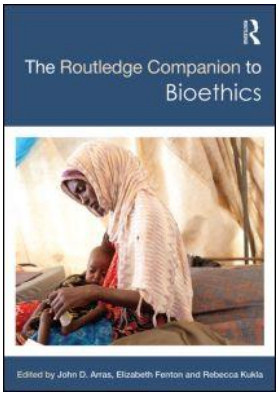

The Routledge Companion to Bioethics

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Part IV

RESEARCH

The ethics of biomedical research pits the personhood, the moral inviolability of the individual against the goal of scientific progress. Research is required not only to develop new cures for dread diseases but also to teach us which existing treatments and diagnostics are beneficial and which are useless or even positively harmful. Are good ethics and good science compatible?

At the beginning of the era of contemporary bioethics, this question focused on the moral necessity of obtaining research subjects' informed consent. The traditional view in medicine had been that physician-researchers should enjoy nearly complete discretion in determining how much information should be shared with prospective subjects and even whether subjects should be asked for their consent. As Jonathan Moreno and Dominic Sisti demonstrate, this longstanding professional prerogative was challenged and eventually overturned by a series of scandalous revelations of research abuses at Nuremberg, Tuskegee, and leading U.S. universities. These authors also show us how what began as a quite narrowly focused and straightforward question—namely, is informed consent a moral requirement of ethical research?—has exploded into a highly variegated set of complex and morally contentious questions: e.g., is the randomized clinical trial (RCT), the current "gold standard" of evidence in biomedicine, compatible with good ethics? Who should be asked to participate? Should monetary incentives be offered to increase enrollment, or would this be "coercive"? Should certain categories of "vulnerable" subjects—e.g., prisoners, children, pregnant women, the poor—be afforded special protections? Are such protections compatible with equitable access to participation in research? Moreno and Sisti also note that biomedical research, formerly a kind of localized cottage industry, has gone global in recent decades, making possible important advances in our knowledge of genetics and pharmaceuticals but also posing serious problems for the ethical conduct and oversight of research in the developing world.

The compatibility of rigorous research design and good ethics is a central concern for the conduct of biomedical research today. How can the key structural ingredients of the RCT, such as randomization, the blinding of subjects and researchers, and placebo controls—i.e., features of the RCT designed to eliminate or reduce biases that can degrade the results of research—be squared with the physician-researcher's fiduciary duties of loyalty to the health and welfare of the individual patient-subject? Charles Weijer, Paul Miller, and Mackenzie Graham argue that good science is indeed compatible with a rigorous, non-utilitarian ethic of patient protection.

Although obtaining research participants' informed consent is now universally regarded as a requirement of ethical research, it is less clear whether informed consent,

as currently practiced, actually succeeds in meeting its original goals of precluding abusive research and enabling participants to make informed decisions. Indeed, many empirical studies have shown that increasingly lengthy consent forms can impede genuine understanding of the goals and most salient risks of research protocols. Moreover, the current practice of consent does little to alleviate the so-called "therapeutic misconception"—i.e., tendency of potential research subjects to assume that the goals and methods of RCTs exist for their own individualized benefit. This confusion is problematic because it means that potential research participants often agree to join studies without a genuine understanding of what they are doing. Paul Appelbaum contributes a helpful history of informed consent in the research context as well as an alternative model of consent that might solve the problems of information overload and the therapeutic misconception.

Issues of informed consent also loom large in particular areas of biomedical research, such as genetics and genome studies, that hold great promise for our understanding of many diseases. Such research is based on tissue samples that can be stored indefinitely, shared with other researchers, and reexamined in future research projects having little, if any, connection to the study for which the tissues were originally obtained. Thus, in addition to the usual problems of informed consent, genetic research poses novel problems relating to unanticipated future uses of stored samples. When we sign onto any given genetics research project, are we consenting to the use of our tissues exclusively within this particular study, to any and all uses of our tissues in a vast array of unrelated studies in the near and distant future, or perhaps only for certain kinds of research on certain kinds of problems, excluding uses that we might find morally objectionable? Such questions, as well as the threats of genetic research to personal privacy, are addressed in Dena Davis's chapter.

The field of research ethics was "born in scandal, and raised in protectionism." The dominant ethos at the birth of contemporary bioethics was one of protecting vulnerable parties—e.g., prisoners, children with mental retardation, pregnant women—from the risks of research participation. This ethos was challenged during the 1980s by advocates for people with HIV/AIDS, women, and children who began to view participation in research as a benefit, and categorical exclusion from research as a violation of justice. Toby Schonfeld surveys the history of this problem and offers a useful analytical framework for more nuanced and respectful approaches to worries about vulnerability.

A related question in research ethics concerns the use of various incentives, including money and medical care, to facilitate greater participation in studies. One proposed remedy for this situation is to make participation more attractive by paying participants extra money or offering access to medical treatments unavailable to them off trial. Such an approach has been resisted by many in the bioethics community as being either coercive, an undue inducement, or exploitative of poor and sick populations. Alan Wertheimer argues that many, if not most, of such criticisms are either mistaken or misapplied.

Finally in this section, Tom Beauchamp tackles the controversial issue of the use of animals in biomedical research. Key questions here focus on the moral status of different species of animals, gauging their most important interests, and discerning how best to protect those interests in research. The most important question, however, is exactly how research on animals might be ethically justified. How much pain and suffering do various kinds of studies inflict? What are the realistic prospects of human benefit, and is research on animals strictly necessary to achieve such benefits?

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BIOMEDICAL RESEARCH ETHICS

Landmark Cases, Scandals, and Conceptual Shifts

Jonathan D. Moreno and Dominic Sisti

Introduction

Charting the history of biomedical research ethics is as much an exercise in reporting a litany of past scandals as it is an examination of shifts in scientific, political, and broader cultural mores. In this chapter, we provide a brief accounting of both by describing landmark cases and how reactions to these cases gave purchase to significant conceptual shifts in the ethics of human subjects research.

To do this, we first present a typology for these cases, which, we should note, is neither strictly chronological nor exhaustive. We begin by describing several infamous scandals in the history of research ethics, such as the experiments conducted on prisoner-victims by the Nazis, the examples inventoried in Henry Beecher's seminal paper, "Ethics and Clinical Research" (Beecher 1966), and the Tuskegee Syphilis study.

From there we present three groups of cases. The first group is culled from findings related to the research conducted by the U.S. and British military from the 1940s through the 1970s. We highlight the work of the Advisory Committee on Human Radiation Experiments, a commission created by President Clinton and charged with the investigation of experiments conducted by half a dozen government agencies on unsuspecting persons.

The second group of cases features examples from psychiatric, psychological, and social science research. These include the well known Milgram Obedience Study and the Stanford Prison Experiment, illustrating the ethically fraught practice of deception in social science research as well as investigator–participant role conflicts.

In the third set of cases, we describe more recent incidents, including the death of Jesse Gelsinger in a 1999 gene therapy experiment. Issues here related to lapses in informed consent, protocol adherence, subject selection, and concerns about financial conflicts of interest. Again highlighting the role of federal ethics committees, we discuss recent revelations concerning the sexually transmissible disease (STD) experiments conducted in Guatemala in the late 1940s in this section as well.

We chose these cases to bring into conceptual relief several key developments in biomedical research ethics. First, as a result of the early scandals, a moment of clarity occurred revealing voluntariness as a necessary but not sufficient condition for ethical research. This now-seemingly common sense notion was not universally apparent to the practitioners of biomedical science prior to 1960. Second and more fundamentally, as we will see, the principle of respect for persons was precipitated by legal issues and, in reaction, theoretical discussions among philosophers as the early bioethicists applied it to bio-behavioral research.

Third, we also find that the scientific enterprise, in general, and human subjects research, specifically, have been transformed from protected activities shielded by the elite status of medicine into a more transparent and publically accountable activity. The advent of human subjects protection rules and committees provided unprecedented power to both the government and the lay public to check the ambitions of scientists.

Finally, the historical arc presented here reveals that the ideals of informed consent and respect for persons—arguably the most fundamental touchstones of American biomedical ethics—are pockmarked with both conceptual ambiguity and practical challenges that make their full realization difficult, if not impossible. These conceptual and theoretical lacunae set the stage for ongoing and future challenges in human subjects research. We conclude by prognosticating about issues on the horizon of research ethics.

Early Scandals

Holocaust-Related Experiments

The atrocities perpetrated by Nazi physicians and scientists are extensively documented (Annas and Grodin 1992; Caplan 1993; Lifton 2000 [1986]). Although these atrocities represent the coalescence of political, social, and scientific ideologies, distinct research programs were designed and executed to support particular military goals, to reinforce claims of Nazi superiority, and to investigate particular "scientific" interests of SS researchers (*U.S. v. Karl Brandt et al.* 1947).

From 1940 to 1945, thousands of victims were culled from concentration and work camps. They included Jews, Roma, Poles, and others who were deemed "scientifically" appropriate subjects or—in the parlance of the efficiently orchestrated Nazi "euthanasia" program— "lives not worthy of life."

On the military research track, victims were forced into cold water and extreme barometric exposure trials. Led by Sigmund Rascher, the researchers at Dachau presided over experiments aimed to better understand the physiology of hypothermia in support of the Luftwaffe, as German pilots were being increasingly shot down or shipwrecked in frigid waters (Berger 1990). In a related episode, 100 victims were forced to drink seawater to observe the impact of extreme dehydration and test new desalination methods (Katz 1992b).

As Lifton describes, experiments were also conducted that were "a direct expression of racial theory and policy" (Lifton 2000 [1986]: 267). For example, at Auschwitz's notorious Block 10, Carl Clauberg conducted mass sterilization experiments of racially "inferior" female prisoners, which involved the injection of caustic compounds into the cervix to block the fallopian tubes (Proctor 1992). Similarly, Horst Schumann implemented X-ray and surgical castration protocols. Of the approximately 1000 victims, all

were left severally maimed or shuttled to the gas chambers and killed (*U.S. v. Karl Brandt et al.* 1946).

Josef Mengele perpetrated the most infamous Holocaust-related experiments. Mengele's studies of identical twins at Auschwitz were an extension of his previous heredity and morphology evaluations conducted under the direction of Baron Otmar von Vertschuer, with whom he worked in the racial courts established by the Nuremberg race laws (Seidelman 1988). At Auschwitz, Mengele was the medical gatekeeper. He selected research subjects for any number of experimental protocols, determining who would be sentenced to the brutality of the Nazi scientific enterprise, to slave labor, or sent to die in the gas chambers.

The curiosities of Nazi doctors were satisfied in a number of horribly strange experimental programs that seemed to be motivated as much by pseudoscientific ambition and a distorted notion of public hygiene as by military strategy or Nazi ideology. Certainly, many of Mengele's twin studies fit within this rubric. These included injecting colored dyes into the eyes of twins to see if eye color would permanently change and the sewing together of twins in an attempt to conjoin them. Mengele was never tried for his crimes. He spent his post-war life in hiding in South America, evading justice.

In the end, as Annas and Grodin (1992) point out, the horrors of Nazi medical research represented several recurrent perverse motivations: The dehumanization of particular members of society, the medicalization of social and political problems, the political indoctrination of physicians, and lack of concern for human rights. Nazi doctors saw their role as physicians not of individual patients but of the Reich, which was existentially threatened by Total War (Caplan 2007). This belief led the Nazi doctors to justify their actions by appealing to both the doctrine of "superior orders" (that they were obliged to those above them in the chain of command) and to a crude utilitarianism that in war some must be sacrificed for the good of the state.

The Nuremberg Trial and Code

"The voluntary consent of the human subject is absolutely essential" (*U.S. v. Karl Brandt et al.* 1947). So reads the first sentence of ten provisions of what posterity has come to know as the Nuremberg Code, promulgated by the three-judge panel in their ruling at the Nazi Doctors trial, delivered in August 1947. The Nuremberg Code represented the embodiment of principles that were thought by the judges to be implicitly accepted by medical researchers.

Of the twenty-three defendants on trial, sixteen were found guilty, and seven of those were executed. In a surprising reversal, the defense argued that the Allies had conducted similar human experiments with prison populations. The claims were accurate (and in fact certain other Allied experiments were not discovered until decades later), but ultimately the court found that the Nazi experiments were uniquely barbaric (Moreno 2000). Ultimately, the defendants were found guilty of murder, not for the violation of research ethics.

Moreover, the prosecution struggled to cite any formal research ethics code with jurisdiction over the conduct of Nazi researchers, with the exception—perhaps ironically—of those previously promulgated in Germany (Katz 1996; Sass 1997). This void prompted Dr Andrew Ivy, the prosecution's primary medical expert witness, to urge the American Medical Association to adopt his proposed principles of research ethics,

which were ratified by the AMA shortly after the trial began and to which Ivy pointed as evidence of prevailing ethics conventions in his testimony (Shuster 1997).

The legacy and impact of the Nuremberg Code on research ethics in the United States continues to be debated. On the one hand, some have argued that, as a matter of historical fact, the Code exerted little practical influence on American researchers, who initially considered "it a good code for barbarians but an unnecessary code for ordinary physicians" (Katz 1992a). In fact, Henry Beecher, himself an icon of research ethics, as we shall see below, expressed reservations about the usefulness and appropriateness of the Code in American research universities (Beecher 1959).

On the other hand, as Faden et al. (1996) state, "the Nuremberg Code stands alone as the most eloquent and principled statement of the significance of human rights in the conduct of research involving human subjects." As such, the Code laid the conceptual foundations for a half-century of research ethics innovations both directly and as a result of reaction to it. For example, physician researchers of the World Medical Association, who were skeptical of the usefulness of the Nuremberg Code—and who perhaps wished to preserve the prerogatives of physicians in framing medical ethics—developed and adopted the Declaration of Helsinki in 1964 and amended it six times. The Declaration is a highly influential set of global standards, but to its detractors it serves as "recommendations by physicians for physicians" (Annas 1992).

Beecher's Inventory

Neither international conventions nor codes of ethics—whether from Nuremberg, Geneva, or Helsinki—proved sufficient to prevent abuses perpetuated throughout the next half century. Harvard anesthesiologist, Henry Knowles Beecher, provided the first inventory of such abuses in his seminal paper, "Ethics and Clinical Research" (Beecher 1966).

In this brief article, Beecher first reiterates his concerns about the applicability of codes of ethics that naively demand full consent, as if it is "readily available for the asking." He instead espouses a model of virtue ethics for biomedical researchers, according to which a "*responsible* investigator" is a "far more dependable safeguard" than consent guidelines (Beecher 1966: 1355; italics in original). But because consent information was not normally reported in published accounts, Beecher's list of 22 ethically compromised experiments focused on those that were scientifically questionable in design, carried a high ratio of risk to benefit, employed bizarre methods, and, most importantly, placed vulnerable subjects at extreme risk for no justifiable therapeutic purpose (Levine 1986).

Beecher referred to one study that did in fact involve questionable consent. Example 16 involved the inoculation of cognitively disabled children with hepatitis who lived in an institution where the disease was endemic. Beecher questioned the validity of the parents' consent, a concern that would be vindicated, as the details of this study were uncovered over the course of the next decade that we now know as the Willowbrook Hepatitis Study.

Willowbrook

In 1954, Dr Saul Krugman, an infectious disease researcher from New York University, began to study hepatitis within the population of children living at the Willowbrook

State School for children who were mentally disabled on Staten Island, New York. The study involved exposing subjects to hepatitis, ostensibly in order to devise preventative measures for the disease, which was endemic in the institution particularly due to its squalid condition.

Critics of the study reiterated Beecher's concern about the means by which the study was conducted—that children who were mentally disabled were intentionally and unjustly harmed for the sake of science—and they argued the consent procedures were coercive. There was a long waiting list for admission to the school and parents who agreed to enroll their children in the study were granted admission. This inducement was viewed as undue and extreme and invalidated the consent process (Rothman and Rothman 1984).

Krugman (1986) contended that his research was ethically justifiable since the study risks were equal to the inevitability of children contracting hepatitis. Moreover, he claimed that carefully controlled inoculation of the virus increased the likelihood of a subclinical manifestation of symptoms, which could bestow immunity later in life. Krugman also insisted that the consent procedures were carefully designed and vetted by all appropriate regulatory entities and endorsed by subjects' parents (Emanuel et al. 2003). Indeed, Krugman found support not only among his professional and scientific boosters and funding agencies, but also the Benevolent Society of Retarded Children—a parents' advocacy group that lauded Krugman's "distinguished, pioneering, humanitarian research in the prevention of infectious disease and their resultant complication in children, born and unborn" (Krugman 1986: 162).

The controversy generated by the Willowbrook Hepatitis Study points to fundamental disagreements over the essential elements of surrogate consent for vulnerable and incapacitated persons. While most would agree that voluntariness is an essential element, ascertaining the limits of subjects' or surrogates' free choice within the context of real world pressures is often exceedingly difficult. Nonetheless, there is a broad if not universal consensus that the Willowbrook Hepatitis Study was patently unethical because of the duress under which the parents agreed to their children's participation.

Jewish Chronic Disease Hospital

Example 17 of Beecher's inventory was the soon-to-be infamous case involving two physicians who injected cancer cells into terminally ill patients at the Jewish Chronic Disease Hospital in Brooklyn, New York. The aim of the study was to examine patients' immune response to foreign cells. Twenty-two patients were never told that they were research subjects and that they were being injected with "live cancer cells." Dr Chester Southam, the study's primary investigator, recounted that a full explanation had been given to patients in the early years of the research, but that,

> . . . as our body of knowledge has increased and the course of reaction to the injections became more predictable, we have simply explained that the procedure was a test which had nothing to do with treatment, that it involved the injection of foreign material, described the expected course of reaction, and that its purpose was to determine the rate at which the expected nodules would develop and then regress.
>
> (Arras in Emanuel et al. 2003)

Southam articulated an unequivocal position in favor of *therapeutic privilege*—the withholding of medical information from patients by physicians (or researchers) because they believe that such disclosure would somehow harm the patient:

> Unless the patient inquired, we refrained from describing the precise nature of the human cells for the reason that in my own professional judgment as well as that of my professional colleagues . . . the precise nature of the foreign cells was irrelevant to the bodily reactions which could be expected to occur . . . Furthermore, in my own clinical judgment . . . to use the dreaded word "cancer" in connection with any clinical procedure on an ill person is potentially deleterious to the patient's well-being because it may suggest to him (rightly or wrongly) that his diagnosis is cancer or that his prognosis is poor . . . I believe such revelation is generally contraindicated in the best consideration of the patient's welfare and therefore to withhold such emotionally disturbing but medically nonpertinent details (unless requested by the patient) is in the best tradition of responsible clinical practice.
>
> (Emanuel et al. 2003)

We also find here the commingling of the therapeutic and research roles by clinicians—a role conflict that is ethically problematic precisely because the duties each role entails are at times directly opposed. For example, physicians, when acting as researchers, are appropriately concerned with the advancement of biomedical science and the treatment of future patients; but when acting in their capacity as clinicians, physicians have a strict duty to advance the best interests of their particular patients. We will see similar role conflicts and their ethical consequences in future cases.

U.S. Public Health Service Syphilis Study

Starting in 1932, the U.S. Public Health Service Syphilis Study (better known as the Tuskegee Syphilis Study) spanned the entire period of the above episodes in research ethics. In fact, the study went on for four decades, and although it was conducted openly and generated several publications, it ended in 1972 only when it was exposed by the popular press.

Dr Taliaferro Clark, Chief of the U.S. Public Health Service, devised the study as a way to learn about the life history of untreated syphilis among black men. He decided that Macon County in rural Alabama would be the ideal location to conduct the study because of the high incidence of untreated syphilis there. As Brandt (1978) argues, the belief held by researchers that black men suffering from syphilis would not avail themselves of treatment, even if available, was a self-fulfilling prophesy steeped in racist ideology. Note that arguments that appeal to the "inevitability" of disease are similar to those made by Krugman in his "natural history" study of hepatitis (Rothman 1982).

The study conscripted 399 black men who had syphilis and, to serve as the control group, 200 who were not infected. Throughout the research, subjects were subjected to spinal taps and physical examinations under the ruse that they were being treated. In the early part of the study, a treatment regime involving heavy metal injections was available but denied to participants of the study. Macon County served as the observatory for untreated syphilis even after penicillin was discovered to cure the disease. Throughout the study, local African American physicians continued to conspire with researchers in denying subjects penicillin.

In the end, 128 men had died of syphilis or complications, 40 wives were infected with syphilis and 19 children were born with the disease. Uproar was sparked by a story in the *Washington Star*, which stimulated political investigations and action that led eventually to the Belmont Report, Common Rule and, much later, an apology and reparations from President Bill Clinton.

It is widely thought that Tuskegee continues to foment and reinforce deep mistrust of medicine and biomedical research among black Americans, but data on the scope of this phenomenon are equivocal (Katz et al. 2006; Wendler et al. 2005). However, it is indisputable that the Tuskegee Syphilis Study represents one of the worst ethical lapses in the history of American biomedical research and stands out as the case that has had the most influence in the reform of ethics standards. The fact that it spanned such a long period and so clearly violated basic principles of medical and research ethics—even while they were being formulated at Nuremberg—illustrates that the American biomedical enterprise was largely shielded from ethical scrutiny. This would change in coming years as Presidential commissions were formed to examine not just Tuskegee but also military experimentation, the topic of our next section.

Military Research

Imperial Japanese Experiments

While the Nazi atrocities of World War II received substantial attention in the West, little attention was paid to the lethal wartime human experimentation conducted by the Imperial Japanese army. Officially the Water Purification Bureau, the construction of the Ping Fan prison complex was completed in 1939 and housed in excess of 1,000 human experimental subjects. Later known infamously as Unit 731, this complex was the site of substantial biological and chemical warfare research. The experimental subjects, predominantly Han Chinese and Soviets, were often prisoners or civilians and included both men and women. From 1939 to 1942 they were subjected to horrendous biological and chemical weaponry testing.

Prior to experimentation the subjects were fed well and generally kept in good health; they also received medical treatment following the completion of successful experimentation. However, the health of the subjects was important to the Imperial Army only insofar as healthy subjects yield superior results. Cyclic experimentation of subjects was therefore continued until the subject was too weak to yield reliable data. Many subjects died during the course of experimentation, while survivors were subsequently killed by poison injection. Subjects were inoculated with any number of diseases, often including anthrax, plague, and/or cholera. Similarly, experiments reminiscent of those conducted in Nazi Germany—for example frostbite studies—were undertaken.

Impressing his superiors in the Imperial Japanese military with preliminary biological warfare experimentation, General Shiro Ishii, chief medical officer, received authorization for the initial construction of Unit 731 and the undertaking of the human experimentation trials. The trials resulted in the subsequent death or intentional extermination of at least 400–600 Ping Fan prisoners a year; the uneven accuracy of the records kept makes precise estimates beyond these figures impossible. Additionally, it is believed that at least 1,485 British, American, Australian, and New Zealand Prisoners of War (POWs) were forced to drink liquids containing a number a pathogens for further human experimentation.

Despite the atrocious level of violence towards human prisoners exercised by Ishii, the U.S. was initially consciously inattentive. Decisions were made by American officials to avoid a war crimes investigation or a compromise of their own biological weapons experimentation. However, following the occupation of Japan and the accumulation of a growing body of evidence, American officials finally prepared charges against Ishii and fellow Unit 731 researchers and conducted a series of interrogations.

As international relations between the U.S. and the Soviet Union began to deteriorate, military intelligence ultimately granted Ishii immunity in exchange for the information previously obtained from Unit 731 warfare experimentation. Despite the insistence that Unit 731 bore information crucial for U.S. intelligence, and the eagerness of American officials to be privy to this information, it became apparent that Unit 731 was unable to discover little more than what had already been learned in the U.S. Subsequently, American officials were concerned less with ethical ramifications than with potential embarrassment if the deal were publicized.

The Plutonium Injections

The bombings of Hiroshima and Nagaski in 1945 during the final days of World War II were the result of significant military funding, known as The Manhattan Project. Manhattan Project scientists were directed by the White House to manufacture nuclear weaponry by January of 1945. It was unlikely that sufficient uranium-235 could be obtained and used to create any more than one atomic bomb by that date, so the managers of the project explored alternative sources of fissionable energy. In 1941 a solution was obtained through the creation of plutonium from uranium. Plutonium could both sufficiently power an atomic bomb and be generated in substantial quantities—with production likely to meet the required deadline.

In light of this discovery, concerns were raised about the risks faced by plutonium workers, given that they were exposed to high levels of plutonium dust and that nothing was known about this newly created and potentially poisonous substance. Following six accidents involving exposure of researchers to plutonium during animal experiments, and only a year until the urgent Manhattan Project deadline, it appears that Manhattan Project director J. Robert Oppenheimer endorsed human experimentation.

The first human trial did not occur until April 1945. Ebb Cade, a 43-year-old cement worker, was brought into the Manhattan Army Project Hospital in March 1945, suffering broken bones in three limbs following a car accident. Requiring several surgeries to set the bones and a number of weeks in hospital, Cade became "Human Product 1." Without his knowledge or consent Cade was injected with 4.7 micrograms of plutonium. Acting physicians were instructed not to divulge the names of the institutions from which they received the plutonium; indeed, the very word *plutonium* was classified until the bombings of Japan in August 1945.

The second and third subjects selected were both patients with carcinoma at the University of California's hospital; like Cade, they were long-stay patients. San Francisco researchers have since claimed that their interest in these patients extended beyond the Manhattan Project, and that they believed plutonium may confer help in the treatment of cancer. Later investigation by the University of California revealed that these subjects could not have benefitted from the injections, nor were they expected to. Fourteen additional patients were subjected to plutonium injections at the Universities of

California and Rochester during wartime, along with one additional patient at the University of California following its cessation.

In October 1995 Clinton's Advisory Committee on Human Radiation Experiments concluded that all but the final subjects were not aware that they were part of experimental procedures relating to the development of the atomic bomb. The plutonium trials raised significant issues of consent, with experiments failing to meet even the most modest ethical expectations for human subjects research. Similarly, when no longer overshadowed by the necessity of wartime—as in the case of subject eighteen—the plutonium trials raised concern regarding the limitations of human experimentation in the U.S.

The Maddison Case

In some instances decades are required for information about unethical human experiments to become available to scholars, especially when the activities take place under the cover of national security. For legal and political reasons, the U.S. has been the site of most of the cases uncovered since World War II. One exception is the series of sarin gas experiments undertaken at Porton Down in the U.K. during the 1950s (Schmidt 2006).

In 1953 a 20-year-old Royal Air Force engineer named Ronald Maddison was one of the servicemen exposed to the lethal gas. He was the only one out of hundreds of test subjects to die in the experiment, a death that was covered up by the Ministry of Defense (MoD). Responding to repeated allegations and rumors in the decades following chemical weapons experiments in the U.K., especially from veterans and their families, a British judge quashed the MoD's original inquest finding in 1953 as "death by misadventure."

Following a new inquest fifty-one years after Maddison's death, in February 2006, the MoD and Maddison's family settled on the charge of "gross negligence." After this ruling, Porton Down veterans filed claims relating to Cold War experiments. The House of Commons agreed to a compensation package worth about $5 billion and an apology in 2008 (Schmidt 2006).

Behavioral and Social Science Research

National Commission Reports

Several of the reports promulgated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research focused on research involving mentally ill persons.

In its 1975 report, *Psychosurgery*, the Commission investigated the use of surgical procedures aimed at "controlling, changing, or affecting any behavioral or emotional disturbance of such individual[s]." Public concern about the misuse of psychosurgery intensified in the late 1960s, as both researchers and the lay press began to publish accounts of the haphazard use of psychosurgery. Popular worries were stoked by books and films centering around the use of psychosurgery for social control, such as Stanley Kubrick's *A Clockwork Orange*, Ken Kesey's *One Flew Over the Cuckoo's Nest*, and Michael Crichton's *The Terminal Man*.

The key ethical issue considered in *Psychosurgery* was the scientific merit of the surgical procedures in increasingly common use. Although surgeons considered psychosurgery to be a therapeutic device, the Commission argued it ought to be "considered experimental and should be conducted within the context of research, subject to all review

provisions and procedures for the protection of human subjects which that implies" (page 10). Indeed, most research had been performed in the context of clinical practice—there were no protocols, ethics reviews, or systematic evaluation of outcomes—using questionably competent research subjects.

In *Research Involving Those Institutionalized as Mentally Ill* (1978) the Commission explicated a set of five comprehensive recommendations for guiding the conduct of research on mentally ill subjects. These recommendations included several criteria to guide IRB review, including clear directives about research involving more than minimal risk to subjects, and recommendations for elevating review to a national board in very specific circumstances. Many of the theoretical underpinnings and practical applications outlined in these reports would be embodied in the *Belmont Report* (1979).

Deception and Forbidden Knowledge

As scrutiny of research involving mentally ill persons increased, ethically fraught psychological research on healthy volunteers continued to attract attention and criticism. These studies involved deception or unauthorized surveillance—methods that continue to be used and are considered permissible in very specific contexts (American Psychological Association 2010). Studies that employ deception involve a basic conflict—or balancing—between utilitarian aims and the deontological duty of veracity (Pittenger 2008).

For example, the Yale psychologist Stanley Milgram conducted an experiment in which subjects were misled to think they were enrolling in a study on the effect of punishment on memory and learning (Milgram 1963). In an elegantly designed protocol, naïve subjects were told they were "teachers" whose job it was to punish "learners" with increasingly high voltages of electricity whenever learners made mistakes in a memory test. The learners were experimental accomplices and actors, who expressed pain and suffering as subjects (i.e., the "teachers") inflicted fake electric shocks. Experimenters prodded the subjects to increase the strength of the electrical shocks despite learners' faux cries and pleas to stop the experiment. A majority of subjects, although visibly disturbed, deeply conflicted, and seriously stressed, obeyed the orders of the experimenter and increased the voltage to what would have been extremely high and possibly lethal levels (450 volts).

According to Milgram, the experiment pointed to conflicting tendencies of human nature—the intrinsic tendency to avoid harming others was in conflict with the disposition to respect and obey persons of authority. In this case, the latter tendency won out. The findings of the Milgram Obedience study, along with video footage of the experiment, raised issues about the ethical permissibility of deception of psychological research subjects, particularly in experiments that may reveal disturbing facts or behavioral dispositions. Although the point of the study was to assess the extent to which "ordinary" people might be induced to engage in sadistic acts, it seemed to many that the experimenters themselves were behaving in a sadistic manner by implementing an experimental design that could traumatize the subjects if they came to see themselves as easily manifesting cruelty.

Similarly, the Stanford Prison experiment, conducted by Philip Zimbardo in 1971, revealed a disturbing tendency of individuals to abuse authority, while others submitted helplessly to their abuse. Zimbardo randomly assigned research subjects to one of two roles—prison guard or prisoner—and then allowed each group to act out their roles in a

mock prison. The experiment lasted only six days, as it became clear that the study had taken on a life of its own, with guards verbally abusing and humiliating prisoners. Even Zimbardo—acting in a conflicted role as prison superintendent—allowed abuse of prisoners to continue. Christina Maslach, a graduate student who would later marry Zimbardo, urged him to stop the experiment after she witnessed the guards abusing prisoners (O'Toole 1997).

The paradigmatic example of behavioral research involving not only deception but also unauthorized surveillance was Laud Humphreys' ethnography of anonymous homosexual encounters that transpired in public restrooms between men. To study this sexual practice—the so-called "Tearoom Trade"—Humphreys impersonated the "watchqueen" who was the third man meant to be a lookout for the other two men engaging in sex. In this role, Humphreys was able to observe and document their behavior, collect their license plate numbers, and identify them in the community. Humphreys then interviewed them under the guise of a health service researcher. He reported his results in his book *Tearoom Trade: A Study of Homosexual Encounters in Public Places* (1970).

The results of Humphreys' study were significant in raising awareness about the nature of sexuality and public versus private personas. Serious ethical concerns were raised about Humphreys' study on the grounds that he had never received consent from his unknowing subjects, that he invaded their privacy by identifying them, and that he lied to subjects about his role and the intent of his interviews. Deception is still viewed as an indispensable tool of much social science research. The deontological concerns raised by critics—e.g., that deception was incompatible with treating subjects as autonomous agents—do not seem to have resonated with social psychologists, many of whose research agendas are based on deceptive practices.

Recent Cases and the Future of Research Ethics

The Case of Jesse Gelsinger

On September 17, 1999, Jesse Gelsinger, an 18-year-old participant in a gene therapy trial at the University of Pennsylvania, died after receiving an experimental adenovirus vector designed to deliver genetic material to treat a metabolic condition. Gelsinger's death triggered a new round of political, scientific, and ethical investigation into deficiencies in subject protections practices across the entire American biomedical research enterprise (Walters 2000). At least three important ethical issues emerged from the Gelsinger affair. The first issue related to the selection of subjects for the experiment. Debate ensued about placing relatively healthy adults such as Gelsinger at unnecessary risk in this phase I trial to test safety. While some argued that newborns with the lethal form of the disorder would have been more appropriate research subjects, others contended that parents of such severely ill newborns could not adequately provide consent without erroneously expecting a therapeutic benefit (Sisti and Caplan 2003).

The second issue concerned the investigators' informed consent procedures, their adherence to the approved protocol, and general problems in study management and oversight. Gelsinger had not been told about problems related to the adenovirus vector found in pre-clinical animal trials and with other research subjects. Animal data are not typically part of informed consent procedures, but it is beyond dispute that issues with other subjects should be addressed. At the time of the experiment, Gelsinger's liver was functioning below the inclusion criteria stipulated on the protocol and he should not have received the infusion. This turned out to be one of several changes the investigators

made to the protocol about which they had failed to inform the proper authorities (Steinbrook 2008).

Third, the Gelsinger case highlighted the complexities of individual and institutional financial conflicts of interest. James Wilson, the lead investigator and director of the research institute at Penn, held a 30 percent equity stake as the founder of Genovo, Inc., which held the rights to market gene therapies discovered at Penn. Likewise, the University and others affiliated with the University held minor equity shares in Genovo.

These relationships raised ethical concerns about the conflicted role of Wilson and others, and sparked a broader conversation about the ethical perils of commingling financial and scientific goals. The number of academic–industry relationships vastly increased in the 1980s and 1990s in part as a result of the *Bayh–Dole Act*, which allowed private institutions or individuals to patent and profit from biomedical innovations made with federal funding. By 2009 academic–industrial relationships had become the norm, with more than half of academic scientists engaged in some form of industrial relationship (Zinner et al. 2009).

Historiography and Human Research Ethics

Historiography refers to the methodology of historical studies. How can valid conclusions be drawn about events in the past? What counts as validity in historical judgment? How can people appreciate the circumstances of those who lived before them, and is "appreciation of prior circumstances" even necessary for doing history? The historiography of ethics is perhaps still more puzzling. Considering that moral judgments are often hard to understand and justify with regard to current or very recent events, valid *moral* judgments about the past as it recedes from living memory seem to add still another layer of complexity. These are not abstract problems. Because so much of the modern regulatory apparatus and the field of research ethics rely on the sorts of crucial cases we have described, "getting the history right" is anything but a trivial pursuit.

Consider, for example, the plutonium injection experiment. In 1945 the boundaries between research and practice were not carefully drawn. Patients were not generally considered to be partners in the research enterprise (although it was not uncommon for scientific articles to express gratitude for their sacrifice). Further, a wartime ethos prevailed under conditions of total mobilization and pervasive government controls that have not been experienced since. Subjects seem to have been selected based on a diagnosis of bone cancer, suggesting that there was a secondary therapeutic intent that might have helped justify the experiment in the minds of the scientists. Can later persons confidently conclude that the experiment was ethically unacceptable?

Here, as in other cases we have described in this chapter, we are confronted with the problem of retrospective moral judgment, a form of anachronistic ethical assessment. Averting this criticism requires a detailed knowledge of the historical facts—a pursuit that is not always evident in casual recitations of landmark cases. For instance, we would need to know that there had been discussions of research ethics in other contexts prior to 1945, including experiments with prisoners, in order for the general ethical principle of subject voluntariness to have been available to persons at the time. Interestingly, just two years after the last plutonium injection, the newly formed Atomic Energy Commission determined that the experiment should be kept secret in order to avoid government embarrassment, a sure indication that the relevant ethical norm was appreciable at the time.

Yet that experiment took place under the auspices of the atomic bomb project, a scientific endeavor that was then and now widely accepted as a matter of military necessity, even national emergency. More than most treatments of the history of human research ethics, we have emphasized the role of national security needs and military sponsorship in a number of the cited cases. As military and intelligence technologies are increasingly reliant on basic science or its products, including the life sciences, we may expect increasing pressures to reconcile the aims of ethical research and national security imperatives.

Research Ethics on the Horizon

Those who believe in moral progress and those who are skeptical about the improvement of regard for the rights and interests of vulnerable human beings may both find support in the history of research involving human subjects. While there is no question that far more systematic attention is paid to the welfare of human subjects of biomedical and behavioral research than was the case prior to World War II, it is also true that abuses continue to be alleged, especially in developing countries where the regulatory environment is lax.

Whether the reporting of current ethical lapses is a result of greater scrutiny or intractable features of scientific research, like professional ambition or simple ethical obtuseness, is hard to know. What is certain is that the increasingly global nature of scientific research has cast a new and brighter light on international research standards. For example, in the wake of the revelations of the Guatemala STD studies of the late 1940s, a Presidential commission published both an historical reconstruction of the incident and a study of the extent to which a similar transgression could occur in the contemporary practice of human experiments in underdeveloped countries (Presidential Commission for the Study of Bioethical Issues 2011).

A debate about whether research standards should in any sense be made more flexible in light of local conditions has long bedeviled the World Health Organization's revisions of the Declaration of Helsinki. There are valid scientific, humanitarian, and business reasons to engage in research in sites beyond the borders of the most highly developed societies, especially in the fields of genetics and public health. In recent years there has also been a discernible shift away from a "protectionist" priority and toward making access to research more available to potential subjects. A variety of groups—including women, patients with HIV, and children's advocates—have argued convincingly that an overemphasis on the "vulnerability" of such groups has precluded them from access to important studies that could potentially improve their health. Taken together, these and other factors suggest that international research ethics will continue to be a site of ethical transgressions and an important field of further inquiry for bioethics.

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Related Topics

Chapter 18, "Research Involving "Vulnerable Populations": A Critical Analysis," Toby Schonfeld
Chapter 20, "The Ethics of Biomedical Research Involving Animals," Tom L. Beauchamp

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