of the world. And it has done so in all its many guises, from early epidemiological research, such as John Snow's investigations of the cholera outbreaks in London in the mid-nineteenth century, to current studies of treatments administered in controlled settings. While interventional methods are the hallmark of sound medical research as it has been practiced at least since the 1950s, earlier examples exist. The eighteenth-century British surgeon James Lind spent six years studying scurvy in sailors aboard HMS *Salisbury.* He provided some of the sailors (but not all of them) with a diet that included fruits and vegetables. Observing the results, Lind concluded that those in the "intervention" group were more likely to remain free of scurvy than were their shipmates.[1] About 25 years later, Edward Jenner tested cowpox vaccine on his own child and on other youngsters in the neighborhood. The vaccinations protected the children from smallpox.[2] These early experiments with humans resulted in the prevention of serious disease in sailors and in future generations of children.

Yet such medical successes were not without cost. There are many examples of studies that violated the rights and dignity of the participants and, in some cases, cost them their health or even their lives. In 1897 the Italian bacteriologist Guiseppe Sanarelli announced that he had isolated the organism that caused yellow fever. To prove his claim, Sanarelli infected five persons with his isolate. Many were quick to criticize Sanarelli for his yellow fever–inducing experiments, and the harm he inflicted on his subjects was not soon forgotten.

Just three years later, the U.S. surgeon general commissioned Walter Reed to identify the cause of yellow fever, then a raging epidemic in Cuba. Largely because concerns about human experiments were running high, Reed established several safeguards. First, self-experimentation would be used, with the members of the Yellow Fever Board serving as subjects.[3] This approach was not without risk; indeed, Jesse Lazear, a member of the board, died in the experiments. Second, only adults would be enrolled. Most important, Reed designed a written contract for the local workers that clearly explained the peril of the undertaking and offered a payment of $100 to those who were willing to be exposed and another $100 to those who became ill with yellow fever. The development of this, one of the first consent forms, was prompted by the recognition that humans were being *used* in experiments, possibly at great personal risk, for the benefit of others.

The heroism of the yellow fever investigators and the development of the process for obtaining the explicit consent of the volunteers helped legitimize medical research with human beings. By the time of World War II, the need to obtain permission from would-be participants in studies was widely accepted, though apparently little thought was given to the nature of this permission in particular circumstances or to precisely what information should be disclosed to

the participants. Yet just as Reed's explicit consent process was instituted in response to an earlier scandal, subsequent protective guidelines and regulations have been instituted in response to investigations that violated fundamental human rights and dignity. It is no exaggeration to say that research ethics—as a discipline that informs and responds to clinical and regulatory practice—was "born in scandal and reared in protectionism," to use Carol Levine's apt phrase.[4]

Part I of this book presents accounts and analyses of some of the most harrowing examples of the abuse of human beings in research, cases that continue to drive ethical debate and governmental policy today. Unlike the other parts of this volume, the selections presented here are not meant to engender discussion as much as to educate and inform. The question is not *whether* the examples discussed are morally justifiable, but rather *how* and *why* such events could ever have happened and, perhaps most important, how they reflect the larger social and ethical questions that have occupied clinicians, scholars, and regulators for more than 50 years.

In the aftermath of World War II, 23 Nazi doctors and bureaucrats were tried by the Allies at Nuremberg (West Germany) for using thousands of concentration camp prisoners as subjects in brutal experiments. The 1,750 victims identified in the indictment were a very small portion of those killed or injured, and the 23 defendants but a token assortment of those who conducted the experiments. In his opening statement before the Nuremberg Military Tribunal, Telford Taylor, a U.S. brigadier general and the chief counsel for the trial, outlined the studies that were performed.[5] The rationale for the experiments is impossible to understand unless one situates them within the context of Nazi Germany's overriding military aims and their efforts to achieve "racial hygiene."[6] While many of the brutalities visited on the Jews and other victims in the name of medical research are well known, they bear repeating:[7]

- *High-altitude (low-pressure) experiments:* Prisoners were put into low-pressure tanks to see how long they could survive with little oxygen. Many of those who did not die immediately were put under water until they died; autopsies followed.
- *Freezing experiments:* Prisoners were forced to remain outdoors without clothing in freezing weather for 9 to 14 hours, or were forced to remain in a bath of freezing water for three hours at a time. Rewarming of the bodies was then attempted, often without success.
- *Malaria experiments:* Prisoners were infected with malaria and then given a variety of supposedly antimalarial drugs. Many died from these drugs.
- *Mustard gas experiments:* Prisoners were deliberately wounded and the wounds then infected with mustard gas, or they were forced to inhale mustard gas. Experimentation with various treatments followed.
- *Sulfanilamide experiments:* Wounds were inflicted on prisoners, and bacterial culture, gangrene-producing culture, wood shavings, or glass shards were forced into the wounds, followed by treatment with sulfanilamide for wound infection. A control group consisted of prisoners who were subjected to the wounds and infections, but not given the sulfanilamide.
- *Typhus experiments:* Prisoners were injected with an antityphus vaccine and then infected with typhus. Prisoners in a control group were infected with typhus and received no treatment; others were infected with typhus simply to ensure that the typhus virus remained active within the prison camps.
- *Poison experiments:* Various poisons were fed to prisoners through their food. Most died immediately, and those who did not die were killed for purposes of autopsy.
- *Incendiary bomb experiments:* Prisoners were burned with phosphorus material taken from English incendiary bombs so that doctors could examine the wounds.
- *Sterilization experiments:* Because sterilization by surgical means was considered too costly and time-consuming, prisoners were subjected to chemical sterilization and x-ray sterilization experiments.

In addition to these experiments, hundreds of prisoners were killed in order to assemble a collection of skeletons for "anthropological investigation." Those killed were considered prototypes of what the Nazis called the "repulsive but characteristic subhuman."[8]

In addition to sentencing the accused the Military Tribunal judges articulated what came to be known as the Nuremberg Code (included in Part II of this volume). The Nuremberg Code, now the most widely known document on the ethics of research, included ten characteristics of acceptable research involving humans.[9]

It is at this point that our first contributors, Ruth R. Faden, Susan E. Lederer, and Jonathan D. Moreno, begin their analysis. Although now widely recognized as a landmark document, the Nuremberg Code did not provoke much of a response at the time that it was issued. Indeed, as Faden and her colleagues explain, the trial of the Nazi doctors had only modest resonance with the popular press and the medical establishment in the United States because their misdeeds were considered an anomaly attributable to a totalitarian regime of unquestionable brutality. The assumption was that researchers working in democratic countries would never do such things. Thus the Nuremberg Code was viewed as a document that was needed to restrain barbarians but was not applicable to "the rest of us."

Nonetheless, the basic tenets of the Nuremberg Code seemed to have an effect on U.S. governmental agencies. The administrators and advisors of the Atomic Energy Commission (AEC) seem to have been well aware of the trials of Nazi doctors then taking place at Nuremberg.[10] The AEC administrators were also aware of a set of secret experiments conducted during the war under the auspices of the Manhattan Project in which hospitalized patients were injected with plutonium, evidently without their knowledge.[11] The purpose of these experiments—publicly revealed only in the early 1990s—was primarily to assess and improve the safety of radiation workers and secondarily to evaluate the potential for the use of plutonium in the treatment of bone cancer. In December 1946, for example, the newly created civilian AEC suspended human studies involving the use of radioisotopes until it had the opportunity to set standards and approve the proposed research. Among the standards ultimately established by the AEC was "informed consent." This appears to have been the first time the term was used, well before its popular introduction in a 1957 malpractice case.[12]

The legitimacy of human experimentation was again questioned when research performed at the Brooklyn Jewish Chronic Disease Hospital came to light. In July 1963 a researcher at the hospital injected live cancer cells into debilitated elderly patients without their fully informed consent. The hospital was sued, and the New York state attorney general brought charges against two physicians involved in the study, Chester M. Southam and Emanuel E. Mandel. Our second selection in this part, as originally excerpted by Katz, Capron, and Glass, includes the court record of Southam's rebuttal to the charges against him, the testimony of a patient who was an unknowing subject in the study, and a news piece summarizing the findings of the trial involving Southam and Mandel.

As Southam explains, the aim of the experiment was to determine the rate of rejection of human cancer cells injected into patients. All evidence available suggested that the cancer cells would cause an immune reaction that would lead to their expulsion from the body; the experiment thus presented no risk to the subjects. In fact, Southam argues, informing the patients of the details of the experiment would have caused them needless psychological distress, and his failure to inform them was a result of the need to minimize the risks to his subjects. Yet critics argued otherwise. Although the so-called therapeutic privilege *might* justify nondisclosure in a physician-patient relationship, the Board of Regents of the University of the State of New York argued that it could not justify nondisclosure in a researcher-participant relationship. One of the lessons that emerged from this case was that a physician-researcher may have conflicting loyalties that are of ethical importance. The Board of Regents thought so and therefore suspended the licenses of Mandel and Southam for a year. This action presaged demands for greater accountability on the part of medical researchers.

In 1966, when Henry K. Beecher, a professor of anesthesiology at Harvard Medical School, published the landmark article "Ethics and Clinical Research" in the *New England Journal of Medicine,* ethical issues in research began to take center stage. In his article, which we excerpt here, Beecher describes 22 studies that he claims violated the basic standards of ethical research with human beings. What was so shocking at the time was that these experiments were performed by respected investigators at leading medical institutions and were published in reputable medical journals. The research performed at the Jewish Chronic Disease Hospital is one case that Beecher cites. Others include a study in which investigators withheld penicillin from soldiers with strep throat infection, even though they knew there was a risk that the soldiers would develop rheumatic fever and die from valvular disease, and research on physiology that involved the insertion of a needle into the left atrium of the heart during bronchoscopy, with unknown risks and no benefits for the participants.

One of the more infamous cases Beecher discusses is the Willowbrook study, in which researchers deliberately exposed children and adolescents with disabilities to hepatitis at a New York state facility. The aim of the study was to find a preventive measure for the hepatitis that was epidemic in the institution. But critics claim that the conditions under which the children were recruited were coercive: The wards of the public facilities were closed to any new admissions

due to overcrowding. Parents of the children with severe disabilities who were on the waiting list were mailed a letter indicating that their children could be admitted if they were placed in the research ward, and that they could then be transferred into the facility. Writing in his own defense, Saul Krugman, the head of the distinguished research team that conducted the study, noted that nearly every child admitted to the facility was likely to contract hepatitis anyway and that this fact mitigated the harm of deliberately exposing the children to hepatitis, as the research required.[13] Indeed, from the time that the research had been initiated at the facility the rates of hepatitis had declined substantially, making it safer than before the research started. Furthermore, Krugman argued, consent to the children's deliberate exposure in the study was obtained from their parents. In addition, the protocol had been reviewed by various university and state government entities, as well as by the Armed Forces Epidemiological Board, which funded the study. But critics argued that because the study population consisted of children with severe retardation whose parents wanted to place them in one of the few public institutions available, the consent obtained was invalid.[14] Krugman protested that the fact that the children had mental retardation was beside the point, but critics argued that it was precisely the point.

Beecher's aim was not to condemn individual researchers but rather to draw attention to serious ethical problems in the conduct of research with humans. Although the prevailing view at the time was that adherence to the Nuremberg Code was unnecessary for conscientious researchers in democracies, Beecher's examples clearly belie this belief. However, Beecher concluded that two things were indispensable for ethical research: informed consent and, more important, a virtuous investigator. His emphasis on the latter requirement suggests that Beecher himself viewed a code of research ethics as of secondary importance.

By the late 1960s medical research involving humans had undergone so many scandals and tragedies that distinguished physicians found it necessary to defend it, mainly by invoking utilitarian considerations. In *Science* Leon Eisenberg, a prominent psychiatric researcher, reminded Americans of the economic and social costs of disease and death, costs that eminently justified human experimentation in spite of the inherent limitations of the informed consent ideal.[15] In addition, citing the Reed example, Walsh McDermott wrote, "Medicine has given to society the case for its rights in the continuation of clinical investigation." McDermott believed that "playing God" was an unavoidable responsibility, presumably one to be shouldered by clinical investigators.[16] Similarly, in 1971 Louis Lasagna posed the rhetorical question, "How many of medicine's greatest advances might have been delayed or prevented by the rigid application of some currently proposed principles to research at large?" Lasagna claimed that "for the ethical, experienced investigator no laws are needed and for the unscrupulous incompetent no laws will help."[17]

Yet only a year after Lasagna's defense of research, the wholesale violations of human rights in the Tuskegee Syphilis Study were revealed.[18] As Allan M. Brandt, our final contributor to Part I, recounts, the study was initiated in 1932 in Macon County, Alabama, in order to assess the natural course of syphilis, which had reached epidemic proportions in African American males in that area. Many researchers, Brandt points out, argued that there was no scientific rationale for the study in 1932 because the natural history of syphilis had already been elucidated by a study in Oslo at the turn of the century,[19] and treatment of latent syphilis was the standard of care. Yet over 400 men, mostly illiterate sharecroppers, were recruited for the Tuskegee study. They were not informed about the true nature of the study or about their condition, nor were their partners informed of their risk. When penicillin became publicly available in the late 1940s, the men were not given the opportunity to use it; in fact, efforts were made to ensure that the men did not receive treatment or become aware of it.

In 1972 press reports prompted the secretary of the Department of Health, Education, and Welfare to stop the study. By this time 74 of the subjects were still alive, and, as Brandt notes, "at least 28, but perhaps more than 100, had died directly from advanced syphilitic lesions." Some observers saw no particular cause for outrage over a project that had never been a secret governmental study. Others argued that the Tuskegee study exemplified a pattern of institutionalized racism in health care in a society that had been struggling with similar issues in housing, employment, and education. In the late 1970s compensation was authorized for the survivors and for the families of those who had died, but they did not receive a formal apology from the federal government until 1997. The apology, issued by President Bill Clinton, was accompanied by a $200,000 grant for the creation of the Tuskegee University National Center for Bioethics in Research and Health.

The Tuskegee Syphilis Study had wide repurcussions. In 1974 the National Research Act became law in the United States and led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, as well as the enactment of federal regulations governing research with humans. Another effect of the Tuskegee study was that it undermined the utilitarian justification of research as articulated by McDermott and Lasagna. Although there may be rare instances in which interventions can be justified on utilitarian grounds—for example, public health interventions undertaken to control an epidemic—such a justification is much harder to sustain in the case of nonemergency research with humans. Alan Donagan argued that, by the lights of the medical profession itself, the utilitarian attitudes exemplified by the Nazi experiments and the research conducted the Jewish Chronic Disease Hospital were unjustifiable. He delineated an alternative to the utilitarian justification of research in which informed consent was taken as nearly a self-evident moral obligation.[20] It is a supreme irony that in the 1960s and 1970s, a time when great advances were being made in medical research, scandals and tragedies were calling into question the ethics of such research. But as subsequent parts of the book demonstrate, this was just the beginning.

1. James Lind, *A Treatise of the Scurvy* (Edinburgh: Sands, Murray and Cochran, 1753).
2. Edward Jenner, *An Inquiry Into the Causes and Effects of Variolæ Vaccinæ* (London: Printed for the author by Sampson Low, 1798).
3. Lawrence K. Altman, *Who Goes First? The Story of Self-Experimentation in Medicine* (Berkeley: University of California Press, 1998).
4. Carol Levine, "Has AIDS Changed the Ethics of Human Subjects Research?" *Law, Medicine and Health Care* 16 (1988): 167–73.
5. Telford Taylor, "Opening Statement of the Prosecution, December 9, 1946," in *The Nazi Doctors and the Nuremberg Code,* ed. G. J. Annas and M. A. Grodin (New York: Oxford University Press, 1992), 67–93.
6. Robert N. Proctor, *Racial Hygiene* (Cambridge, Mass.: Harvard University Press, 1988); Michael Burleigh, *Ethics and Extermination* (New York: Cambridge University Press, 1997).
7. This is a summary taken from the Allies' opening statement at the Nuremberg trial; see Taylor.
8. S.S. Colonel Wolfram Sievers, as quoted in Taylor, 84.
9. A slightly abridged version of the final judgment is included in Annas and Grodin, 94–104.
10. Jonathan D. Moreno, *Undue Risk: Secret State Experiments on Humans* (New York: W. H. Freeman and Company, 2000).
11. Eileen Welsome, *The Plutonium Files* (New York: Delacorte Press, 1999).
12. *Salgo* v. *Leland Stanford Jr. University Board of Trustees,* 154 Cal. App.2d 560, 317 P.2d 170 (1957).
13. Saul Krugman, "The Willowbrook Hepatitis Studies Revisited: Ethical Aspects," *Reviews of Infectious Diseases* 8 (1986): 157–62.
14. David J. Rothman and Sheila M. Rothman, *The Willowbrook Wars* (New York: Harper & Row, 1984).
15. Leon Eisenberg, "The Social Imperatives of Medical Research," *Science* 198 (1977): 1105–10.
16. Walsh McDermott, "The Changing Mores of Biomedical Research: Opening Comments," *Annals of Internal Medicine* 67, Suppl. 7 (1967): 39–42.
17. Louis Lasagna, "Some Ethical Problems in Clinical Investigation," in *Human Aspects of Biomedical Innovation,* ed. Everett Mendelsohn, Judith P. Swazey, and Irene Taviss (Cambridge, Mass.: Harvard University Press, 1971), 109.
18. Susan M. Reverby, ed., *Tuskegee's Truths* (Chapel Hill: University of North Carolina Press, 2000).
19. E. Gurney Clark and Niels Danbolt, "The Oslo Study of the Natural History of Untreated Syphilis," *Journal of Chronic Diseases* 2 (1955): 311–44.
20. Alan Donagan, "Informed Consent in Therapy and Experimentation," *Journal of Medicine and Philosophy* 2 (1977): 307–29.