MEDICAL RESEARCH MISCONDUCT:
A CHALLENGE TO SCIENTIFIC INTEGRITY

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Throughout history—and even today—medical research involving human subjects has not infrequently been confounded by ethical transgressions that cause scientific progress to be tainted in a way that undermines and devalues achievements that can otherwise benefit the human condition.

Examples of such abusive practices include:

- Inappropriate or even repugnant behaviors against vulnerable populations and disadvantaged persons;
- Unethical or morally challenging actions taken in the name of science, ranging from the merely discriminatory to the frankly illegal; and
- Conflicts of interest, defined as situations in which the concerns or aims of two different parties are incompatible, or circumstances in which someone is in a position to derive personal benefit from actions or decisions made in their official capacity. This is arguably the foremost concern of the scientific community in the current era, perhaps exemplified by the suppression of research in the tobacco industry that established the dangers of smoking, or the competitive nature of today's research in the pharmaceutical industry.

How can we understand such behavior? Can we explain how otherwise sincere and well-meaning investigators sometimes act or appear to act immorally in their pursuit of knowledge?

Some have argued that such unfortunate episodes need to be reinterpreted in terms of the historical contexts in which they occurred and the lessons learned applied to the design and execution of future research.[1]

THE INFAMOUS TUSKEGEE SYPHILIS STUDY

One of the most notorious clinical investigations in modern American history was the Tuskegee Study of Untreated Syphilis in the Negro Male, conducted from 1932 to 1972 by the United States Public Health Service. In collaboration with the Tuskegee Institute, a historically black college in Alabama, the PHS included in this study more than 600 subjects, all impoverished black men, many of whom worked as sharecroppers.[2,3]

The purpose of this study was to observe the natural progression of untreated syphilis in rural African-American men in Alabama. Additional objectives, to determine the optimal time to administer treatment medication and calculate proper dosages, were later abandoned, principally due to underfunding of the project.

The study has been called infamous for the sheer number of ethical lapses that characterized the project. Among them were:

- Subjects were misinformed about the purpose of the study, told only that they were being treated for "bad blood," a colloquialism that described various conditions, including syphilis, anemia, and fatigue. None of the men who were actually infected with syphilis were ever told that they had the disease.
- Subjects were chosen from a particularly vulnerable population and were given compelling inducements to participate in the study, including free medical care, meals, and free burial insurance. Although they were initially told the study would last only six months, in fact, their participation would be life-long.
- Once funding for treatment was lost, the study was continued without informing the subjects that they would never be treated, even after it became possible to cure syphilis with penicillin, in 1947.

Finally, in 1966, a venereal disease investigator in San Francisco informed the Centers for Disease Control—the agency then controlling the study—of his concerns about what he perceived as irregularities in this study. Amazingly, the CDC reaffirmed the need to continue the study to completion, a position even more amazingly supported by the American Medical Association, as well as the National Medical Association, which represented black physicians. The investigator then "blew the whistle," by leaking information to the press, leading to a great public outcry, Congressional hearings, and a determination to end the study.

US Government compensation was offered to the surviving study participants and their families and a public apology was proffered by President Clinton, in 1972.

While this episode is today regarded as unjust and exploitative, it should be recalled that at the time the study began, it was widely assumed that syphilis was biologically different in blacks and needed special study. In addition, prior to the introduction of penicillin, treatment of syphilis with arsenical compounds, aside from being of dubious value, was prohibitively expensive, thus otherwise depriving those affected individuals of the customary treatment. Even after curative therapy was available, in 1947, penicillin therapy was denied. Nevertheless, at the study's onset and in the historical context, the researchers believed it to be ethically justified.

The controversial Tuskegee study was one of the factors that subsequently led to the creation of The Office for Human Research Protections (OHRP), within the US Department of Health and Human Services, and to Federal laws and regulations requiring medical research groups and hospitals to establish Institutional Review Boards for the protection of human subjects of research.

HENRIETTA LACKS AND HER HeLa CELLS

In the early 1950s, Henrietta Lacks, a poor, young African-American woman, developed cervical cancer, from which she ultimately died. However, prior to her death, cells collected from a biopsy of her cancer were harvested and cultured—without her knowledge or permission—to develop a cell line, called HeLa cells, that represented the first immortal cell line. Over the ensuing decades, research using HeLa cells led to scores of medical advances in the fields of cancer and genetics, as well as the development of vaccines, including the Salk polio vaccine.[4]

Curiously, much of the early work in the cultivation, production, and distribution of HeLa cells was done on the campus of the Tuskegee Institute—at the very same time that state officials were conducting the infamous Tuskegee syphilis studies.

The saga of Henrietta Lacks and her HeLa cells raises a number of fraught ethical issues:

- Lacks never provided her informed consent for use of her cells for research, thus representing a threat to the principle of personal autonomy. Many feel intuitively that one should be able to control how their biospecimens are used, even if they remain anonymous.
- Lacks' family was not told how her cells were being used until 20 years after her death. While the production and distribution of HeLa cells became an extraordinarily profitable commercial industry, the family initially received no compensation. This raises the issue of whether or not patients or their families should be paid if their discarded specimens may lead to advancements down the line from which other individuals or companies may profit.
- Questions of social justice are also raised:
    --Racism that characterized the health care system of the day was discriminatory toward blacks;
    --Arguably, the health care benefits from research on HeLa cells would more likely accrue mainly to affluent whites, rather than poor or destitute blacks.

This provocative story was told in a book entitled: *The Immortal Life of Henrietta Lacks,* by Rebecca Skloot, published in 2010.[4]

JONAS SALK AND CONTROVERSIAL ETHICS IN VACCINE RESEARCH

Many are familiar with the life and work of Jonas Salk, whose innovative vaccine brought a welcome end to the plague of polio in the middle of the last century.

Salk was a hard-driving investigator, labeled by some as ambitious and egocentric. In his efforts to advance research on the development of a polio vaccine, he sometimes came into conflict with those who were concerned that his investigations required performing clinical trials in children, traditionally viewed as a particularly vulnerable population.[5]

Prior to his work developing a polio vaccine, Salk, in the early 1940s, introduced the first influenza vaccine trial, in which he inoculated some 8,000 psychiatric patients at two hospitals, without obtaining prior informed consent from any of the subjects. It should be noted, however, that deliberately infecting institutionalized patients was considered accepted practice at that time. It wasn't until 1947, following the Nuremberg Trials, that human subjects were to have been protected by a set of ethical standards.

Later, in the 1990s, when he was working on the development of a potential AIDS vaccine, in order to expedite the performance of early human trials, Salk took an end run around the FDA requirements by convincing that agency to authorize regulatory approval for human testing prior to the satisfactory completion of animal trials.

Around the same time, a French investigator, Dan Zagury, was also developing an AIDS vaccine in Europe. After inoculating himself, and with no animal studies to test for efficacy or safety, he proceeded to vaccinate healthy children in Zaire, the central African nation. The trial "generated more ethical debates than advances in the field," as he had not obtained informed consent and had ignored international consensus that children should not be used in AIDS vaccine trials. Further, he refused to allow NIH investigators to review his records.[6]

IDENTICAL STRANGERS

One of the more perplexing questions about human behavior is how personal experience influences hereditary determinants that are genetically—and immutably—based: the so-called nature versus nurture debate. One way to explore this phenomenon is to observe similarities and differences between twins who have been separated at birth and raised independently.

Behavioral research on this topic, however, has been hampered by ethical conflicts relating to how subjects are selected for study and biased methodologies that undermine credibility. Further, there is a matter of potential exploitation of what may be considered a particularly vulnerable population.

Despite these drawbacks, innumerable investigators have wondered about this question since at least the time of Darwin, if not since antiquity. The issues have been highlighted by revelations during recent years of a secret study sponsored by the Jewish Board of Family and Children's Services in New York City and conducted through the Louise Wise adoption agency. This agency sent each of twin sets to different homes, without telling the respective

adoptive parents that the children would be separated. Then, the researchers studied the children's development and progress surreptitiously, without revealing the true intent of the study and never informing the subjects or their adoptive parents of their true origins.

The principal investigator of the twins study, Peter B. Neubauer, was a child psychiatrist and psychoanalyst on the staff of Bellevue Hospital, who had studied with Anna Freud in London and who had a particular interest in child personality development. Perhaps cognizant of the ethical improprieties of the twins study that he conducted, he remained evasive whenever questioned about it and never published the results. The records of the study have been sealed and placed in a repository at Yale University, not to be opened until 2066.

In spite of the secrecy surrounding the study, some of the subjects eventually discovered that they had a twin sibling—and in one case, triplet siblings—and were dismayed, if not appalled, that they had been victims, if you will, of a deceitful investigation that subsequently had impacted their lives in profound ways, once they learned the truth. The story of the triplets was the subject of a movie that played in theaters in August 2018, called "Three Identical Strangers." In addition, a memoir, published in 2007 and entitled, *Identical Strangers: A Memoir of Twins Separated and Reunited*, was written by identical twins who had also been subjects in the study and who were reunited after some 35 years.[7]

JESSE GELSINGER AND THE GENE THERAPY THAT CAUSED HIS DEATH

Jesse Gelsinger, an 18 year-old college student, suffered from ornithine transcarbamylase deficiency, an X-linked genetic disorder of the liver. Symptoms include an inability to metabolize ammonia, a byproduct of protein breakdown, and the condition is generally fatal at birth. Jessie had a milder form of the disease and because the enzyme deficiency was partial, he was able to survive on a restricted diet and special medications.

In 1999, Jesse participated in a phase one clinical trial, run by the University of Pennsylvania, aimed at developing a treatment for infants born with severe disease. In mid-September 1999, he was injected with an adenoviral vector carrying a corrected gene, but within a few days he developed a severe anaphylactic reaction that led to his death.[8]

An FDA investigation of this episode revealed several ethical lapses:

- Jesse apparently had high blood ammonia levels that should have excluded him from participating in the trial.
- Failure of the University to report that two prior patients had experienced serious side effects from the gene therapy.
- Failure of the informed-consent process to mention the deaths of monkeys given a similar treatment.

In addition, conflicts of interest were identified in that one of the investigators, as well as the University of Pennsylvania, had financial stakes in the research that were improperly acknowledged.

The episode resulted in substantial delays in the further development of gene research for this and other indications.

J. MARION SIMS: GENIUS OR RACIST?

One of the 19th century's leading surgeons, J. Marion Sims, has been called the "father of gynecology." He was distinguished, among other things, for originating new examination techniques and for introducing an instrument called the speculum, to facilitate examination and treatment of the organs of the female pelvis. He was the founder and organizer of the first medical institution in New York City devoted exclusively to the treatment of diseases of women.

But Sims' principal interest was in developing an operation to correct vesicovaginal and rectovaginal fistulas, common problems for many women in the 19th century, but notorious for producing a debilitating and miserable clinical condition for which there was no remedy. Recognized as a talented and forward-looking surgeon—he was one of the first to perform successful gall bladder surgery—he was at one time prevailed upon by a colleague to consult on a young black woman who had developed a vesico-vaginal fistula following injury to the birth canal from an obstructed delivery (cesarean section was unknown). Initially, he refused to see her, saying he could do nothing to help what was widely acknowledged to be a hopeless condition. However, upon discovering the benefits of the speculum and of the examination techniques that he had introduced, he reconsidered and, in fact, then became obsessed with the possibility of developing and perfecting a surgical technique to cure women of the loathsome condition.

His early efforts were not successful; indeed, most were failures. Death from sepsis was inevitable and frequent. Nevertheless, through extraordinary dedication and encouragement from grateful patients that other doctors refused to attend because of the remarkable challenges they presented, he persisted. Over time, he improved his methods for operating—including replacing silk suture material with fine and flexible silver wire—that resulted in complete cures in at least three patients—Anarcha, Betsey, and Lucy—about whom he reported enthusiastically.

Nevertheless, Sims is widely criticized by members of the lay public because he developed and refined his surgical techniques on slave women, the suggestion being that he was racist and exploited a disadvantaged population for his own selfish reasons. This ultimately resulted in the removal from its location in New York's Central Park of a statue previously erected in his honor *(Figures 1,2)*.

Figure 1

Figure 2

Notwithstanding the accusations of racism, Sims' own autobiography—edited by his son, Dr. H. Marion Sims, published in 1884—tells another story, one that describes a man of "noble character," one who could, instead, be described as humane and compassionate *(Figure 3)*.[9] These traits are illustrated by Sims' assuming not only the responsibility, but also the expense, of caring for the women who came to him for relief of their terrible distress when no other physicians would have anything to do with them.

In his own words, Sims says:

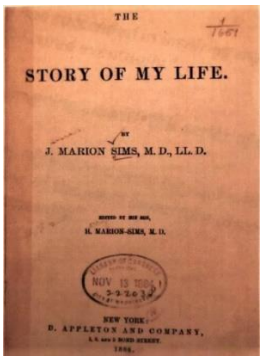
- *I kept all these negroes at my own expense all the time.*
- *When I began the experiments, the other doctors in the city were all willing to help me…(b)ut two or three years of constant failure and fruitless effort rather made my friends tired, and it was with difficulty that I could get any doctor to help me. But, notwithstanding the repeated failures, I had succeeded in inspiring my patients with confidence that they would be cured eventually. They would not have felt that confidence if I had not felt confident too; and at last I performed operations only with the assistance of the patients themselves.*[10]

Sims' brother-in-law, Dr. Rush Jones, citing the expense and inconvenience, tried to convince Sims to give up his efforts, but Sims persisted, saying:

- *…I am…sure that I shall carry this thing through to success…. My patients are all perfectly satisfied with what I am doing for them. I am going on with this series of experiments to the end. It matters not what it costs, if it costs me my life.*[11]

After his introduction of the silver suture material described previously, which led to the cures of Anarcha, Betsey, and Lucy—and later, others—Sims concludes:

- *…my efforts had been blessed with success, and…I had made, perhaps, one of the most important discoveries of the age for the relief of suffering humanity.*[12]


THE

STORY OF MY LIFE.

BY

J. MARION SIMS, M. D., LL. D.

NOV 13 1884

NEW YORK:
D. APPLETON AND COMPANY,
1884.

Figure 3

HISTORICAL CONTEXT OF CLINICAL TRIALS WITH HUMAN SUBJECTS

The origins of clinical trials using human subjects can be traced to the time of Razi, a Persian physician who lived during the ninth century *(Figure 4)*. Razi has been described as a polymath who contributed greatly to advances in medicine, as well as other fields, including chemistry and astronomy. He is recognized as one of the first to introduce the concept of clinical trials, in which he divided a group of patients with meningitis into an intervention group (bloodletting) versus a control group (no bloodletting), thus providing the foundation for the modern randomized, controlled clinical trial.[13]

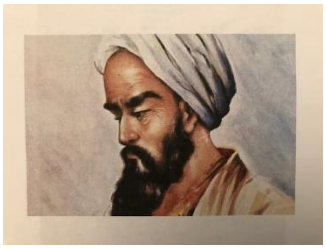


Figure 4

About 100 years after Razi, during the latter part of the tenth centrury, Ibn Sina (also known as Avicenna), who lived in what is present-day Uzbekistan *(Figure 5)*, applied the principles of the scientific method to the testing of drugs, thus providing the basis of the modern clinical trial. He listed some half-dozen conditions that should apply to such studies, including the requirements that the drug being tested be pure and unadulterated and that it be tested in only one condition at a time. He also acknowledged the concept of preliminary testing in animals by recognizing that drug metabolism may differ among species, being active in one, but possibly harmful in another.[14]

Figure 5

By the 16th century, clinical trials already played a substantial role in medical practice. But with the rise of industrialism and commodification, drugs to be sold in the market needed closer scrutiny and more intense regulation. The reason for this had to do with the phenomenon of false or misleading claims by those having a biased interest.

In 1580, for example, a miner named Andreas Berthold traveled around Germany to advertise a poison antidote made from special clay dug from the hills outside of a town in Eastern Europe and processed into small tablets *(Figure 6)*. Like many antidotes, it was touted as a panacea, effective against every type of poison as well as several diseases, including plague. To his credit, however, Berthold did encourage pre-testing the material in dogs.[15]

An early example of human subject testing involved Prince Wolfgang II of Hohenlohe, who, in 1541, had his physicians test a poison antidote on a condemned prisoner, who survived, thus providing, it was believed, evidence of efficacy. Nevertheless, this arguably represented the earliest example of exploitation of a particularly vulnerable population.[16]

In the late 1600s, the Bourbon kings of France regularly granted monopoly privileges to inventors of new pharmaceutical preparations. Applicants would submit their "secret remedies" to the king's personal physician, and if successful, would receive approval to market their products.[17] In some cases, approvals would be granted in exchange for money, a phenomenon still seen today, as represented by conflicts of interest between investigators, the institutions they represent, and the pharmaceutical industry. Case in point: Memorial Sloan-Kettering Cancer Center, where, in September 2018, the institution's chief medical officer was forced to resign because of failure to reveal his financial ties to the pharmaceutical industry.[18] In addition, it was revealed that other investigators, as well as the institution itself, also had financial conflicts of interest with so-called start-up companies developing new anti-cancer treatments.[19]

Figure 6

FRAMEWORK FOR ETHICAL CONDUCT OF RESEARCH ON HUMAN SUBJECTS

As we have observed, sincere and well-meaning scientific curiosity can be readily corrupted by the human failings of dishonesty, cheating, and conflicts of interest. The examples offered here represent only a fraction of the global experience that has motivated efforts to protect research subjects from unnecessary harm or exploitation.

Arguably, among the most egregious examples of what we might regard today as government-sanctioned research misadventure were the human radiation experiments conducted under government sponsorship during the development of nuclear weapons in the middle of the last century. These included the injection of plutonium into unknowing subjects by researchers at several major universities; cases in which nuclear facilities had intentionally released radiation into the environment; subjecting prisoners to non-therapeutic testicular radiation; arbitrarily administering total body irradiation to cancer patients; and in many cases, failing to obtain informed consent from subjects of research.[20]

These and other events have stimulated efforts to better regulate and to enforce standards that govern the protection of human research subjects.[21]

One of the landmark efforts was the creation, in 1974, of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This Commission created a document called Ethical Principles and Guidelines for the Protection of Human Subjects of Research, known colloquially as the Belmont Report, published in 1979 and named after the Senator who chaired the Commission.[22] The basic principles of the Belmont Report include:

- Respect for persons: Reflecting the ethical conviction that individuals should be treated as autonomous agents, this concept provides the rationale for the informed consent process. In addition, there is a requirement to protect those who are vulnerable by virtue of having diminished autonomy, such as children and prisoners.
- Beneficence: Relating to the obligation to properly assess both benefits and risks, by recognizing the possibility of harm caused by the research.
- Justice: The principle requiring fairness in distribution of research opportunities so as not to arbitrarily exclude individuals or groups of individuals who may potentially benefit from the findings of research.

Federal regulations governing the conduct of research were established in 1991 with the publication of a Code of Federal Regulations, known as the "Common Rule." This code, which is periodically updated, explicitly addresses the protections to be afforded to human research subjects, including pregnant women, fetuses, neonates, prisoners, and children, as well as other individuals with diminished personal autonomy.[23]

The regulatory process for clinical research has recently been widened in scope and updated by an organization called the Association of Clinical Research Professionals (ACRP), a nonprofit, tax-exempt organization established to assure that clinical research is performed ethically, responsibly, and professionally and to promote integrity and excellence in clinical research. The ACRP has taken particular interest in recognizing the reality and potential

capacity of conflicts of interest to distort quality and credibility of otherwise honorable research activities.[24]

CONCLUSION

As scientific knowledge evolves from empiricism to rationalism, few can doubt or undervalue the medical progress that has resulted from clinical research involving human subjects.

Examples include:

- Control of infectious diseases—from smallpox to HIV.
- Advances in treatment of cardiovascular disorders—from heart valve replacements to management of coronary artery disease.
- Movement toward the cure of cancer—through surgery, radiation therapy, chemotherapy, immunotherapy, and now, molecular biology and the growth of precision or "personalized" medicine.

Nevertheless, history, and even our contemporary experience, shows that not uncommonly, researchers can demonstrate ethical and moral misjudgments that threaten to undermine the credibility of their achievements. Examples include:

- Discrimination against minority or disadvantaged populations (e.g. Tuskegee, Lacks, Sims).
- Egotistical behavior on the part of investigators (e.g. Salk).
- Inadvertent or unintended consequences caused by poor study design or failure to appreciate unintended ramifications (e.g. Twins studies).
- Actual or perceived conflicts of interest (e.g. Gelsinger).

What do we learn from this?

- The conduct of scientific inquiry can be influenced by the historical context in which it occurs. As the ethicist Arthur Caplan has expressed it, this is "not meant to exonerate past transgressions but rather to explain them."[1]
- Adherence to proper ethical standards is essential to safeguarding the autonomy of persons participating as subjects of medical research, including the principles of informed consent, protection from unwarranted harms, and equitable distribution of potential benefits and risks *(Figure 7)*.

Figure 7

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Figures

Fig. 1. The memorial statue of J. Marion Sims, MD was removed in 2017 from its prominent location in Central Park.

Fig. 2. J. Marion Sims, MD, was recognized as a surgeon, philanthropist, and hospital founder.

Fig. 3. Sims' autobiography, *Story of My Life*, was edited by his son and published in New York in 1884.

Fig. 4. Muhammad ibn Zakariya al-Razi (854-c930).

Fig. 5. Ibn Sina [Avicenna] (980-1037).

Fig. 6. Berthold's poison antidotes (1580).

Fig. 7. Ethical challenges to medical research integrity?