CDC Report on Findings from the U.S. Public Health Service Sexually Transmitted Disease Inoculation Study of 1946–1948, Based on Review of Archived Papers of John Cutler, MD, at the University of Pittsburgh

29 September, 2010

Executive Summary

From 1946–1948, the U.S. Public Health Service (USPHS) Venereal Disease Research Laboratory (VDRL) and the Pan-American Sanitary Bureau collaborated with several government agencies in Guatemala on U.S. National Institutes of Health-funded studies involving deliberate exposure of human subjects with bacteria that cause sexually transmitted diseases (STD). Guatemalan partners included the Guatemalan Ministry of Health, the National Army of the Revolution, the National Mental Health Hospital, and the Ministry of Justice. Studies were conducted under the on-site direction of John C. Cutler, MD, in Guatemala City, who worked under the supervision of R.C. Arnold, MD, and John F. Mahoney, MD, of the USPHS VDRL in Staten Island, New York. The primary local collaborator was Dr. Juan Funes, chief of the VD control division of the Guatemalan Sanidad Publica.

The work by Dr. Cutler and VDRL colleagues was recently brought to light by Professor Susan Reverby of Wellesley College, as a result of archival work conducted as part of the research of her 2009 book on PHS syphilis studies, *Examining Tuskegee*. Her article on the STD Inoculation studies is scheduled to be published in the Journal of Policy Studies in January 2011 and will be available on her departmental homepage in October 2010 (www.wellesley.edu/WomenSt/fac_reverby.html).

Upon learning of Professor Reverby's work, staff from the Centers for Disease Control and Prevention (CDC) conducted a review of materials in the papers of Dr. Cutler, archived at the University of Pittsburgh. These papers included several summary reports, experimental logs, correspondence between Dr. Cutler and professional colleagues, and subject-specific records. The findings from this review are consistent with the observations to be published in Dr. Reverby's paper and are summarized as follows.

According to materials in the archives, the primary purpose of the studies was to develop human models of transmission of *Treponema pallidum*—the bacteria that causes syphilis—by sexual transmission and cutaneous and mucous membrane inoculation in order to assess the effectiveness of potential chemoprophylactic regimens. Additional studies were conducted to: assess the potential for re-infection of persons with

untreated, latent syphilis or of those with recent treatment of syphilis with penicillin; compare performance of various serologic tests for syphilis; and develop human models of transmission and chemoprophylaxis of the agents of gonorrhea (*Neisseria gonorrhoeae)* and chancroid *(Hemophilus ducreyi)*.

Subjects for the transmission studies included female commercial sex workers (CSWs), prisoners in the national penitentiary, patients in the national mental hospital, and soldiers. These subjects were also involved in comparative serologic studies. Transmission studies initially included sexual exposure of prisoners to female CSWs, experimentally infected with either syphilis or gonorrhea. Later, subjects underwent direct inoculation—primarily of skin and mucous membranes—by viable *T. pallidum, N. gonorrhoeae, and H. ducreyi.* The design and conduct of the studies was unethical in many repects, including deliberate exposure of subjects to known, serious health threats; lack of knowledge of, and consent for, experimental procedures by study subjects; and the use of highly vulnerable populations.

According to a "Syphilis Summary Report" and experimental logs in the archives, syphilis studies included CSWs, prisoners, and patients in the mental hospital. In the series of syphilis studies, a total of 696 subjects of individual experiments (some representing the same patients involved in several experiments) were exposed to infection (by sexual contact or inoculation). Of these, 427 (61%) were judged to be infected, of whom 369 (86%) received what was considered to be "adequate treatment" with injections of penicillin (defined by the investigators as ≥3.4 million units).

Gonorrhea studies included CSWs, prisoners, soldiers, and mental hospital patients. In the series of gonorrhea studies, a total of 772 subjects of individual experiments (some apparently representing the same patients involved in several experiments) were exposed to infection (by sexual contact or inoculation). Of these, a summary report and experimental logs indicate that 234 (30%) were infected, 233 (99.5%) of whom were stated to have received treatment with injections of penicillin (300,000 units).

Chancroid studies included soldiers and mental hospital patients. A total of 142 subjects were exposed to infection by inoculation. Of these, a summary report and experimental

logs indicate that 138 (97%) were infected, 129 (93%) of whom were stated to have received treatment with sulfathiazole (1 gram PO per day for 5 days).

To supplement findings in the "Syphilis Summary Report" and experimental logs, a detailed review of subject-specific records for the syphilis inoculation studies was carried out for persons involved in the majority of the syphilis experiments. This allowed for the unduplication of subjects involved in multiple experiments and included some subjects who may not have been included in the "Syphilis Summary Report". This review included subject-specific records from 532 persons, 497 (93%) of whom were inoculated with infectious syphilis. Of these 497, prescription of adequate therapy with penicillin (≥3.4 million units) could be documented for 332 (67%). Based on laboratory assessment, 433 (87%) could be considered to have evidence of syphilis. Of these 433, adequate penicillin therapy was prescribed for 331 (76%), although completion of therapy was documented for only 85 (26%). Over the course of observation, 71 subjects were noted to have died, including one who developed fatal status epilepticus during penicillin therapy, although the records do not allow determination of the relationship of the deaths to study procedures. There was no systematic description of other adverse events arising during the study or follow-up observation period.

The study appears to have ended in 1948, although some follow-up laboratory testing and patient observation continued until the early 1950s. There is no indication that results of the STD inoculation experiments were ever published in the scientific literature or other forums.

Outline of the Cutler files

As outlined in the Appendix, the Cutler files at the University of Pittsburgh consist entirely of files from the PHS-funded STD Inoculation Study of 1946–1948. The files include the following:

a. a long 7-part summary report of the rationale, methods, and results of the syphilis studies (designated as the "Syphilis Summary Report");
b. shorter summary reports of the studies of gonorrhea ("Experimental Studies in Gonorrhea") and chancroid ("Chancroidal prophylaxis");
c. correspondence between Dr. Cutler and USPHS colleagues;
d. experimental records, logbooks, and summaries; and
e. short, subject-specific records of subjects involved in the syphilis inoculation studies that included records of baseline history, physical exams, and syphilis serologic results; experiment number(s) and *T. pallidum* inoculation(s); follow-up syphilis serologic results and periodic clinical examination findings; and dates and doses of penicillin treatment.

The files cover the period primarily from mid-1946 until late-1948, with limited patient records regarding follow-up serologic testing for the next several years. Descriptions from the "Syphilis Summary Report" provide many details and are the source of the quotations in the following sections, unless otherwise specified. The "Syphilis Summary Report" is not dated, but it includes mention of the subsequent study of syphilis inoculation at Sing-Sing prison (in New York state) in the 1950s, as well as several other published references from as late as 1954 (including a 1954 report from the Tuskegee study). A note included with a handwritten table of "Individual patient response in each experiment" indicates that the table was compiled by Sacha Levitan and John Cutler in December, 1948, and that it was the basis for the final analysis and write-up by Henry Miller and John Cutler from 1951–1954.

The subject-specific records contain information about subjects in the syphilis experiments, many of whom were included in multiple experiments and followed with frequent serologic tests over time. These records contain limited personal identifying information, apart from name, gender, and the institution with which they were affiliated,

although some do specify age, names of parents, and city of residence. Subject record forms are identified with an inscription at the bottom of each page: "Centro de Adiestramiento e Investigaciones de las Enfermedades Venereas, Sandidad Publica, Guatemala, C.A."

Background of the research studies

The USPHS VDRL had an active program investigating chemoprophylaxis of STDs (i.e., chemical agents to prevent acquisition of STD following sexual exposure) in the 1940s, assessing preparations that might be more effective and acceptable than the agent in widespread use by U.S. military services in World War II (U.S. Army Pro-kit—a topical preparation containing 33% calomel, 15% sulfathiazole, 40% white petrolatum, 14% light mineral oil, and 1% cetyl alcohol). There was interest in both alternative topical preparations (e.g., Orvus—an aqueous solution of 0.15% mapharsen and 1.0% alkyl aryl sulfate) as well as systemic penicillin. It is noted that studies in rabbits and small pilot studies among sailors in the U.S. Navy had been performed and provided promising initial results, although the role of the Departments of the Army and Navy in these studies was not specified. However, before these alternative prophylactic approaches could be widely adopted by the U.S. military, "it was felt that carefully controlled studies on relatively small groups of individuals exposed to a high risk of infection were required before the [new and presumably more effective and acceptable chemoprophylactic] preparation could be proposed for widespread use, particularly in the Armed Services (Part I, pg 7). " Thus, the primary rationale for the studies was to develop models of human transmission to assess the impact of various chemoprophylactic regimens as well as to re-assess an understanding of syphilis immunology in the penicillin era (especially immunity to reinfection with latent or recently cured syphilis).

Dr. Cutler's report indicates that Guatemala was selected for these studies at the suggestion of Dr. Juan Funes, chief of the VD Control Division of the Guatemalan Sanidad Publica. Dr. Funes had studied for a year at the VDRL in NY as a fellow assigned by the Institute of Inter-American Affairs, during which time he became interested in the subject of chemoprophylaxis of STD. Since "prostitution was legalized to the extent that prostitutes were allowed to pay regular visits to men in penal

institutions" and because the VD Control Division was "responsible for medical supervision of prostitution and of all rapid treatment centers where all VD patients could be hospitalized for free treatment" (Part I, pg 8), Guatemalan prisons were thought to represent useful settings to study the effectiveness of chemoprophylaxis after sexual exposure to STD.

Dr. Funes explored these ideas with colleagues when he returned from the United States to Guatemala. The idea was "officially approved" and representatives of the VDRL continued discussions about project feasibility. The Pan-American Sanitary Bureau (PASB—the precursor to the Pan-American Health Organization), which was "actively interested in developing VD-control programs, as well as training and research facilities outside of the United States [Part I, pg 9]," agreed to collaborate. A research grant was made by the USPHS Division of Research Grants (the unit in charge of U.S. NIH extramural funding) to PASB. The VDRL "assumed responsibility for scientific and technical direction of the project and provided necessary personnel for assignment to the PASB to head the project (Part I, pg 9)," while the government of Guatemala "signed agreements with PASB permitting establishment of the research and training center and allowing cooperative working arrangements between the PASB staff and various units of the government for research and training purposes (Part I, pg 9)." There was an agreement that, "the laboratory and equipment set up in Guatemala for the study would revert to the government when the PASB relinquished interest in the training and research program; also, that local personnel would be trained to work in the public health service and to take over the unit as a governmental activity if so desired (Part I, pg 9)."

The potential scope of envisioned activities was broad, including assessing the burden of disease in the country, training personnel to conduct disease control activities, establishing services for diagnosis and treatment, and research in diagnosis, treatment, and chemoprophylaxis. As summarized by Dr. Cutler, "this meant that the staff had authority to work with the medical and other authorities of the public health service rapid treatment center for venereal diseases; in the government hospitals; with medical installations and officers of the military; with institutions caring for orphans and the insane; and with the penal system (Part I, pg 10)."

There seems to have been relatively widespread knowledge in the scientific community about the proposed studies. A letter from Dr. John F. Mahoney, director of the VDRL, to Dr. Cutler (dated October 15, 1946) mentions that: "Your show is already attracting rather wide and favorable attention up here. We are frequently asked as to the progress of the work; Doctor T.B. Turner of Johns Hopkins wants us to check on the pathogenicity in man of the rabbit spirochete; Doctor Neurath of Duke would like to have us follow patients with his verification procedure; Doctor Parran (the Surgeon General) and probably Doctor Moore might drop in for a visit at the first of the year." A subsequent letter from Dr. Mahoney (dated December 23, 1946) indicated continued high-level support, emphasizing that "The Surgeon General has become keenly interested in the Guatemala project."

Review of Summary Reports and Experimental Logs: Study Populations

Study Populations.

According to the "Syphilis Summary Report", the initially targeted population of research subjects were prisoners in the Central Penitentiary, housing about 1,500 male inmates ranging from short-term offenders to those with life sentences, and female CSWs engaged to provide services to prisoners. Medical care in the prison included an entry physical exam to "assure freedom from venereal disease, ecto-parasitic infestations, and gross physical deformity..."; quality and quantity of care was noted as being, "better than that available to most of the inmates when they were free (Part I, pg 13)."

Several problems arose with the prison studies. First, initial studies indicated problems with specificity of syphilis serologic tests. Tests previously considered to have good performance characteristics in North America and Europe (e.g., Mazzini and Kahn tests) appeared to perform non-specifically as screening tests in the prisoners and other Guatemalan populations studied, in spite of what was believed to be the rarity of endemic, non-venereal treponematoses such as yaws or pinta in Guatemala. Resolving this issue required studies comparing a battery of serologic tests in several populations.

Second, while it was ultimately determined that more newly developed serologic tests (i.e., VDRL slide test and Kolmer test) performed more accurately with far fewer false

positive tests. Attempts to collect sequential serum samples revealed that most inmates were unwilling to submit to frequent blood sampling. "Most of them believed that they were being weakened by weekly or biweekly withdrawals of 10cc of blood," and this fear "could not be countered by promises of or actual administration of penicillin for syphilis and iron tablets to replace blood (Part I, pg 16)."

Finally, while a primary stated rationale for conducting studies in Guatemala was the legal environment allowing prisoners to have sexual contact with CSWs, initial studies indicated that sexual transmission of syphilis was relatively inefficient. For the studies of sexual transmission, two CSWs were inoculated by intra-cervical injection of infected rabbit tissue. Both developed serologic evidence of infection without visible lesions and subsequently became seronegative "after specific therapy" of unstated type. A total of 12 male "volunteers" from the penitentiary had a single sexual exposure to one of these women. Despite the absence of condoms or chemoprophylaxis, none developed clinical infection, and based on incomplete serologic follow-up (due to reluctance to undergo repeated bleedings), it was estimated that at most, one or two (8-16%) were asymptomatically infected. There is no description of specific knowledge of experimental details (e.g., risk of infection), nor consent by the subjects.

The issues noted above led the investigators to consider several changes: a change in design from studies of sexual transmission to human inoculation studies and a change in population from prisoners to a primary focus on patients in the National Mental Health Hospital. This facility was the only one of its kind in Guatemala, was estimated to serve patients derived from a population base of 3.5 million people, and had a daily census of 800–1,000 men and women. The asylum was described as "desperately and pathetically poor, both financially and in terms of personnel and medical attention," although it was noted that "the standards of housing and feeding and medical care of the inmates were, with but few exceptions, superior to that of normal members of the families from which they came." Specifically, there were limited supplies of anti-convulsants (although many patients had epilepsy), antibiotics, refrigeration space, and tableware, and no funds to support cigarettes or recreational items such as a motion picture projector for the patients. It is noted that the director of the hospital, "was anxious to institute serologic screening of the inmates (Part 1, pg 17)." Also of note is that one of the authors (who appears to have worked in the hospital) suggested "that

since we had available a certain and sure cure for syphilis, it should be possible to set up experiments with his patients which could give conclusive answers to a number of questions (Part 1, pg 21)." These included questions about the effectiveness of chemoprophylactic regimens, performance of serologic tests, and issues about reinfection following treatment. There is a lengthy description of the process involved in deciding to conduct the studies, the background of the investigators in performing human challenge studies, and the need to avoid widespread knowledge of their occurrence (Part I, pg 23):

> "Responsible medical officials representing all groups concerned decided to undertake studies involving inoculation with syphilis at the insane asylum. Members representing the VDRL had previous experience in inoculation of volunteers both with gonorrhea and syphilis and the organizations concerned had been involved with inoculation studies with other types of diseases, such as malaria and infectious hepatitis, so that there was a large background of experience in the methods of working in human inoculation and with safeguards for the individuals concerned. But as a result of experience elsewhere, it was deemed advisable, from the point of view of public and personal relations, to work so that as few people as possible knew the experimental procedure. As will be appreciated, this necessitated certain compromises in experimental design and patient management which were believed necessary in the interests of the total experiment."

Although there seems to have been institutional support for the studies and even participation by institutional staff in some study elements such as subject tracking for follow-up, the question of subject consent is not addressed. It is noted, that although funds had originally been "allocated in the budget for payment of volunteers (Part I, pg 25)," with the shift of primary focus to patients in the asylum rather than the prison, "it was decided to use these funds for the benefit of the institution rather than for the individual (Part I, pg 25)." Such institutional support included provision of items noted as lacking, such as anti-convulsant medications, a refrigerator, a motion picture projector, and tableware. Subjects were offered cigarettes as an incentive: a pack for involvement in an experiment or if blood or cerebrospinal fluid (CSF) was collected, or a single cigarette for a clinical observation. It is noted that "patients would often attempt to make

numerous trips past the physician, for bloodletting, cisternal puncture or examination, just to augment their supply of tobacco (Part I, pg 33)."

Studies of syphilis.

A compilation of subjects involved in studies of syphilis, gonorrhea, and chancroid is outlined in Table 1.

According to the "Syphilis Summary Report", following the initial pilot studies of sexual transmission of syphilis from experimentally infected female CSWs to male prisoners through sexual activity, which resulted in limited transmission, a series of 17 additional experiments involving human inoculation with syphilis were carried out from May 13, 1947, until July 4, 1948. It was recognized quickly that exposure of subjects to infectious material through intact mucous membranes (cotton pledgets soaked in known quantities of viable *T. pallidum* placed under the foreskin of the penis) was also relatively inefficient and infection could be more reliably transmitted by intracutaneous injection or exposure of skin surfaces abraded with a fine needle (into the foreskin of the uncircumcised penis or the skin of the arm), analogous to techniques used for smallpox vaccination. These approaches were used in most experiments, although a few assessed transmission of infection by intravenous inoculation, oral ingestion, or inoculation of the CSF by cisternal puncture.

The primary focus of most of the experiments was to assess various chemoprophylactic regimens or to assess the ability to re-infect subjects with recently treated syphilis or untreated latent syphilis. Subjects in these experiments largely came from the mental hospital, with subject selection based on baseline serologic findings and history of syphilis, perceived cooperativity, and the likelihood that the subject would not be released prior to post-inoculation observations. It appears that attempts were made to exclude subjects with known homosexual behavior due to concerns about potential sexual contact inside the hospital.

Particular attention was given to identity of patients during follow-up because "some inmates did not know their names and were designated as, for example, 'The Mute of St. Marcos'. Others used several names interchangeably, and some would be known by

one name to one nurse and by another designation to a second nurse (Part I, pg 32)." A minority of subjects came from the prison. Overall, as enumerated in the "Syphilis Summary Report", these 17 experiments included exposures (summed across experiments without unduplication of individual subjects) of 712 subjects, 682 (96%) of whom were exposed to infectious materials. The "Syphilis Summary Report" indicates that 404 (59%) of the 682 were infected, although the "Individual patient response in each experiment" table indicates that the number infected was as high as 423 (62%).

As noted, one experiment assessed response to central nervous system inoculation in seven subjects via intracisternal puncture. The subjects were described as, "deteriorated and debilitated epileptics," apparently studied in this way in part because "it was hoped that by shock of inoculation it might be possible to influence favorably their epilepsy." It was also noted that "this experiment was undertaken at the expressed desire of the clinical director [of the asylum] in hopes that he might be able to do something for these women who had been completely resistant to all types of anticonvulsant therapy (Part III, pg 23)." All developed stiff neck, headache, and fever within several days, presumed to be due to bacterial meningitis and all of which responded to sulphonamides. Subsequently, the subjects developed what was thought to be acute syphilitic meningitis, with headache, neck stiffness, and, in one case, transient paralysis of the lower extremities. It is noted that "following therapy all patients revealed complete reversal of signs and symptoms (Part VI, pg 14)."

Studies of gonorrhea

For gonorrhea, initial experiments focused on sexual exposure from experimentally infected female CSWs to male soldiers. Although "it proved extremely difficult to obtain prostitutes willing to serve under experimental conditions (Experimental Studies in Gonorrhea, pg.3)," 12 women were recruited and inoculated with gonorrhea 5–14 days prior to the studies. While "none of the females thus infected showed evidence of acute infection such as a rich outpouring of thick yellow pus from the cervix or by signs of pelvic inflammatory disease…, all of them showed evidence of infection by cervical discharge (Experimental Studies in Gonorrhea, pg 3)" and all were culture-positive. However, as with experiments with syphilis, sexual exposure resulted in a low efficiency

of transmission (only 5 infections in 138 exposures by 93 men). The duration of sexual contact was timed (average 1–2 minutes), but not directly observed by study personnel. These studies were followed by more extensive studies of direct inoculation, performed either as "superficial inoculation" (of the urethral meatus) or "deep inoculation" (in which the thin end of a toothpick wrapped in cotton was inserted ½ inch into the urethra)—noted to be more painful. (The latter technique was based on observations of soldiers who, to secure hospitalization for treatment and avoid duty assignments, inoculated themselves with gonorrhea-infected pus, obtained from an infected man and inserted into the urethra with a matchstick.) Both techniques resulted in more efficient transmission and were the basis for a series of studies assessing the effectiveness of various chemoprophylactic regimens. The studies were primarily conducted among soldiers, and over the course of 41 experiments performed in soldiers between March 1947 and July 1948, review of experimental tables indicates that 663 subjects were included, 214 (33%) of whom were judged to be infected.

Study records (experimental logs) also mention gonorrhea inoculation experiments in four mental hospital subjects. One man, inoculated in the penis, developed a urethral discharge, and two men were inoculated in both penis and rectum, one of whom had a microscopic smear positive for gonorrhea with no information for the other. The fourth subject was a female described as having an unspecified "pre-terminal" illness, who was inoculated in the urethra, rectum, and the conjunctiva of both eyes and who developed bloody discharge from the urethra and bilateral conjunctivitis; she was also inoculated with syphilis at the same time.

Thus, in total, 772 subjects were exposed in the gonorrhea studies, 234 (30%) of whom were judged to be infected. Study records for gonorrhea studies identify subjects only by name, gender, and study number as for the syphilis studies; no other identifying information is available in the archives. Likewise, there was no documentation of any informed consent or incentives for study enrollment, or any documentation that subjects understood that they were participating in research.

Studies of chancroid

For chancroid, a single experiment described in the "Chancroidal Prophyaxis" summary report included 131 subjects (presumably from the military since they are described as a "company of 131 men"), each inoculated with *H. ducreyi* in three sites on the arms: one site treated with the standard U.S. Army Pro-kit, one with Orvus, and one site serving as an untreated control. All appear to have been infected. In addition, experimental logs indicate that 11 subjects from the mental hospital were inoculated in single-person experiments. Thus, in total, 142 subjects were exposed in the chancroid studies, 138 (97%) of whom were judged to be infected. Again, the only identifying subject information is name in the study records, and there is no discussion of subject knowledge, consent, or incentives to participate.

Review of Summary Reports and Experimental Logs: Subject Follow-up and Documentation of Treatment

As noted above, Table 1 summarizes what is known about subject treatment from each set of studies.

Studies of syphilis.

According to the "Syphilis Summary Report", in the syphilis studies, patient assessment included physical exams of the site of inoculation, other skin surfaces, and lymph nodes; darkfield microscopy of suspected lesions; a battery of serologic tests on blood samples; and CSF examination after cisternal puncture. Results of a positive darkfield examination or positive VDRL slide and Kolmer standard tests were considered more specific evidence of infection, while Mazzini and Kahn test results were considered too non-specific for diagnostic classification (III, pg 4). It does appear that quantitative Kahn titers were used in assessing course of infection among those diagnosed with syphilis by other criteria (IV, pg 5). Blood samples were collected at weekly intervals through December 1948, 6–19 months after performance of the experiments. There was also an attempt to collect blood samples at 6-month intervals or more frequently after December 1948. Since there was a high mortality rate among asylum inmates, primarily as a result

of tuberculosis, attempts were made to perform autopsies on all experimental subjects who died for special spirochetal and histologic studies.

For treatment, three preparations of penicillin were used and administered by intramuscular injection: aqueous solution of sodium or potassium salt of penicillin G (concentration 25,000 units/cc); "POB," a calcium penicillin in beeswax peanut oil mixture (concentration 300,000 units of PCN per cc), and Duracillin, consisting of the procaine salt of penicillin in a peanut oil base (concentration 300,000 units of penicillin per cc). Needles and syringes were sterilized between experiments by boiling, although the same needle was used for administering entire contents of one syringe without sterilization between individual patients (Part IV, pg 3). Allergic reactions were monitored closely and the Summary Report describes no cases of anaphylaxis, serum sickness, or cutaneous reactions. Likewise, the report noted "no sign of hepatitis or jaundice developing in any of the experimentally treated patients (Part IV, pg 3)" (although specific laboratory testing for viral hepatitis could not have been conducted in that era). It is noted that "one patient developed status epilepticus during the course of therapy with aqueous penicillin for primary syphilis on the 6th day, and despite efforts to control the condition, died." There is no comment about the possible relationship of the death to penicillin therapy, although the report states that, "he was known to have had constant, severe attacks and had been a problem in management of epilepsy prior to the experimental work (Part IV, pg 3)."

Based on extensive studies performed by VDRL scientists elsewhere, "adequate" treatment was considered to be ≥3.4 million units of penicillin administered over 7–8 days, with aqueous preparations given every 2 hours (for 85 injections) and longer-acting preparations (POB and Duracillin) given at 12- or 24-hour intervals (for 20 injections). It is noted that "scrupulous care was taken to ensure…that each patient…received each injection for which he was scheduled (Part I, pg 39)." The timing of treatment was not clearly specified other than the comment that "we attempted to treat patients immediately upon the finding of the first evidence of secondary lesions so as to prevent possible person-to-person transmission within the institution (Part VI, pg 53)."

Response to treatment was apparently determined by clearance of lesions and serologic responses over time, although criteria for treatment response are not precisely stated.

Although the authors were expert syphilologists with vast clinical experience, their assessment of treatment adequacy was limited by the nature of the serologic tests used and the duration of clinical and serologic follow-up after treatment. Quantitative titers were available only with less specific tests (e.g., Kahn test), with VDRL results available only qualitatively as positive or negative.

Part IV of the "Syphilis Summary Report" outlines a "Summary of Treatment Results". It notes that of 248 subjects given "adequate" treatment, only one was considered to have failed treatment based on persistently high serologic titers and mucocutaneous relapse of lesions. Following a second course of penicillin, his titers fell six-fold (from 1:512 to 1:8 Kahn units), and the subject remained asymptomatic over approximately 8 months of follow-up. Additional subjects were intentionally given lower doses of penicillin (expected to maintain therapeutic levels for only 12–24 hours) in order to observe clinical and serologic patterns of relapse, and 10 of 36 (28%) such subjects were considered to have failed treatment.

The most complete compilation of treatment in the archives is the "Individual patient response in each experiment" table, which provides a listing of the clinical response and treatment history of subjects involved in each inoculation experiment. Review of experimental logs indicates that in total, the syphilis inoculation experiments included 638 experimental subjects, 423 (66%) of whom were judged to have been infected. Of the 423, the table records adequate treatment for 369 (87%) subjects, "partial treatment" for 10 (3%) subjects, and for 44 (10%), no prescribed treatment. For 3 of the 44, it was noted that subjects left the asylum before they could be treated (n = 2) or that they died before treatment (n = 1). Some of these "experimental subjects" represent the same subjects included in multiple experiments after their initial infection was treated, which may explain the discrepancy in the numbers from Part IV, cited above.

Overall, combining the results from the "Individual patient response…" document with those from the initial studies of sexual transmission with infected CSWs (i.e., 2 infected CSWs of uncertain treatment status and 12 uninfected prisoners) yields the following totals (again, not correcting for persons involved in multiple experiments): 726 "experimental subjects", 696 (96%) of whom were exposed to infectious materials. Of

the 696, 427 (61%) were judged to be infected, and 369 (86%) were recorded as receiving adequate treatment with penicillin.

Studies of gonorrhea

Based on statements in the "Experimental Studies in Gonorrhea" summary report, all 232 of the infected soldiers and CSWs appear to have been treated with "adequate" doses of penicillin (injection of 300,000 units), although there are no subject-specific records to document treatment. Of the 3 mental hospital patients with documented infection, 2 were treated with penicillin, while the third subject—the woman with the unspecified "pre-terminal illness" inoculated with both gonorrhea and syphilis in her urethra, rectum, and eyes—died 4 days later with no recorded treatment.

Studies of chancroid

Based on statements in the "Chancroidal Prophylaxis" summary report, all 131 military subjects developed lesions at the site of chancroid inoculation. Of the 131 subjects, 129 (98%) were treated with sulfathiazole 1 gram PO four times a day for 5 days, with rapid lesion healing, although there are no subject-specific records to document treatment. Treatment of the other two was deferred to allow further observation, since they had experienced partial benefit from chemoprophylaxis, and is not documented as having been administered. Of the 11 subjects from the asylum, 7 developed typical lesions at the site of inoculation, 3 had no findings, and one had no follow-up. Treatment was not documented for any of the 11.

Detailed Review of Subject-Specific Records for the Syphilis Inoculation Studies

To enhance the archives review process, a detailed review of the short, subject-specific records of subjects involved in the syphilis inoculation studies was conducted by a record review team of medical epidemiologists, physicians, and analysts at the CDC in consultation with an internal Institutional Review Board chair. The purpose of the review was to provide greater detail about experimental exposures and treatment outcomes of individual patients, thus allowing an opportunity to supplement findings from the "Syphilis Summary Report" and experimental logs. Given the many unethical aspects of the

design and conduct of the study, there was explicitly no attempt to use the record review findings to assess the experimental hypotheses of the study investigators, nor to create generalizable scientific information.

The dates of documented, experimental activities ranged from 1947–1953. Experimental inoculations were conducted from 1947–1948 with follow-up clinical examinations, including blood tests and CSF analysis obtained through blood draws and cisternal punctures, continuing through 1953 for some subjects. Of the 17 experiments, protocols from experiment numbers 1–15 were available for review, listing 580 named persons who had been subjects in any of the experiments, 532 (92%) of whom had subject-specific records that could be reviewed. Experiment numbers 16 and 17 included 74 and 48 unnamed subjects, respectively, potentially up to 122 different subjects, and because no records could be reviewed for these subjects, it cannot be determined whether they participated in prior experiments or whether they represent specific subjects in addition to the 580. Overall, of the 532 subjects in experiment numbers 1–15 with reviewable records, 416 (78%) were from the mental hospital, including 242 males and 174 females, while 116 (22%) were from the prison, 113 men and 3 women (noted to be "staff"). Apart from name, institution, and gender, other identifying information was available only in a limited number of subjects: age for 113 (21%), city or state of residence for 63 (12%), and names of family members for 43 (8%). For the 113 subjects with recorded ages, they ranged from 15–58 years, with 6 subjects under 18 years of age. Though most of the subjects with stated residence were from Guatemalan states, other named countries of residence included Mexico, El Salvador, Nicaragua, and Honduras, though citizenship status was not recorded.

Over the course of the 15 experiments, a total of 530 (99.6%) subjects received inoculations with experimental material; the other 2 subjects were followed with repeated serologic tests but had no documentation of inoculation. Of the 530 inoculated, 497 (94%) subjects were inoculated with live *T. pallidum* (derived from either chancres from other infected humans or from ground testicles of infected rabbits), while 33 (6%) were inoculated with what was thought to be uninfected material (e.g., suspensions of bacteria that had been heat-killed, or ground testicles of uninfected rabbits). Live bacterial inoculations occurred among 414 (99.5%) of the subjects from the mental hospital and 83 (72%) of the subjects from the prison. Overall, at least 184 subjects were involved in

more than one experiment, ranging from two to five experiments. Over the 15 experiments, a total of 771 inoculations with experimental material were administered. These 771 inoculations occurred most commonly by subcutaneous injection into the skin of the arms (438, 57%), with other methods including scarification or abrasion of the skin of the penis before applying cotton pledgets soaked in infectious material (205; 27%) or soaked cotton pledgets applied topically under the intact foreskin of the penis (63; 8%); subcutaneous injection into the coronal sulcus of the penis (38; 5%); intravenous inoculation into the antecubital fossa (13; 2%); oral ingestion (7; 0.9%); and central nervous system injection by cisternal puncture (7; 0.9%).

The records contained no documentation of informed consent for study enrollment, any indication that subjects understood they were participating in research, or enumeration of incentives received by specific subjects for participation.

The subject record review revealed a variety of problems in assessing subjects after inoculation. There was variable documentation of serologic follow-up, because of either insufficient sample quantity, samples not being collected (due to patient refusal or unavailable staff), or patients having left the institution. Overall, 104 (21%) of 497 subjects inoculated with infectious organisms were noted to have been “freed”, “transferred”, or otherwise discharged at some point following inoculation. In addition, dates of some serologic results were the dates of the report of the test result in some cases conducted at the VDRL in the United States, not the collection of the sample. There were also concerns that serologic results may have been recorded for the wrong patient, either due to mislabeling at the time of collection or errors in transcription of results.

Table 2 summarizes findings from the record review about likely infection status post-inoculation and subject treatment. Of the 497 individual subjects exposed to infection by inoculation, 433 (87%) were considered to have evidence of syphilis by a series of hierarchical laboratory criteria: 49 (10%) by identification of the organism using darkfield microscopy, 303 (61%) by post-inoculation seroconversion of the VDRL test, 62 (14%) by a positive VDRL test pre-inoculation, and 19 (4%) by post-inoculation seroconversion by the less-specific Kahn test. Of the remaining 64, 17 (27%) were considered to have “possible” syphilis based on physical examination findings in the absence of positive

laboratory tests, while 47 (73%) had neither laboratory nor physical examination evidence of syphilis, but had variable periods of serologic follow-up, limiting the ability to completely rule out syphilis.

Regarding subject treatment, since completion of all doses of penicillin injections was documented in only 85 subjects, treatment is noted as being "prescribed" if initiation of a specified course of therapy is documented in the records. Of the 497 subjects exposed to infection, what were considered to be adequate doses of penicillin (>3.4 mu) were prescribed to 332 (67%), with partial doses prescribed for 45 (9%), and no doses prescribed at all for 120 (24%). Of the 433 subjects with laboratory evidence of syphilis, adequate doses of penicillin were prescribed for 331 (76%), partial doses for 39 (9%), and no doses for 64 (15%). Of the 64 patients with possible syphilis or in whom syphilis could not be ruled out, 12 (3%) were prescribed adequate doses of penicillin, 7 (11%) partial doses, and 55 (85%) no doses. Of the 104 subjects who left the institution after inoculation with infectious material, 61 (59%) were prescribed adequate doses of penicillin, 2 (2%) partial doses, and 41 (39%) no doses. Of note, among the subjects not prescribed treatment was one of the 7 with CNS inoculation.

There were no clear indications in the records about timing of initiating penicillin. Many subjects had progressed to and even resolved signs of primary or secondary syphilis before treatment was initiated. In several subjects, CSF abnormalities were noted, and in one, symptoms of neurosyphilis (loss of leg function following inoculation by cisternal puncture—a syndrome compatible with transverse myelitis) were documented after inoculation. Some subjects received penicillin for other reasons, including "political reasons", "security reasons before departure", "for reasons of fear of not having been completely treated", or "because of pronounced homosexual tendencies".

While there is no evidence that medical or psychiatric complications during and following the experiments were routinely elicited or recorded, a number were documented in the records, although relationship to study procedures is unclear. Nonfatal complications included many Jarisch Herxheimer reactions, one allergic reaction attributed to rabbit tissue, one skin abscess, and five seizures. One subject required an arm amputation as a result of gangrene; this was described as following injection of the anti-seizure medication, pentothal, and it occurred in the same arm as an experimental inoculation

two months earlier. In addition, one subject was noted to have findings consistent with neurosyphilis (i.e., tabes dorsalis, as evidenced by absent lower extremity reflexes and Argyll Robertson pupils) prior to inoculation.

Patient death during the months of prospective observation was documented for 71 subjects: 71 of 416 (17%) from the mental hospital, and none of the 116 from the prison. Records did not indicate likelihood of relationship of death to study procedures. However, subjects who were already suffering from other illnesses were not excluded from the study: at least one patient had a "pre-terminal" disease documented at the time of inoculation and died within days. One person with a seizure disorder died of status epilepticus on the last day of penicillin treatment, although, again, whether treatment precipitated the uncontrollable seizures is not clear. In many cases, "date of death" could be approximated only by the date at which it was recorded that the subject had recently died, an assessment that appears to have been recorded several months later in some cases. For most subjects, no cause of death was noted. Although an attempt was made to perform autopsies on patients who died, only 12 patients were noted to have had an autopsy. Results of autopsies that did occur were not routinely documented in the subject records, and the only findings described were tuberculosis in three subjects. In addition, clinical notes indicate that one subject died following thyroid surgery; one died of barbiturate (a treatment for epilepsy) intoxication; and two who died were noted to have had epilepsy. Temporally, the interval from the date of first experimental inoculation to the "date of death" for the 71 subjects who died was within 90 days for 13 (18%), from 91–180 days later for 8 (11%), from 181–365 days later for 9 (13%), from 1–2 years later for 15 (21%), and >2 years later for 26 (37%).

In summary, the greater detail provided by data from the "Review of subject-specific records for the syphilis inoculation studies" supplements information provided by the "Review of the summary reports and experimental logs", especially regarding involvement of patients in multiple experiments, problems with patient follow-up after inoculation that hindered accurate assessment of how many exposed subjects were actually infected, and precise determination of adequacy of treatment. A direct comparison of results between the two sources of data has several limitations. These include the uncertainty regarding how determination of "infected subjects" was made by the USPHS investigators, as well as reasons for higher estimates of those with infection

who received adequate treatment according to the USPHS investigators (369 of 427; 86%) than could be confirmed by subject record review (332 of 497; 67%, of all exposed, and 331 of 433; 76%, of those with laboratory evidence of infection). Among the potential explanations for these differences, are possible missing documentation in the subject-specific records available for review of treatments actually administered, possible errors in tabulating outcomes by the USPHS investigators, or the possibility that the "Syphilis Summary Report" was not considered to be final and ready for public dissemination. In addition, there was indication in the subject record review that some subjects were excluded from analysis for unknown reasons. Regardless of the differences, by either estimate, while the majority of exposed and infected subjects appear to have eventually been prescribed what was considered to be adequate doses of penicillin, treatment was routinely delayed for several months after exposure and a substantial number of subjects were not treated.

The Conclusion of the Study

A series of letters in early-to-mid 1948 offers some insight as to the conclusion of the study. A letter from Dr. Cutler's supervisor, Dr. R.C. Arnold, on April 19, 1948 raises questions about comfort of the VDRL with the use of the asylum patients as subjects:

> "I am a bit, in fact more than a bit, leary [sic] 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. I think the soldiers would be the best or the prisoners for they can give consent... In the report, I see no reason to say where the work was done and the type of volunteer."

Two months later (June 21, 1948), a letter from Dr. J.F. Mahoney notes that, "we are making the necessary arrangements for financing the terminal phases of the Guatemala study," and that, "it will be recalled that two local physicians were to be maintained on duty for the purpose of continuing the observation of certain of the patient groups...with Doctors Salvado and Funes ...to be considered for these appointments," with arrangement of this phase of work to "be carried out directly with the Pan-American

Sanitary Bureau." A subsequent letter from Dr. Cutler to Dr. Mahoney (August 26, 1948) notes that Dr. Cutler and several others "discussed thoroughly the matter of the continuation of our experimental studies" and lists the need to support "Juan M. Funes, MD, physician in charge of carrying on the present research program" and "Julio Salvado, MD, physician at Insane Asylum".

As per the understanding at the inception of the study, laboratory equipment was to be turned over to the Sanidad Publica of Guatemala for use in training in collaboration with PASB, and Guatemalan physicians and scientists whose names are mentioned in this regard, in correspondence from Drs. Cutler and Mahoney over the summer of 1948, include a Dr. Bianchi, the Minister of Health and Public Welfare, who is noted as having signed an agreement for the Government of Guatemala with Dr. Cumming of PASB; Dr. Abel Paredes Luna, who was to be trained at the VDRL in serology and the clinical aspects of venereal diseases; Rolando Funes, who was to serve as interim director of the serology lab in Guatemala; Dr. Galich, Director of the Sanidad Publica of Guatemala; and Dr. Carlos Tejeda, chief of the Medical Service of Military Hospital and involved in arranging training of American physicians in tropical medicine.

There was also strong interest in providing capacity-building efforts for serologic testing and venereal disease control more broadly in Central America. A letter (July 26, 1948) on which Dr. Cutler was copied from the Assistant Director of PASB, John Murdock, to the Chief of the Caribbean Sector of PASB, Dr. William McAnally, notes that a Dr. Mario Mollari of Georgetown University would be visiting El Salvador, Honduras, Nicaragua, Costa Rica, and Panama to promote training of lab technicians and standardization of laboratory practices.

Although syphilis serologic results and follow-up clinical observations were recorded on some subjects until 1953, there is no record of what activities occurred after patient follow-up was taken over by PASB and the two local physicians, nor whether further human inoculation studies were performed in Guatemala or other Central American countries. The only studies known to have been published from the Guatemalan work addressed comparisons of serologic tests. There is no evidence, either in the Cutler archives or by PubMed literature review, that the results of the STD inoculation experiments were ever published in the scientific literature or in any other forum.

As of this writing, of the individuals cited in the archives, Drs. Cutler, Levitan, Arnold, Mahoney, and Parran are known to be deceased. The status of the Guatemalan physicians—Drs. Funes, Bianchi, Gallich, Tejeda, and Salvado—is unknown.

Table 1: Overview of the USPHS STD Inoculation Study, 1946–1948, Based on Review of Summary Reports and Experimental Logs in the Archived Papers of John Cutler, MD

Study characteristic	Syphilis	Gonorrhea	Chancroid
Source of subjects	Commercial sex workers, mental hospital patients, prisoners	Commercial sex workers, prisoners, soldiers, mental hospital patients	Soldiers (presumed), mental hospital patients
Type of exposure*			
--sexual contact with commercial sex workers**	12	93	0
--cutaneous or mucous membrane inoculation**	656	679	142
--intravenous inoculation	13	0	0
--intra-CSF inoculation (via cisternal puncture)	7	0	0
--oral ingestion	6	0	0
Total number of subjects exposed**	696	772	142
Number of subjects judged to be infected**	427 (61%)	234 (30%)	138 (97%)
Type of treatment considered to be adequate	Penicillin (≥3.4 million units)	Penicillin 300,000 units	Sulfathiazole (1 g PO qid X 5 days)
Number (%) of subjects with indication of adequate treatment**	369 (86%)	233 (99.5%)	129 (93%)

*Numbers include exposure to both infected and uninfected experimental materials (e.g., heat-killed bacteria, uninfected rabbit tissue)

**Numbers are totals summed from numbers of subjects in specific experiments. Their total is greater than the number of individual subjects overall since some subjects were included in multiple experiments.

Table 2: Infection Outcomes and Treatment of Experimental Subjects Involved in USPHS Syphilis Inoculation Studies, 1946–1948, Based on Review of Subject-specific Records from Archived Papers of John Cutler, MD

Outcomes of patients exposed to infectious Treponema pallidum	Total no. (%)	Treatment prescribed[1]		
		No. (%) ≥3. 4 million units penicillin (PCN) G	No. (%) ≤3.4 million units PCN G	No. (%) no PCN G
TOTAL	*497*	*332 (66.8%)*	*45 (9.1%)*	*120 (24.1%)*
Hierachical laboratory evidence of syphilis	*433*	*331 (76.3%)*	*39 (9.0%)*	*64 (14.7%)*
--Positive darkfield microscopy	49	46 (93.9%)	1 (2.0%)	2 (4.1%)
--Seroconversion by VDRL test	303	247 (81.5%)	15 (5.0%)	41 (13.5%)
--VDRL-positive pre-inoculation	62	31 (50.0%)	21 (33.9%)	10 (16.1%)
--Serologic evidence by Kahn test)[2]	19	6 (31.6%)	2 (10.5%)	11 (57.9%)
No laboratory evidence of syphilis	*64*	*2 (3.1%)*	*7 (10.9%)*	*55 (85.0%)*
---Possible syphilis by physical examination[3]	17	2 (11.8%)	1 (5.9%)	14 (82.4%)
---Others (exposed, but no laboratory or physical examination evidence)	47	0 (0%)	6 (12.8%)	41 (87.2%)
--<3 m serologic follow-up	12	0 (0%)	4 (33.3%)	8 (66.7%)
--3–6 m serologic follow-up	6	0 (0%)	1 (16.7%)	5 (83.3%)
-->6 m serologic follow-up	29	0 (0%)	1 (3.4%)	28 (96.6%)

[1]Based on documentation of initiation of a prescribed course of multiple injections of penicillin therapy. In most cases, there was no documentation in the records that therapy was completed.

[2] A ≥4-fold rise Kahn titer at any point 3 weeks or more after exposure to infection.

[3] Physical findings included ulcer, papule, nodule, or other cutaneous abnormality at the site of inoculation; lymphadenopathy; maculopapular rash; or new focal neurologic deficit

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