

The Guatemala Sexually Transmitted Disease Studies: What Happened

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In September, 2010, the public and medical communities were stunned by the disclosure of syphilis and other sexually transmitted disease studies conducted in 1946 to 1948 by the US Public Health Service in Guatemala, after being hidden for more than 60 years. The ensuing controversy and public embarrassment resulted in an acknowledgement of major ethical transgressions and an official public apology to Guatemala from President Barack Obama and Secretary of State Clinton (*NY Times* October 1, 2010). At the direction of the President, a subsequent investigations and public hearings with US Presidential Commission on Bioethical Issues were conducted, resulting in the review of more than 125,000 pages of documents obtained from various archives and publication of a report in both English and Spanish titled “Ethically Impossible,”¹ which documents the known history of the studies, the major characters involved, and the procedures that were performed in Guatemala. At all steps of the process, from the discovery of the materials through the final publication of the Commission studies, there was acknowledgement at all levels of the US Government that this work involved major ethical lapses.

The studies were discovered by Dr Susan Reverby, a historian at Wellesley College in Massachusetts. Dr Reverby’s research has focused on the Tuskegee studies of untreated syphilis.² She was researching the work of Dr John Cutler at the University of Pittsburgh, who was one of the United States Public Health Service (USPHS) physicians involved in the Tuskegee studies, including publication of some of the Tuskegee studies. After his USPHS career, Dr Cutler had a long and distinguished public health career, including being the Dean at the University of Pittsburgh School of Public Health. Ironically, his only publication in this journal was an obituary for Dr Robert Arnold,³ a physician-scientist who was also involved in the Tuskegee project and was aware of the Guatemala studies as they occurred.

Dr Cutler died in 2003. The Pittsburgh archive he left included more than 12,000 pages of documents describing the studies in Guatemala, including experimental notebooks, cards for individual participants, participant photographs, and correspondence. None of the material had been ever published. The National Archives has made the materials, including de-identified medical records and photographs of the studies, available on their Web site (<http://www.archives.gov/research/health/cdc-cutler-records/>)

The Presidential Commission’s study is extensive and describes in detail the historical context, the process, the studies

themselves, and aftermath of its investigation. I had the privilege of being a technical consultant to the Commission and providing input on the medical and biomedical historical context. My objectives here are to

1. provide a context for the Guatemala studies’ scientific rationale;
2. provide a brief overview of the studies that were performed and the populations that were involved; and
3. briefly review the technical correspondence between Dr Cutler and other key individuals. The American Sexually Transmitted Diseases Association (ASTDA) is particularly interested in the role that Dr Thomas Parran, the contemporaneous surgeon general, had in the development and implementation of these studies and what knowledge he had of the actual fieldwork that was ongoing.

The Rationale

During World War II, venereal diseases were a major public health issue, and the incidence rates of syphilis and gonorrhea in both the European and Pacific theaters of military operations were high. Public health interventions promoted by the military included the distribution of condoms and postexposure “Pro-kits,” consisting of calomel ointments, and access to medical care. Venereal disease control was a major military concern because soldiers being treated were not deployable.

Treatment of both syphilis and gonorrhea was revolutionized by the development of penicillin, and by the end of the war, early clinical studies in both diseases had demonstrated its efficacy, resulting also in the establishment of Rapid Treatment Centers for syphilis treatment in the civilian population. The contemporaneous state of syphilis diagnosis and treatment was comprehensively reviewed in a 1947 *New England Journal* review by Crawford.⁴ Venereal diseases research was centered at the US Public Health Service Hospital in Staten Island, New York, directed by Dr John Mahoney. This center was the predecessor of the current Division of STD Prevention at the Centers for Disease Control and Prevention.

The impact of penicillin therapy for syphilis treatment cannot be underestimated. Previous treatment regimens with arsenical compounds required a year of weekly injections and were not as efficacious. However, there were major concerns and questions regarding the treatment of individuals who were exposed to an infected contact (preventive treatment). For example, the major textbooks of the time (e.g., Stokes⁵) provided no information on the treatment of contacts, and there were no official recommendations. The development of rapidly effective treatments provided an opportunity and an exigency to further understand these issues.

In 1946, Dr John Cutler was a 32-year-old physician researcher at the USPHS Venereal Diseases Research Laboratory (VDRL; which was the precursor of the present-day Centers for Disease Control and Prevention, Division of Sexually Transmitted Diseases). Cutler was assigned by the VDRL Director, Dr John Mahoney, to investigate this problem. The USPHS had collaborators in Guatemala, as well as a clinical research site that could be developed and access to a variety of experimental

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populations. A grant proposal was written and reviewed and funded by the National Research Council (predecessor to the National Institutes of Health) Syphilis Study Section. Members of the Study Section included major luminaries in the field including the following: Drs Mahoney and John Heller from the USPHS; representatives of the US Army, Navy, and Veterans Administration; and key faculty from Johns Hopkins University, Harvard University, and the University of Pennsylvania. The final funding decisions were made by the Surgeon General, Dr Thomas Parran. Although no copy of the final proposal exists, contemporaneous correspondence refers to it as “the Guatemala study dealing with the experimental transmission of syphilis to human volunteers and improved methods of prophylaxis.”

In 1946, Dr Cutler and a number of colleagues went to Guatemala and established the field site. The field site included a laboratory where treponemal strains could be maintained in rabbits and where serological assays for syphilis and gonococcal cultures could be done. The field site required continual resupply, which was provided by a regular US military transport to Guatemala.

A series of experiments were designed, which followed a logical framework. The underlying question was “Can a preventive treatment regimen be evaluated in a model where humans are infected under controlled conditions?”

The initial human infection model used commercial sex workers. Commercial sex workers were recruited and intentionally infected with carefully pedigreed *Treponema pallidum* or gonococcal strains. After the infection was established, the sex workers had intercourse with uninfected male individuals—either Guatemalan soldiers or prisoners in the penitentiary. Participants were examined immediately after intercourse and followed. To the investigators’ surprise, the transmission rates were less than 10%, so this model was abandoned.

Cutler then developed a series of inoculation models. Participants recruited for these studies came from 3 groups of “captive” populations—patients in the local psychiatric hospital, penitentiary inmates, and Guatemalan soldiers. There is no evidence that informed consent, in any form, was obtained.

The infected material that was inoculated included either infectious materials harvested from patients’ ulcers or secretions (e.g., ulcer or urethral exudates), or, for the syphilis experiments, testicular homogenates from the infected rabbits used to maintain the culture line. The methods used to inoculate the human subjects for primary infection models included the following:

- Local application to the intact mucous membrane of the penis
- Local application to the abraded mucous membrane of the penis
- Intracutaneous or subcutaneous injection
- Submucosal injection of the penis
- Scarification of the penile mucosa
- Multiple pressure vaccination of the skin, deltoid region or glans penis

It was found that the most effective transmission method was scarification or intracutaneous injection into the prepuce, with “take” rates that were between 83% and 100%. In each of the cases, detailed records were maintained, including serial photographs. Serial serological assays were performed using the serological methods available at the time, including the VDRL, Kahn, Kolm, and Mazzini tests. Most patients infected with *T. pallidum* also had serial lumbar punctures, including many who had cisternal punctures. After infection was confirmed, participants were treated, often with parenteral penicillin that was scheduled to be given intramuscularly every 2 hours.

After the infection transmission models were developed, a series of controlled prophylaxis experiments were conducted using therapeutics applied either locally or systemically. The compound of primary interest was orvus-mapharsen, which was a newly formulated arsenical compound with antitreponemal activity but which was thought to have fewer adverse effects and chemical properties, which made it easier for local application. There was also interest in evaluating penicillin. The experiments included the following:

- Is the orvus-mapharsen prophylaxis local application effective as postexposure prophylaxis?
- How does orvus-mapharsen prophylaxis compare with the arsenical preparation in then current use, containing 3% calomel and sulfathiazole (comparing different regimens for postexposure prophylaxis)?
- Is oral penicillin effective as prophylaxis, if so, in what dosage?
- Is parenteral penicillin effective? for prophylaxis

For each of the questions, participants were recruited, infected, and given either the experimental treatment regimen or no regimen (control), and then followed to see if infection developed. Detailed records were kept, serial serological examinations were performed, and serial lumbar or cisternal punctures were performed in most of the participants. Although most of the participants were “confined” to either the penitentiary or the psychiatric hospital, it was assumed by the investigators that there were no outside sexual contacts.

In addition to the prophylaxis experiments, review of the experimental notebooks also indicated that Cutler and his group were interested in the following questions:

- Can reinfection take place after treatment?
- What is the clinical course of reinfection as compared with infection?
- Can reinfection or superinfection take place in treated or untreated latent or late syphilis?
- What is the significance of a positive serological test result for syphilis in regard to possible immunity to reinfection and as related to stage and treatment?

Reinfection studies were performed in some of the populations. Some of these studies involved also the surgical removal of penile chancres. The most egregious experiments were Cutler’s attempt to establish a human experimental model of secondary syphilis (via direct intravenous infusion of infected material) or neurosyphilis, which was performed by cisternal injection directly into the cerebrospinal fluid of infected material. Each of these experiments had small numbers of participants, and no prophylaxis studies were performed.

A total of 1308 participants were enrolled in the infection studies. Although Cutler claimed that the participants were all treated, review of the documentation reveals that the treatment documentation was spotty and there is documentation for only 678 (52%). Also, it is difficult to believe that complex treatment regimens would be consistently delivered in difficult, resource-poor settings. Autopsies were performed on penitentiary or psychiatric hospital participants who died either during or after the studies, but the records on these were incomplete.

The reader is encouraged to read the full report at www.bioethics.gov. In addition, the original source documentation is available at the National Archives (Web site). After reviewing the materials, I came to the following (albeit obvious) conclusions:

1. There were profound lapses in research ethics, including respect for individuals' autonomy, justice, respect for persons, and non-maleficence.
2. No consent was obtained, either direct or implied, for any of the studies.
3. The studies themselves put the participants' health at unreasonable risk.
4. The studies' design and documentation, in many cases, were faulty.
5. The studies used multiple groups who would be classified as vulnerable populations under current practice. These include prisoners, persons with mental illness, persons with limited literacy and cognition, and commercial sex workers.

One of the most troubling aspects of these studies is the contemporary context, as well as correspondence between the principals suggesting that they were keenly aware of the ethical issues involved in the work. The studies commenced shortly after the end of World War II, and the disclosures of Nazi medical experimentation that led to the Nuremberg trials of 1946. Examples of the correspondence or reports are cited below.

May 17, 1947, Cutler to Mahoney. We have had the first success with a normal exposure with 1 patient of 6 showing positive results... In the same issue of the *New York Times* which Neurath's works were reported was a little note about the work on the prevention of syphilis in rabbits by small doses of penicillin. It went on to speculate on the method of proving his hypothesis in humans and said "Such work could not be ethically carried out." Then in the *Journal of The American Medical Association* appeared a notice about the grant to the Pan American Sanitary Bureau for the study of syphilis. It is becoming just as clear to us as it appears to be to you that it would not be advisable to have too many people concerned with this work in order to keep down talk and premature writing. I hope that it will be possible to keep the work strictly in your hands without necessity for outside advisors or workers other than those who fit into your program and who can be trusted not to talk. We are just a little bit concerned about the possibility of having anything said about our program that would adversely affect its continuation.

June 22, 1947, Cutler to Mahoney. I'm writing this letter personally and unofficially to ask you about several very important matters. First, as you know it is imperative that the least possible be known and said about this project, for a few words to the wrong person here or even at home might wreck it or parts of it. We have found out that there has been more talk here than we like with knowledge of the work turning up in queer places...

April 14, 1948, Robert Arnold to Cutler. I am a bit, in fact more than a bit, leery of the experiment with the insane people. They cannot 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. I think the soldiers would be best or the prisoners where they can give consent.

In 1948, the work abruptly stopped. Despite the enormous body of data collected, none of the findings were ever published in the scientific literature. This is very intriguing because Cutler and other colleagues (Drs John Mahoney and Sasha Levitan) involved in the Guatemala work were no stranger to controversy and published extensively on the Tuskegee study until that was shut down in 1972. My suspicion is that the Guatemala studies were discontinued by leadership either at the Public Health Service or at the US military. The Presidential

Commission performed an exhaustive search of US government archives and could not find any existing documents that shed light on this curious chain of events. Furthermore, the Guatemala studies were archived in Cutler's University Of Pittsburgh studies, suggesting that he either intended to write up the studies at a later date or had concerns about them being stored in a government archive.

The Role of Thomas Parran and the Challenge to the ASTDA

Dr Thomas Parran had an esteemed public health career, largely because of his innovations in venereal disease control. As Director of the New York State Health Department during the 1930s, he made syphilis control a major priority, designed the syphilis control program, and published *Shadow on the Land*, which describes the public health challenges of venereal disease and, specifically, syphilis. The ASTDA Lifetime Achievement Award is named after Dr Parran.

Dr Parran was the Surgeon General of the United States from 1936 to 1948, which included the period that the studies were conducted in Guatemala. He was the Public Health Service official who approved the funding of the studies in 1946, on the recommendation of the National Research Council study section. Correspondence in late 1946 between the investigators also mention that "the Surgeon General (i.e., Dr Parran) has become keenly interested in the Guatemala project." Therefore, there can be no doubt that he was aware of these experiments. To the best of our knowledge, he never visited the site, and there is no direct correspondence available between Dr Parran and the investigators. There is one incriminating although indirect reference to Dr Parran in the files in 1947.

February 17, 1947 G. Robert Coatney (scientist/malariologist) National Institutes of Health Bethesda to Dr John Cutler. I saw Dr. Parran on Friday and he wanted to know if I had a chance to visit your project... he was familiar with all of the arrangements and wanted to be brought up to date on what progress had been made. As you well know, he is very much interested in the project and a merry twinkle came into his eye when he said "you know, we couldn't do such an experiment in this country."

SUMMARY

The United States has acknowledged the profound ethical lapses that occurred in Guatemala and has undertaken an open discussion and disclosure of the events. Besides the Commission's report and release of the Cutler archival materials, the Commission abstracted all of the participants' clinical and testing data and prepared a large spreadsheet that is accessible via the bioethics.gov Web site. The dilemma we face as researchers and clinicians is understanding and processing Dr Parran's legacy in the context of the materials uncovered in the Guatemala story.

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