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Intentional Infection of Vulnerable Populations in 1946-1948

Another Tragic History Lesson

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UNETHICAL USES OF HUMANS AS RESEARCH SUBJECTS represent appalling chapters in the history of medicine.¹ To ensure that effective protections against such abuses continue to evolve and improve, it is essential to continue to learn from historical examples. Sadly, a new example has recently come to light.

While conducting research on the Tuskegee study of untreated syphilis,² Wellesley College Professor Susan Reverby recently reviewed the archived papers of John Cutler, a US Public Health Service (PHS) medical officer and a Tuskegee investigator. Instead of finding Tuskegee records, however, Reverby found the records of another unethical study. In this study, vulnerable populations in Guatemala—mentally incapacitated patients, prison inmates, sex workers, and soldiers—were intentionally exposed to sexually transmitted infections (syphilis, gonorrhea, and chancroid).

The work was directed by Cutler and was done with the knowledge of his superiors, including then Surgeon General Thomas Parran Jr. Funded with a grant from the National Institute of Health (NIH) to the Pan American Sanitary Bureau (which became the executive arm of the Pan American Health Organization), the study was conducted in cooperation with Guatemalan investigators by the USPHS Venereal Disease Research Laboratory, which 10 years later became a part of the Centers for Disease Control and Prevention (CDC).

As described by Reverby,³ the study's initial syphilis experiments used female sex workers, intentionally infected with *Treponema pallidum*, as a source of infection to male prison inmates. At that time, sex workers were allowed into Guatemalan prisons. When the rates of female-to-male transmission proved to be low, the research approach changed to the direct inoculation of prison inmates and patients in the Guatemalan mental hospital. Most inoculation experiments involved subcutaneous injection of *T pallidum* or exposure of the penile foreskin to infectious material. The majority of study subjects were treated with penicillin, although available study records do not document therapy or completion of therapy for all subjects and some received only partial treatment.⁴

One study subject, a patient with a history of severe epilepsy, died of status epilepticus during treatment with penicillin. Although additional deaths occurred during the conduct of the study in the mental hospital, they were most likely

related to the high rates of underlying disease, such as tuberculosis. The investigators provided some items for institutional support, such as anticonvulsant medications and refrigerators to store vaccines, and offered cigarettes as an incentive to study subjects. The archives provide no indication that individuals understood that they were participating in research.

Most of the gonorrhea and chancroid experiments were conducted with Guatemalan soldiers. While the initial studies involved sexual contact of soldiers with female sex workers who had been infected with gonorrhea, subsequent subjects were infected through intraurethral inoculations of *Neisseria gonorrhoeae* and cutaneous inoculations of *Haemophilus ducreyi*, and then treated with penicillin and sulfathiazole, respectively.

Ethical Violations

Ethical violations in this study clearly include the following: (1) study subjects were members of vulnerable populations including institutionalized and mentally disabled persons, prison inmates, and soldiers (who could not give valid informed consent); (2) individuals were intentionally infected with pathogens that could cause serious illness; and (3) deception was used in conducting the experiments. Correspondence between the investigators and their superiors also recognized the unethical nature of the work. A letter from Cutler's supervisor, R. C. Arnold, written in 1948, notes that, "I am a bit, in fact more than a bit, leery of the experiment with the insane people. They can not give consent, do not know what is going on, and if some goody organization got wind of the work, they would raise a lot of smoke."⁴ The study was never published.

Unfortunately, such studies were not rare at the time. For example, intentional infection of prison inmates with gonorrhea and syphilis was conducted in Terre Haute, Indiana, and Sing Sing prison, respectively.^{5,6}

Safeguards

Over the past 60 years, regulations safeguarding humans participating in research have been enacted⁷ (TABLE). The Nuremberg Code, which articulated the requirement for voluntary consent of research participants, was issued in 1947, in response to Nazi human experimentation. The Declaration of Helsinki, the first international set of ethical principles for

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medical research involving human research participants, was adopted in 1964 by the World Medical Association. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, created following the revelation of the Tuskegee study, issued the landmark Belmont Report on ethical principles and guidelines for research involving humans in 1979.⁸ In 1981, these guidelines were embodied in Health and Human Services (HHS) regulations to protect research participants (45 CFR 46).⁹ In 1991, Subpart A of these regulations (“The Common Rule”) was adopted by an additional 16 federal agencies.

Table. Evolution of Human Subjects Research and Guidelines

| Year | Event |
|-----------|--|
| 1932-1972 | Tuskegee Syphilis Study |
| 1939-1944 | Experiments on concentration camp prisoners by Nazi scientists |
| 1944-1974 | Secret human radiation experiments |
| 1946-1948 | Guatemalan STD inoculation studies |
| 1947 | Nuremberg Code |
| 1950 | NIH Clinical Center requires informed consent for its studies |
| 1953-1954 | Sing Sing Prison syphilis inoculation study |
| 1956-1972 | Hepatitis studies at Willowbrook State School for the Retarded |
| 1960 | NIH Clinical Center requires independent ethical review for its studies |
| 1962 | Kefauver-Harris drug amendments |
| 1963 | Jewish Hospital cancer study |
| 1964 | World Medical Association Declaration of Helsinki |
| 1966 | US Surgeon General policy statement on human subjects research (IRB origin) |
| 1971 | NIH Office for Protection from Research Risks established |
| 1974-1978 | National Commission for the Protection of Human Subjects |
| 1974 | HHS regulations for human subjects research |
| 1975 | CDC Office of Human Research Protections established |
| 1978-1983 | President's Commission for the Study of Ethical Problems |
| 1979 | Belmont Report released |
| 1981 | HHS 45 CFR 46 and Food and Drug Administration 21 CFR 50, 56 regulations published |
| 1985 | NIH Clinical Center Bioethics Program founded |
| 1991 | 45 CFR 46 (Common Rule) adopted |
| 1993 | CIOMS guidelines released |
| 1994 | Presidential apology for secret radiation experiments |
| 1995 | World Health Organization Guidelines for Good Clinical Practice |
| 1996-2001 | National Bioethics Advisory Commission |
| 1996 | Department of Bioethics established at NIH Clinical Center |
| 1997 | Presidential apology for Tuskegee |
| 1998 | NIH support for bioethics training and research expanded |
| 1999 | NIH support for international research and ethics training |
| 2000 | World Health Organization operational guidelines for ethics committees |
| 2001-2009 | President's Council on Bioethics |
| 2002 | Secretary's Advisory Committee on Human Research Protections |
| 2005 | UNESCO Universal Declaration on Bioethics and Human Rights |
| 2009 | Executive order to create Presidential Commission for the Study of Bioethical Issues |

Abbreviations: CDC, Centers for Disease Control and Prevention; CFR, Code of Federal Regulations; CIOMS, Council for International Organizations of Medical Sciences; HHS, Department of Health & Human Services; IRB, institutional review board; NIH, National Institutes of Health; STD, sexually transmitted disease; UNESCO, United Nations Educational, Scientific and Cultural Organization.

Could such unethical studies happen today? For research funded or conducted by the US government, the answer is no. All federally funded research projects in which human participants are exposed to more than minimal risk must be reviewed by an institutional review board (IRB) before proceeding, and, as described in the Common Rule, must involve written, signed informed consent of research participants or their legally authorized representative (except in rare cases). Federal regulations instruct IRBs to be “. . . particularly cognizant of the special problems of research involving vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.”⁹ For institutions violating these regulations, sanctions are imposed by the HHS Office for Human Research Protections. Furthermore, the HHS Office of Research Integrity takes administrative action against individual investigators for whom a determination of research misconduct has been made.

As clinical research increases in volume and complexity and more frequently crosses country borders—often to reach the most affected populations—continued scrutiny of guidelines governing research involving human subjects remains critical. As technologies evolve, it is essential to continuously consider what new risks—physical, psychological, or informational—might be raised by research, and how investigators can best inform, engage, and protect research participants.

While effective protections against unethical research continue to evolve across the world, the past exploitations of vulnerable populations, including the subjects of the study in Guatemala in the 1940s, are regrettable and deeply saddening. For them, the basic ethical principle of respect for persons was flagrantly violated. The NIH and CDC are committed to ensuring that lessons drawn from the past help shape actions to protect all future research participants, no matter where studies are conducted. The 1946-1948 inoculation study should never have happened, and nothing like it should ever happen again.

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REFERENCES

- Lederer SE. *Subjected to Science: Human Experimentation in America Before the Second World War*. Baltimore, MD: The Johns Hopkins University Press; 1995.
- Reverby SM. *Examining Tuskegee: The Infamous Syphilis Study and Its Legacy*. Chapel Hill: University of North Carolina Press; 2009.
- Susan M. Reverby faculty page. http://www.wellesley.edu/WomenSt/fac_reverby.html. Accessed October 6, 2010.
- Information on the 1946-1948 United States Public Health Service STD Inoculation Study. US Department of Health & Human Services Web site. <http://www.hhs.gov/1946inoculationstudy>. Accessed October 5, 2010.
- Mahoney JF, Van Slyke CJ, Cutler JC, Blum HL. Experimental gonococcal urethritis in human volunteers. *Am J Syph Gonorrhea Vener Dis*. 1946;30:1-39.
- Magnuson HJ, Thomas EW, Olansky S, Kaplan BI, De Mello L, Cutler JC. Inoculation syphilis in human volunteers. *Medicine (Baltimore)*. 1956;35(1):33-82.
- National Institutes of Health, Office of Human Subjects Research. Regulations and ethical guidelines. <http://ohsr.od.nih.gov/guidelines/index.html>. Accessed August 15, 2010.
- The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. 1979. <http://ohsr.od.nih.gov/guidelines/belmont.html>. Accessed October 6, 2010.
- Code of Federal Regulations, Title 45 Public Welfare: Part 46, Protection of Human Subjects. <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>. Accessed October 6, 2010.