A STUDY GUIDE TO

"Ethically Impossible" STD Research in Guatemala from 1946 to 1948

Presidential Commission *for the* Study of Bioethical Issues

November 2012

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http://www.bioethics.gov

ABOUT THE PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

The Presidential Commission for the Study of Bioethical Issues (the Commission) is an advisory panel of the nation's leaders in medicine, science, ethics, religion, law, and engineering. The Commission advises the President on bioethical issues arising from advances in biomedicine and related areas of science and technology. The Commission seeks to identify and promote policies and practices that ensure scientific research, health care delivery, and technological innovation are conducted in a socially and ethically responsible manner.

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INTRODUCTION

In what is now recognized as an infamous episode in the history of research ethics, the U.S. Public Health Service (PHS) conducted sexually transmitted disease (STD) experiments in Guatemala from 1946 through 1948. The Guatemala STD experiments were carried out with ongoing oversight by PHS and with the approval and engagement of Guatemalan government officials. They involved intentionally exposing and infecting several vulnerable Guatemalan research subject populations—prisoners, soldiers, and psychiatric patients—to disease, without their consent.

After a scholarly publication disclosed the existence of records of these experiments in 2010, the Presidential Commission for the Study of Bioethical Issues (the Commission) conducted a detailed investigation of the events surrounding and including the experiments. Its report, *"Ethically Impossible:" STD Research in Guatemala from 1946 to 1948*, provides a detailed description and ethical evaluation of these studies.

The Commission designed this Study Guide to assist those who wish to focus on the ethical significance of these experiments. Each section of the Guide includes a recitation of relevant facts, excerpts from documents contemporaneous to the experiments, and a set of further readings. This material will assist readers who wish to explore the record in further detail or prepare for a more informed discussion of research in light of this gross violation of ethics.

SETTING THE STAGE FOR THE GUATEMALA EXPERIMENTS

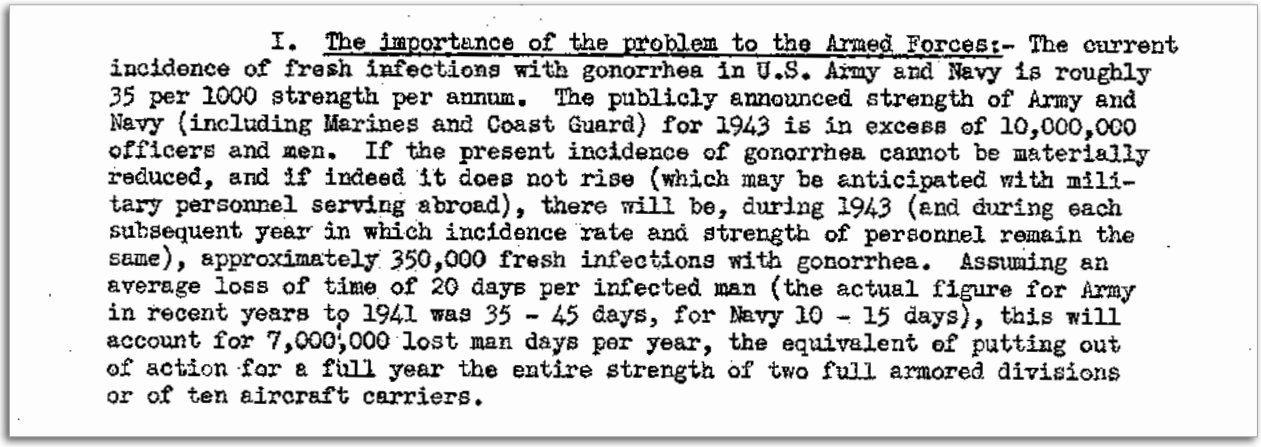
Developments in the Science and Prevention of Sexually Transmitted Diseases

Although STDs are as old as human history, effective treatments for them have been available for less than 60 years. From the European Renaissance through the 19th century, medical practitioners used highly toxic heavy metal therapies such as mercury and arsenic to treat both syphilis and gonorrhea. In 1879, the German physician Albert Neisser discovered the *gonococcus* bacteria and identified it as the causative agent for gonorrhea. The cause of syphilis was discovered in 1905, and the next year a test was developed for diagnosing the disease.

These discoveries paved the way for more focused attention on addressing the presence of specific microbes in infected patients. One arsenical compound called Salversan, announced in 1909 by Nobel Prize winner Dr. Paul Ehrlich, seemed to represent a promising new treatment. Although Salversan, like earlier medicines, appeared to reduce the infectiousness of patients, it did not cure syphilis. When World War II broke out 30 years later, clinicians still had no reliable cure for gonorrhea or syphilis, the most deadly of the "venereal diseases."

Researchers and government officials were particularly concerned about the affect of STDs on the health and readiness of the armed services. Before World War I, an expert noted that "there is no one factor or condition in the army which produces more sickness, decreases the efficiency of the men so greatly, or affects their morale more than diseases of venereal origin…and there is no military problem which confronts the War Department which is more worthy of discussion or requires more prompt or energetic action."[1]

Dr. J.E. Moore was the Chairman of the Subcommittee on Venereal Diseases under the National Research Council (constituted to perform research for the National Academy of Sciences). In early 1943, he described the impact of STDs on the military in a letter to the Chair of the Medical Research Committee of a newly established government office, the Office of Scientific Research and Development:



I. The importance of the problem to the Armed Forces:- The current incidence of fresh infections with gonorrhea in U.S. Army and Navy is roughly 35 per 1000 strength per annum. The publicly announced strength of Army and Navy (including Marines and Coast Guard) for 1943 is in excess of 10,000,000 officers and men. If the present incidence of gonorrhea cannot be materially reduced, and if indeed it does not rise (which may be anticipated with military personnel serving abroad), there will be, during 1943 (and during each subsequent year in which incidence rate and strength of personnel remain the same), approximately 350,000 fresh infections with gonorrhea. Assuming an average loss of time of 20 days per infected man (the actual figure for Army in recent years to 1941 was 35 - 45 days, for Navy 10 - 15 days), this will account for 7,000,000 lost man days per year, the equivalent of putting out of action for a full year the entire strength of two full armored divisions or of ten aircraft carriers.

Joseph Moore to A.N. Richards. (1943, February 1). Correspondence. Presidential Commission for the Study of Bioethical Issues Human Subjects Protections I (PCSBI HSPI) Archives, NARA-II_0000176.

[1] Maus, L.M. (1910). Venereal diseases in the United States Army—Their prevention and treatment. *The Military Surgeon*, 27(2), p. 130.

Dr. Moore would later become the Chair of the Study Section that recommended the Guatemala STD experiments for federal funding.

After World War II began, the Surgeon General of the United States, Dr. Thomas Parran, joined with the Surgeon General of the Army and briefly introduced a dramatic film to teach members of the military the cost of STDs to the war effort (see *Recommended Reading*). Dr. Parran was also the final level of approval for the Guatemala STD experiment funding.

In 1943, Drs. John Mahoney and Richard Arnold of the PHS Venereal Disease Research Laboratory in New York discovered that penicillin cured syphilis in four human volunteers. This discovery prompted researchers to focus on the use of penicillin as the "magic bullet" to eradicate venereal disease in the armed services as well as in the general population.

Comment

What was the primary motivation for the government's interest in the prevention and treatment of STDs? What are the implications for the treatment and prevention of other diseases when a government entity becomes focused on a particular disease? What aspects of the above description suggest the need for independent and objective review of research protocols? What ethical principles would provide a framework for considering the appropriateness of focusing government efforts and spending on particular diseases affecting the armed services? Are there specific ethical issues that should be considered when this research is carried out during a "time of war?"

Recommended Reading

Beauchamp, T.L., and J.F. Childress. (2001). *Principles of Biomedical Ethics*. New York: Oxford University Press.

Emanuel, E.J., et al., (Eds.). (2008). *The Oxford Textbook of Clinical Research Ethics*. New York: Oxford University Press.

Katz, J. (1972). *Experimentation with Human Beings: The Authority of the Investigator, Subject, Professions, and State in the Human Experimentation Process*. New York: Russell Sage Foundation.

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National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: Department of Health, Education, and Welfare.

Committee on Science, Engineering, and Public Policy, National Academies of Sciences. (2009). *On Being a Scientist: A Guide to Responsible Conduct in Research: Third Edition*. Washington, DC: National Academies Press.

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PCSBI. (2011, December). *"Moral Science:" Protecting Participants in Human Subjects Research*. Washington, DC: PCSBI.

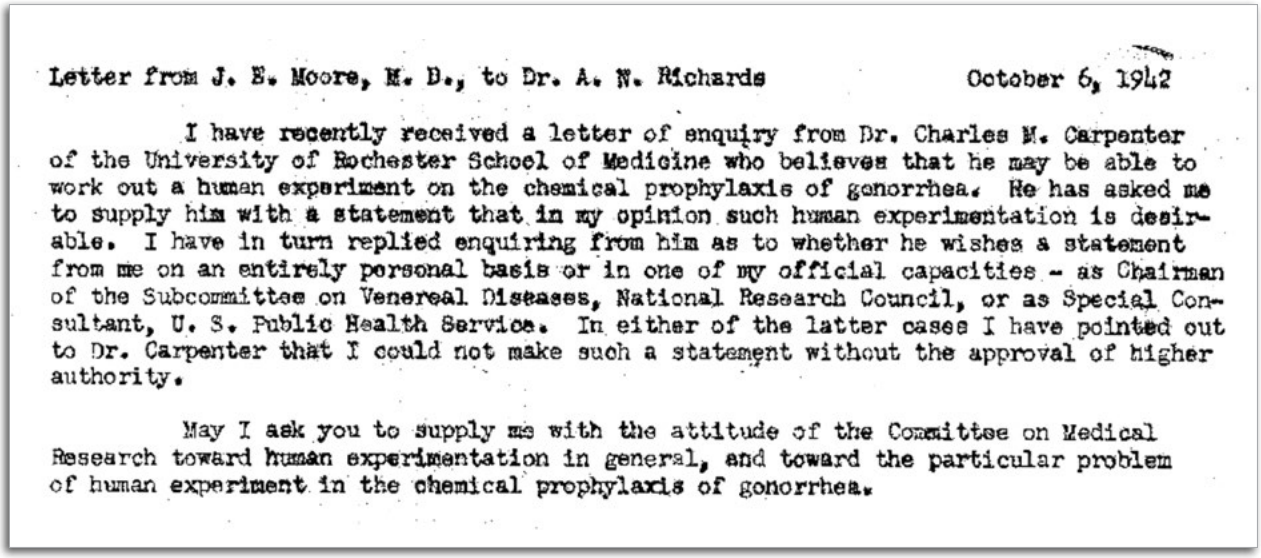
World Medical Association. (2008). *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Ferney-Voltaire, France: World Medical Association.

45 C.F.R. § 46. (2009). *Protection of Human Research Subjects*.

Terre Haute Prison Experiments

At the onset of World War II, the same STD prevention protocol had been in use in the U.S. Army and Navy for 30 years. A measure taken as a prevention for a disease is called a prophylaxis, and can be one of two types: pre-exposure prophylaxis (when someone employs a prophylaxis *before* they might be exposed to an STD, e.g. a condom), and post-exposure prophylaxis (when someone employs a prophylaxis *after* they are exposed to an STD but before they become infected, e.g., an antibacterial wash). The post-exposure prophylaxis procedure in use during World War II required men, after engaging in sexual intercourse, to inject a silver proteinate (bactericide) into their penises to prevent gonorrhea and rub a thick white calomel ointment (related to mercury) over their penis and pubic region to prevent being infected with syphilis. These methods had been adopted based on field studies of questionable scientific accuracy. Speaking on the need to re-evaluate the regimen of prophylaxis followed by the Armed Services, STD expert Dr. John F. Mahoney, pointed out that "[t]he prevention of the primary invasion of the male by the syphilis spirochete, as a means of minimizing the loss of effectiveness which is incident to established disease, still constitutes one of the most pressing problems of military medicine."[2]

In October 1942, Dr. Charles M. Carpenter, a researcher at the University of Rochester School of Medicine and Dentistry, contacted Dr. J.E. Moore, the Chairman of the National Research Council subcommittee on Venereal Disease, to ask about possible research funding. Dr. Carpenter proposed conducting gonorrhea prevention research in humans following intentional artificial exposure to the bacteria that causes the disease. Dr. Moore then wrote to Dr. A.N. Richards, Chair of the Committee on Medical Research of the Office of Scientific Research and Development. Dr. Richards replied three days later.



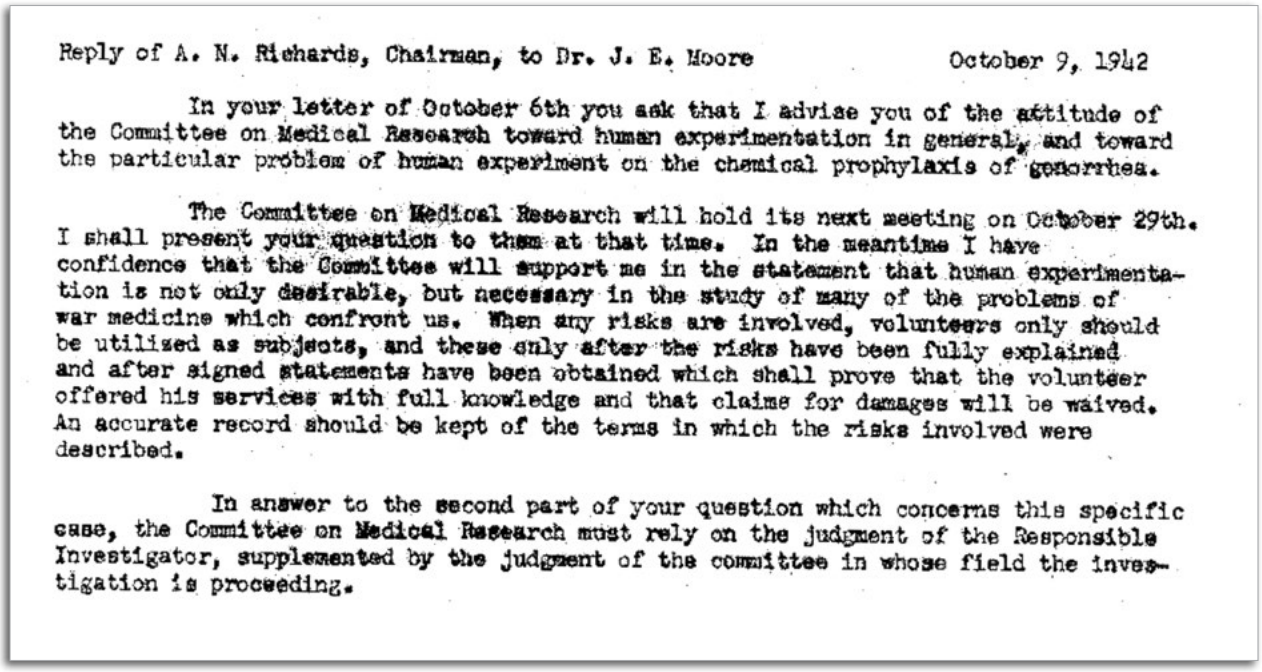
Letter from J. E. Moore, M. D., to Dr. A. N. Richards October 6, 1942

I have recently received a letter of enquiry from Dr. Charles M. Carpenter of the University of Rochester School of Medicine who believes that he may be able to work out a human experiment on the chemical prophylaxis of gonorrhea. He has asked me to supply him with a statement that in my opinion such human experimentation is desirable. I have in turn replied enquiring from him as to whether he wishes a statement from me on an entirely personal basis or in one of my official capacities - as Chairman of the Subcommittee on Venereal Diseases, National Research Council, or as Special Consultant, U. S. Public Health Service. In either of the latter cases I have pointed out to Dr. Carpenter that I could not make such a statement without the approval of higher authority.

May I ask you to supply me with the attitude of the Committee on Medical Research toward human experimentation in general, and toward the particular problem of human experiment in the chemical prophylaxis of gonorrhea.

Joseph Moore to A.N. Richards (1942, October 6). Correspondence. PCSBI HSPI Archives, NARA-II_0000346.

[2] Mahoney, J.F. (1936). An experimental resurvey of the basic factors concerned in prophylaxis in syphilis. *The Military Surgeon*, 78-79, 351.



Reply of A. N. Richards, Chairman, to Dr. J. E. Moore October 9, 1942

In your letter of October 6th you ask that I advise you of the attitude of the Committee on Medical Research toward human experimentation in general, and toward the particular problem of human experiment on the chemical prophylaxis of gonorrhea.

The Committee on Medical Research will hold its next meeting on October 29th. I shall present your question to them at that time. In the meantime I have confidence that the Committee will support me in the statement that human experimentation is not only desirable, but necessary in the study of many of the problems of war medicine which confront us. When any risks are involved, volunteers only should be utilized as subjects, and these only after the risks have been fully explained and after signed statements have been obtained which shall prove that the volunteer offered his services with full knowledge and that claims for damages will be waived. An accurate record should be kept of the terms in which the risks involved were described.

In answer to the second part of your question which concerns this specific case, the Committee on Medical Research must rely on the judgment of the Responsible Investigator, supplemented by the judgment of the committee in whose field the investigation is proceeding.

A.N. Richards to Joseph Moore. (1942, October 9). Correspondence. PCSBI HSPI Archives, NARA-II_0000346.

Eventually Surgeon General Dr. Thomas Parran endorsed Dr. Carpenter's proposed study, saying "[b]ecause of the great prevalence of gonorrhea and its importance in the production of noneffective [sic] man-days both in the armed forces and civilian population, I believe that the human inoculation experiments proposed by Doctor Carpenter are justifiable if the human subjects are selected on a voluntary basis."[3]

Following this exchange of letters and many rounds of discussions, researchers began a study at the federal penitentiary at Terre Haute, Indiana to test medications on men who consented to being intentionally exposed to the gonorrhea bacteria. The study proceeded for about 10 months, but was discontinued when it became clear that despite the researchers injecting gonorrhea bacteria into prisoners, many did not become infected. Without being able to reliably infect subjects, the researchers could not study the prevention of infection.

Comment

Today prison experimentation is subject to extensive regulation, and studies of prisoners are generally discouraged. From the documents cited above, what seemed to be the major concern of officials who evaluated the Terre Haute plan? What reasons were given to justify the studies that eventually took place at Terre Haute?

In the absence of rules to prohibit experiments on prisoners, do you think that relying on "the judgment of the responsible investigator," as suggested by Dr. Richards, is sufficient? What characteristics of the prison environment present challenges to the ethical justification of research conducted with this population?

[3] Thomas Parran to Lewis H. Weed. (1942, November 19). Correspondence. PCSBI HSPI Archives, NARAII_0000284.

Recommended Reading

Brandt, A.M. (1993). *No Magic Bullet: A Social History of Venereal Disease in the United States Since 1880*. Oxford: Oxford University Press.

California Department of Public Health in cooperation with U.S. Public Health Service. (1944). *To the People of the United States*. Retrieved from http://archive.org/details/TothePeo1944.

Elliot, C., and R. Abadie. (2008). Exploiting a research underclass in phase I clinical trials. *New England Journal of Medicine*, 358(22), 2316-2317.

Emanuel, E.J. (2004). Ending concerns about undue inducement. *The Journal of Law, Medicine & Ethics*, 32(1), 100-105.

Gostin, L.O. (2007). Biomedical research involving prisoners: Ethical values and legal regulation (Reprinted). *Journal of the American Medical Association*, 297(7), 737-740.

Hodges, R.E., and W.B. Bean. (1967). The use of prisoners for medical research. *Journal of the American Medical Association*, 202(6), 513-515.

Hornblum, A.M. (1997). They were cheap and available: Prisoners as research subjects in twentieth century America. *British Medical Journal*, 315, 1437-1441.

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Lederer, S.E. (1995). *Subjected to Science: Human Experimentation in America Before the Second World War*. Baltimore, MD: Johns Hopkins University Press.

Parascandola, J. (2008). *Sex, Sin, and Science: A History of Syphilis in America*. Westport: Praeger.

Parran, T. (1937). *Shadow on the Land*. New York: Reynal & Hitchcock.

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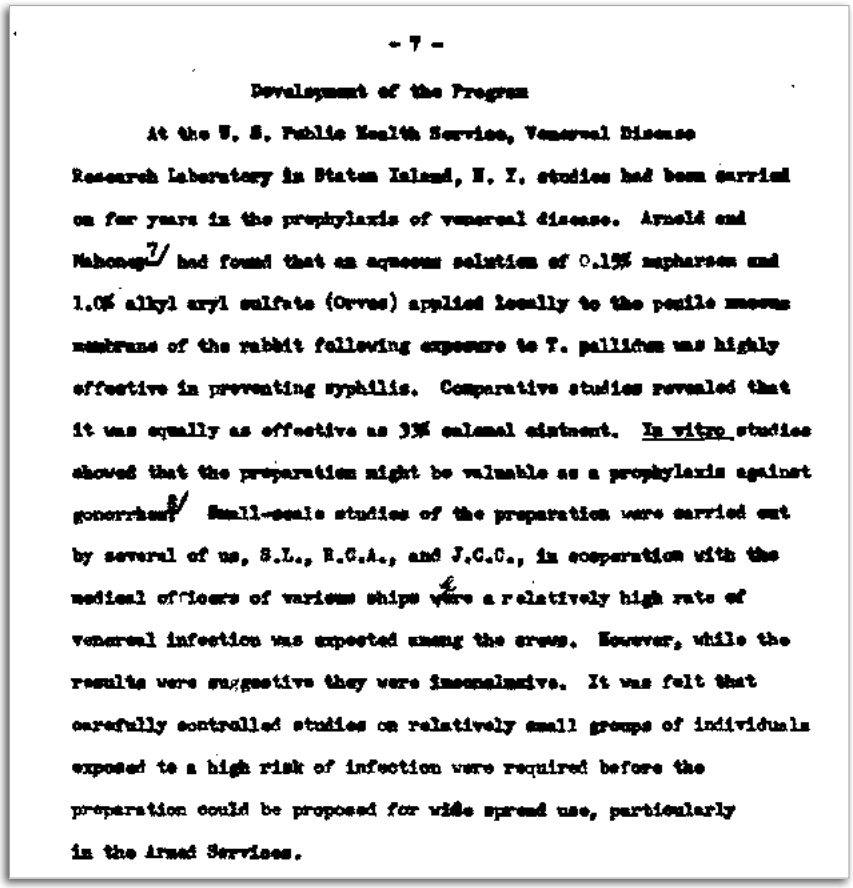
Thompson, D.F. (1993). Understanding financial conflicts of interest. *New England Journal of Medicine*, 329, 573-576.

OVERVIEW OF THE GUATEMALA EXPERIMENTS' RESEARCH DESIGN

Overview of the Treatment Programs, Serology Studies, and STD Experiments

The Terre Haute Prison experiments exposed human research subjects to gonorrhea "by almost every conceivable expedient except…[using] pus taken directly from…infected females or by the natural method of infection—sexual intercourse."[4] Dr. John Cutler, the lead investigator on the ground in Guatemala, claimed in his final syphilis report that Dr. Juan Funes, a physician in training from Guatemala, offered researchers just such an option in Guatemala. That is, conducting research on disease transmission after subjects became infected through the "natural method"—sexual intercourse with infected persons.



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Development of the Program

At the U. S. Public Health Service, Venereal Disease Research Laboratory in Staten Island, N. Y. studies had been carried on for years in the prophylaxis of venereal disease. Arnold and Mahoney[7] had found that an aqueous solution of 0.15% mapharsen and 1.0% alkyl aryl sulfate (Orvus) applied locally to the penile mucous membrane of the rabbit following exposure to T. pallidum was highly effective in preventing syphilis. Comparative studies revealed that it was equally as effective as 33% calomel ointment. In vitro studies showed that the preparation might be valuable as a prophylaxis against gonorrhea.[8] Small-scale studies of the preparation were carried out by several of us, S.L., R.C.A., and J.C.C., in cooperation with the medical officers of various ships where a relatively high rate of venereal infection was expected among the crews. However, while the results were suggestive they were inconclusive. It was felt that carefully controlled studies on relatively small groups of individuals exposed to a high risk of infection were required before the preparation could be proposed for wide spread use, particularly in the Armed Services.

-7-

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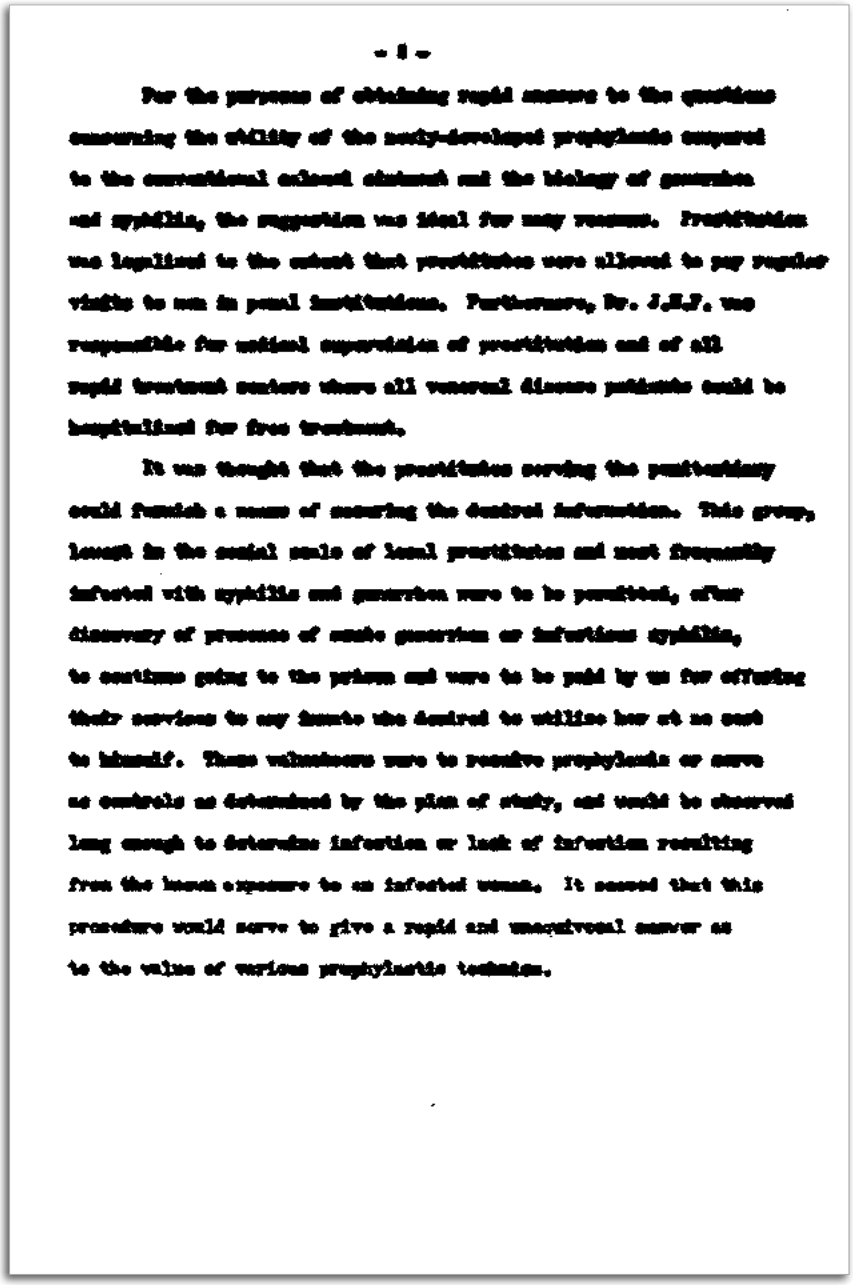
At the U.S. Public Health Service, Venereal Disease Research Laboratory [VDRL] in Staten Island, N.Y. studies had been carried on for years in the prophylaxis of venereal disease. [Drs. R.C.] Arnold and [John] Mahoney had found that an aqueous solution of 0.15% mapharsen and 1.0% alkyl aryl sulfate (Orvus) applied locally to the penile mucous membrane of the rabbit following exposure to T[reponema] pallidum was highly effective in preventing syphilis. Comparative studies revealed that it was equally as effective as 33% calomel ointment. In vitro studies showed that the preparation might be valuable as a prophylaxis against gonorrhea. Small-scale studies of the preparation were carried out by several of us, S.L. [Sasha Levitan], R.C.A. [Richard C. Arnold], and J.C.C. [John C. Cutler], in cooperation with the medical officers of various ships where a relatively high rate of venereal infection was expected among the crews. However, while the results were suggestive they were inconclusive. It was felt that carefully controlled studies on relatively small groups of individuals exposed to a high risk of infection were required before the preparation could be proposed for wide spread use, particularly in the Armed Services.

[4] Draft of CMR History, Section on Venereal Disease attached to Feb. 25, 1946 Memorandum from E. Cowles Andrus to Chester S. Keefer. (n.d.). PCSBI HSPI Archives, NARA-II_0000419.

During the period of development of penicillin therapy and the orvus-mapharsen prophylaxis, J.M.F., chief of the VD control Division of his country's Public Health Service was assigned as a fellow at the VDRL by the Institute of Inter American Affairs. For almost a year he took an active part in the experimental studies. Fully appreciating the problems and possible methods of solution he suggested the possibility of carrying out carefully controlled studies in his country.



During the period of development of penicillin therapy and the orvus-mapharsen prophylaxis, J.M.F. [Juan M. Funes], chief of the VD [venereal disease] control Division of his country's [Guatemala] Public Health Service was assigned as a fellow at the VDRL [Veneral Disease Research Laboratory] by the Institute of Inter American Affairs. For almost a year he took an active part in the experimental studies. Fully appreciating the problems and possible methods of solution he suggested the possibility of carrying out carefully controlled studies in his country.

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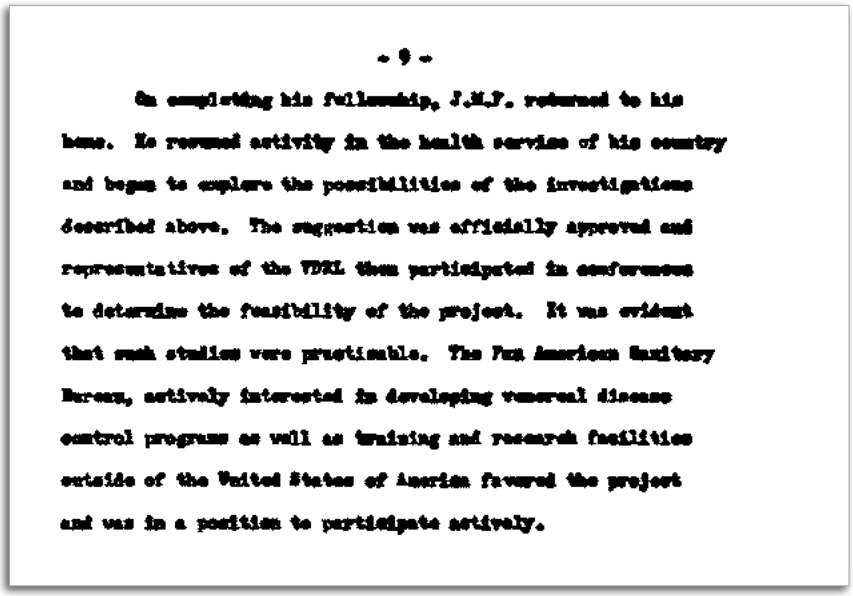
For the purposes of obtaining rapid answers to the questions concerning the utility of the newly-developed prophylaxis compared to the experimental calomel ointment and the biology of gonorrhea and syphilis, the suggestion was ideal for many reasons. Prostitution was legalized to the extent that prostitutes were allowed to pay regular visits to men in penal institutions. Furthermore, Dr. J.M.F. [Funes] was responsible for medical supervision of prostitution and of all rapid treatment centers where all venereal disease patients could be hospitalized for free treatment.

It was thought that the prostitutes serving the penitentiary could furnish a means of securing the desired information. This group, lowest in the social scale of legal prostitutes and most frequently infected with syphilis and gonorrhea were to be permitted, after discovery of presence of acute gonorrhea or infectious syphilis, to continue going to the prison and were to be paid by us for offering their services to any inmate who desired to utilize her at no cost to himself. These volunteers were to receive



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On completing his fellowship, J.M.F. returned to his home. He resumed activity in the health service of his country and began to explore the possibilities of the investigations described above. The suggestion was officially approved and representatives of the VDRL then participated in conferences to determine the feasibility of the project. It was evident that such studies were practicable. The Pan American Sanitary Bureau, actively interested in developing venereal disease control programs as well as training and research facilities outside of the United States of America favored the project and was in a position to participate actively.

Cutler, J.C. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000639-40.

prophylaxis or serve as controls as determined by the plan of study, and would be observed long enough to determine infection or lack of infection resulting from the known exposure to an infected woman. It seemed that this procedure would serve to give a rapid and unequivocal answer as to the value of various prophylactic techniques.

-9-

On completing his fellowship, J.M.F. [Funes] returned to his home. He resumed activity in the health service of his country and began to explore the possibilities of the investigations described above. The suggestion was officially approved and representatives of the VDRL then participated in conferences to determine the feasibility of the project. It was evident that such studies were practicable. The Pan American Sanitary Bureau, actively interested in developing venereal diseases control programs as well as training and research facilities outside of the United States of America favored the project and was in a position to participate actively.

Transcription of Cutler, J. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000639-41.

Treatment Programs

To facilitate the STD experiments, the U.S. researchers developed "cooperative working arrangements" with Guatemalan government officials. The agreements gave the researchers authority to work with institutions across Guatemala and with officials including "the medical and other authorities of the public health service rapid treatment center for venereal diseases, in the governmental hospitals, with medical installations and officers of the military, with institutions caring for the orphans and the insane, and with the penal system."[5] Researchers contemplated many different activities, including:

- Assessing the prevalence of STDs in the country;
- Developing an improved system of STD control through personnel training;
- Establishing prevention, diagnostic, and treatment facilities;
- Investigating and refining diagnosis and treatment of STDs; and
- Experimenting with pre and post-exposure prophylaxis for STDs.

The researchers planned to train local personnel to take over a new research laboratory as a Guatemalan government facility in the future.

Dr. Cutler set up a "treatment program" in a Guatemalan military hospital as a way of obtaining cooperation for future inoculation research. Dr. Cutler also provided penicillin, recently shown to be an effective treatment for syphilis and possibly other STDs (rarely available in Guatemala) as part of "demonstration programs and to build goodwill." [6]

Serology Studies

In a separate line of study, researchers took blood and/or spinal fluid from thousands of subjects in an effort to refine diagnostic techniques for STDs. This line of testing occurred in two populations: those that researchers had exposed to STDs and a second group made up of various populations, including orphans and school children, assumed to be free of STDs.

STD Experiments

Eventually, researchers brought infected commercial sex workers to visit the Guatemalan prison and have sexual intercourse with inmates. Researchers then tested the prisoners to see if they had contracted STDs. They then monitored the success of various treatments or post-exposure prophylactic measures.

Because the "natural" infections were not proceeding fast enough, Dr. Cutler's team injected research subjects with syphilis and gonorrhea bacteria in further studies of the effectiveness of various medications, including penicillin. Throughout the time that U.S. researchers worked in Guatemala, they intentionally exposed some 1,300 people to STDs, either through sexual intercourse with infected sex workers or through artificial inoculation designed to transmit disease. While *exposing* a person to an STD does not necessarily mean that that person becomes *infected* with the disease, the team provided some form of treatment to only half of the persons that they exposed.

5 PCSBI. (2011, September). *"Ethically Impossible:" STD Research in Guatemala from 1946 to 1948*. Washington, DC: PCSBI., p. 32.
6 Ibid, p. 33.

Comment

American officials, such as the then Surgeon General, would later describe the Guatemala studies as something that could not have been done in the United States. One barrier to such studies was the illegality of prostitution in the United States. Are there any situations where U.S. researchers should be allowed to conduct research in other countries under conditions that would be illegal in America?

Dr. Cutler attempted to build goodwill that he later hoped to exploit for his STD exposure studies, by making medical supplies available to treat patients/future subjects and involving local medical personnel in the work of the new medical laboratory. How should we weigh these activities as part of our evaluation of the ethical appropriateness of the entire PHS research effort in Guatemala?

Should the involvement and acquiescence of Guatemalan doctors and governmental officials in the overall research effort change our evaluation of the PHS studies?

Under what conditions would we judge it ethically appropriate to intentionally expose healthy people to disease as a way of studying a disease?

Recommended Reading

Benatar, S.R., and P.A. Singer. (2000). A new look at international research ethics. *British Medical Journal*, 321(7264), 824-826.

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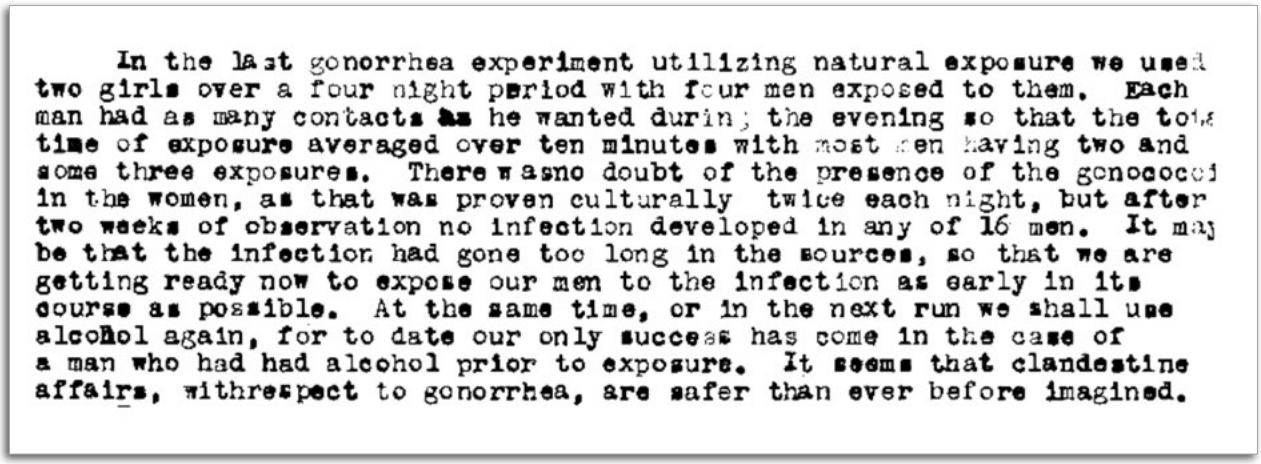
VULNERABLE POPULATIONS OF THE GUATEMALA EXPERIMENTS

Subject Populations in the Guatemala Experiments

Researchers used Guatemalan commercial sex workers, soldiers, prisoners, and psychiatric patients in two types of intentional exposure experiments.[7] One involved "normal exposure," that is, soldiers and prisoners had sexual intercourse with commercial sex workers, in some cases repeatedly. For example, one commercial sex worker that the researchers infected with gonorrhea had contact with eight soldiers in 71 minutes.



In the last gonorrhea experiment utilizing natural exposure we used two girls over a four night period with four men exposed to them. Each man had as many contacts as he wanted durin; the evening so that the tot time of exposure averaged over ten minutes with most men having two and some three exposures. There wasno doubt of the presence of the gonococci in the women, as that was proven culturally twice each night, but after two weeks of observation no infection developed in any of 16 men. It may be that the infection had gone too long in the sources, so that we are getting ready now to expose our men to the infection as early in its course as possible. At the same time, or in the next run we shall use alcohol again, for to date our only success has come in the case of a man who had had alcohol prior to exposure. It seems that clandestine affairs, withrespect to gonorrhea, are safer than ever before imagined.

Cutler, J.C. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001299-1302.

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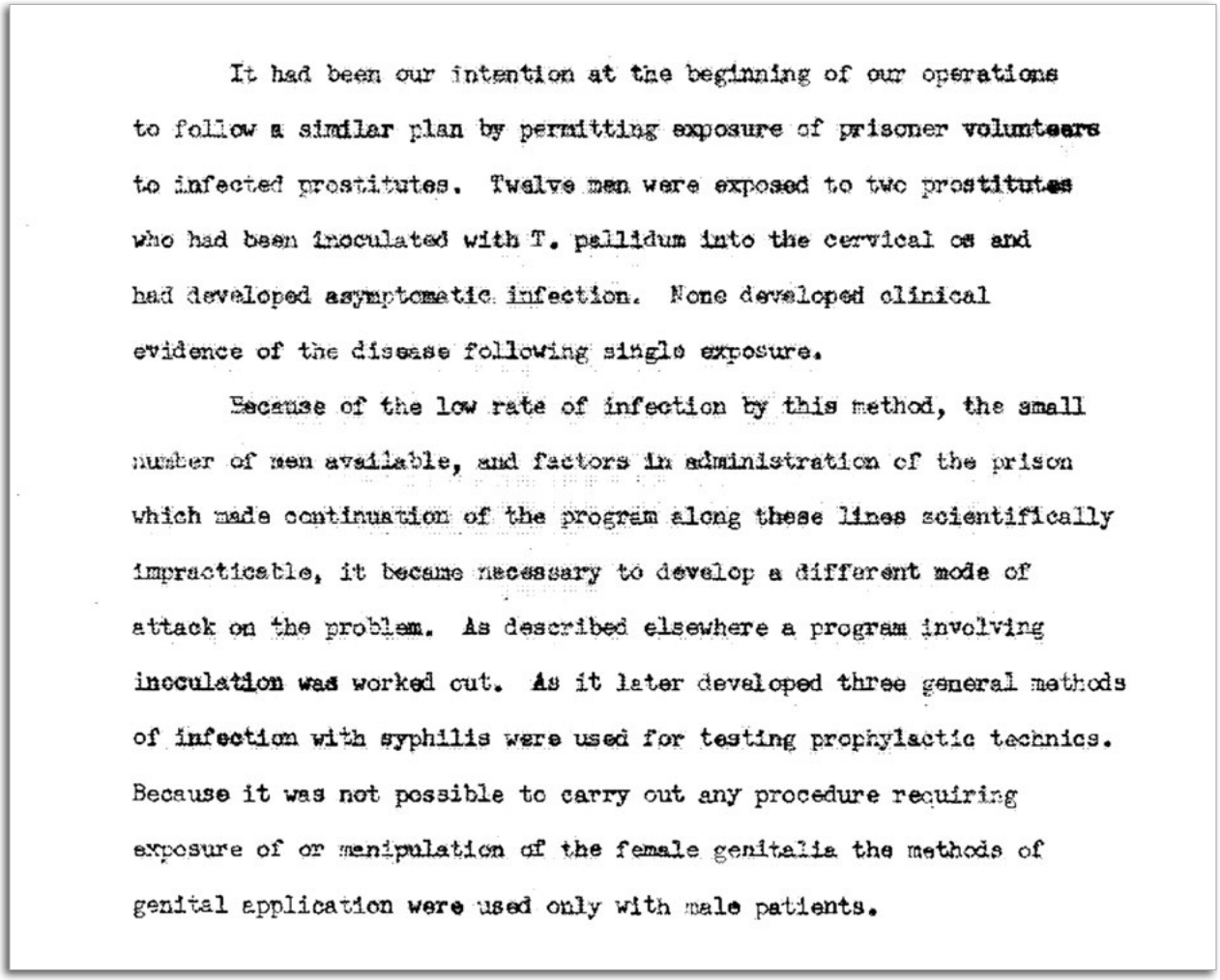
Transcription of Cutler, J.C. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001299-1302.

[7] The ages of subjects involved in the exposure experiments ranged from 10 to 72 years.

Dr. Cutler later concluded that the "natural exposure" research had been unsuccessful:



It had been our intention at the beginning of our operations to follow a similar plan by permitting exposure of prisoner volunteers to infected prostitutes. Twelve men were exposed to two prostitutes who had been inoculated with T. pallidum into the cervical os and had developed asymptomatic infection. None developed clinical evidence of the disease following single exposure.

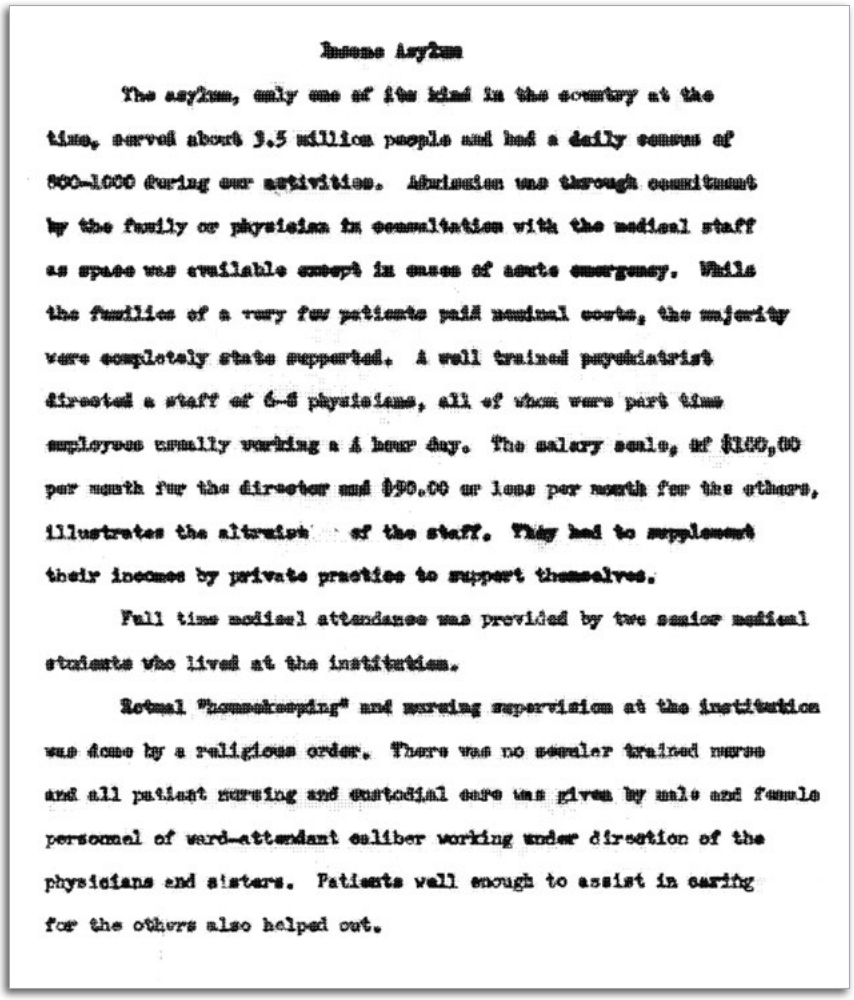
Because of the low rate of infection by this method, the small number of men available, and factors in administration of the prison which made continuation of the program along these lines scientifically impracticable, it became necessary to develop a different mode of attack on the problem. As described elsewhere a program involving inoculation was worked out. As it later developed three general methods of infection with syphilis were used for testing prophylactic technics. Because it was not possible to carry out any procedure requiring exposure of or manipulation of the female genitalia the methods of genital application were used only with male patients.

Cutler, J.C. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000759.

After the failure of the sexual intercourse experiments, the second type of experiment included a variety of methods to induce gonorrhea and syphilis infection: from surface application of infected material on the genitals, to injection of infected material under the skin, to deep injection of infected material into other parts of the body. Researchers fed infected material to some subjects and injected others with the material via cisternal puncture (a spinal injection at the base of a person's skull).

Researchers conducted a third type of study to verify the utility of various diagnostic tests, and to determine how likely various populations were to have already been infected with STDs. The serology studies required physical examinations and withdrawing blood from most subjects. Researchers sometimes conducted lumbar punctures (spinal taps) or cisternal punctures to confirm the results of blood tests or to look for infection in the spinal fluid that might not have been found using blood tests.

Researchers conducted syphilis blood test experiments on Guatemalan commercial sex workers, prisoners, children, psychiatric patients, leprosy patients, soldiers, and a few U.S. military personnel.



Insane Asylum

The asylum, only one of its kind in the country at the time, served about 3.5 million people and had a daily census of 800-1000 during our activities. Admission was through commitment by the family or physician in consultation with the medical staff as space was available except in cases of acute emergency. While the families of a very few patients paid nominal costs, the majority were completely state supported. A well trained psychiatrist directed a staff of 6-8 physicians, all of whom were part time employees usually working a 4 hour day. The salary scale, of $100.00 per month for the director and $50.00 or less per month for the others, illustrates the altruism of the staff. They had to supplement their incomes by private practice to support themselves.

Full time medical attendance was provided by two senior medical students who lived at the institution.

Actual "housekeeping" and nursing supervision at the institution was done by a religious order. There was no secular trained nurse and all patient nursing and custodial care was given by male and female personnel of ward-attendant caliber working under direction of the physicians and sisters. Patients well enough to assist in caring for the others also helped out.

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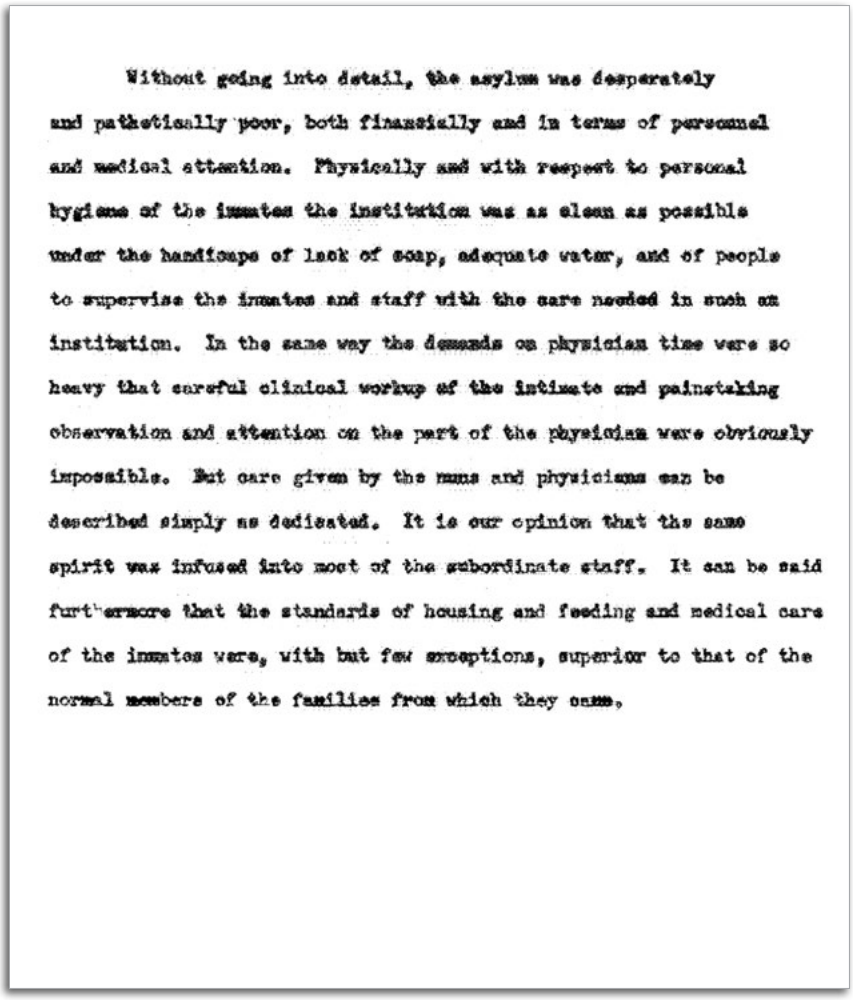

Without detail, the asylum was desperately and pathetically poor, both financially and in terms of personnel and medical attention. Physically and with respect to personal hygiene of the inmates the institution was as clean as possible under the handicaps of lack of soap, adequate water, and of people to supervise the inmates and staff with the care needed in such an institution. In the same way the demands on physician time were so heavy that careful clinical workup of the intimate and painstaking observation and attention on the part of the physician were obviously impossible. But care given by the nuns and physicians can be described simply as dedicated. It is our opinion that the same spirit was infused into most of the subordinate staff. It can be said furthermore that the standards of housing and feeding and medical care of the inmates were, with but few exceptions, superior to that of the normal members of the families from which they came.

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Transcription of Cutler, J.C. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000649.

Cutler, J.C. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000649.

Comment

In reviewing the different groups of people listed below, which do you think would be appropriate to include in medical research, if any? Would your feelings change if the research involved just the diagnostic blood testing rather than intentional exposure to STDs? What ethical principle(s) would provide justification for your responses to the previous two questions?

- Soldiers
- Prisoners
- Psychiatric patients
- Orphans
- Leprosy patients

There was no evidence that consent was solicited from any persons involved in either serological tests or intentional infection research. If we assume that the Guatemalan soldiers and prisoners were adults capable of giving consent to research participation, are there any conditions that you would require be met before starting the research? What makes the remaining three groups vulnerable? What ethical principles would either prohibit or support research in these populations?

The commercial sex workers were never considered research subjects. They were thought of as "carriers" or "vectors" of disease instead. Would it be appropriate also to think of them as another subject population? Why or why not?

Recommended Reading

Chapter 10: The Ethics of Research in Infectious Disease: Experimenting on This Patient, Risking Harm to That One. In Battin, M.P., et al. (2009). *The Patient as Victim and Vector: Ethics and Infectious Disease*. Oxford: Oxford University Press, pp. 164-183.

Grodin, M., and L. Glantz. (1994). *Children as Research Subjects*. New York: Oxford University Press.

Kipnis, K. (2001). Vulnerability in Research Subjects: A Bioethical Taxonomy. In National Bioethics Advisory Commission. (2001, August). *Ethical and Policy Issues in Research Involving Human Participants—Volume II: Commissioned Papers and Staff Analysis*. Retrieved from http://bioethics.georgetown.edu/nbac/human/overvol2.pdf.

Lederer, S.E. (1995) *Subjected to Science: Human Experimentation in America Before the Second World War*. Baltimore, MD: Johns Hopkins Press.

Levine, C., et al. (2004). The Limitations of "Vulnerability" as a Protection for Human Research Participants. *The American Journal of Bioethics*, 4(3), 44-49.

Marten, L. (2005). Commercial sex workers: Victims, vectors or fighters of the HIV epidemic in Cambodia? *Asia Pacific Viewpoint*, 46(1), 21-34.

PCSBI. (2011, September). *"Ethically Impossible:" STD Research in Guatemala from 1946 to 1948*. Washington, DC: PCSBI.

Vanderpool, H.Y. (1996) *The Ethics of Research Involving Human Subjects: Facing the 21st Century*. Frederick, MD: University Pub. Group.

ETHICAL ISSUES WITH THE RESEARCH DESIGN

Issues of Race

Tuskegee Study of Untreated Syphilis

The story of the infamous Tuskegee syphilis experiments provides a useful backdrop and comparison for the Guatemalan experiments. The similarities between the two cases were stark. The cases arose from the same PHS laboratory, the Venereal Disease Research Laboratory, involved some of the same researchers, and both focused on syphilis.

In 1932, the PHS began a 40-year observational study of untreated syphilis in men in Tuskegee, Alabama. The investigators in Tuskegee did not expose the study subjects to syphilis; all of the subjects acquired syphilis on their own. The investigators did not inform the impoverished African American male subjects that they intended to study the natural progression of syphilis without treatment. In fact, investigators told subjects the opposite: that they would *treat* the men's syphilis, or "bad blood." Three of the researchers in the Tuskegee Syphilis Studies, Drs. Mahoney, Van Slyke, and Cutler, also later had key roles in the Guatemala STD experiments. The Tuskegee investigators continued to withhold treatment from their subjects until the media brought the study to light in 1972, at which point it was discontinued.

When the Tuskegee syphilis studies began, many clinicians believed that a person's race played a part in how they were affected by syphilis. For example, at the turn of the century, a group of researchers published in the *American Journal of Syphilis* that "the negro's well-known sexual impetuosity may account for more abrasions of the integument [skin] of the sexual organs, and therefore more frequent infections than are found in the white race."[8] The authors believed that if sexual organs were abraded, they were more likely to become infected with STDs. Presumptions about race and syphilis persisted through the 1930s and 1940s. As an illustration of this view, to the left is an excerpt from the 1938 testimony of Dr. Thomas Parran, then U.S. Surgeon General, to Congress on the investigation and control of venereal disease.

Dr. PARRAN. These surveys have been made in cities and in rural areas in about the same proportion as the population of the urban and the rural areas bears to the population of the country as a whole.

I would point out also on the chart which I have just submitted that the attack rate of the disease varies greatly by communities. In some communities the disease is much more prevalent; practically epidemic in the boom oil towns of the Southwest, or the mining towns, while it is relatively rare in the settled rural areas.

A point has been made concerning the excess of syphilis among the Negro population. Wherever we find ignorance and poverty, there syphilis flourishes, whether among the Negro or the white race.

Additional facts are emerging which show that there is a biologic difference between the disease in the Negro and the white. The most important of these facts from a public health point of view is that the Negro woman has three times the tendency to relapse after the same amount of treatment as the white woman. So that biological difference is of importance. We know, of course, also, that the Negro has a much greater susceptibility for involvement of the heart and blood vessels, but not so much susceptibility of involvement of the nervous system.

Moreover, wherever the disease is dealt with adequately, wherever the Negro has a chance for education and medical treatment, there the rate goes down.

Thomas Parran. Testimony to the U.S. Congress. House. Committee on Interstate and Foreign Commerce. Hearings on Investigation and Control of Venereal Diseases. 75th Congress, 3rd Session, April 12-14, 1938, at 139.

[8] Thompson, L., and L.B. Kingery. (1919). Syphilis in the Negro. *American Journal of Syphilis*, 3, 386-87. As cited in: Jones, J.H. (1993). *Bad Blood: The Tuskegee Syphilis Experiment*. New York: The Free Press, pp. 24-25.

Previous Syphilis Research in Guatemala

In the 1930s, U.S. syphilis researchers in Guatemala also speculated that syphilis affected Latin Americans differently than Caucasian North Americans or Europeans and that the "clinical lesions of syphilis found in the Central American Indian and the Mixture of Indian-European or Indian-European-Negro are different from those found in the white European."[9] In his "Final Syphilis Report" regarding the Guatemala STD experiments, Dr. Cutler cited an excerpt from an article by a U.S. researcher in Guatemala. This article on syphilis, below, begins with a discussion of the "sexual promiscuity" of the researcher's subjects:

SYPHILIS IN THE HIGHLANDS OF GUATEMALA

WILLIAM CURTH, M.D., NEW YORK, N. Y.

From the Department of Dermatology, College of Physicians and Surgeons, Columbia University

(Received for publication, January 6, 1933)

FOREWORD

THE data to be presented were collected between Feb. 6 and March 6, 1932, by a medical expedition* which worked among the mountains of Guatemala, and particularly in the neighborhood of Lake Atitlan.

Inasmuch as the Carnegie Institution now has in press a volume entitled *The Peninsula of Yucatan* by George C. Shattuck, M.D., et al., containing a chapter by Shattuck discussing the prevalence and clinical manifestations of syphilis among the Mayan Indians and Maya-Spanish crosses or Mestizos of the State of Yucatan, some of the data presented there will be compared below with our findings in Guatemala. It had not been practicable for Dr. Shattuck to study closely the clinical manifestations of syphilis in Yucatan and, therefore, I was asked to accompany him to Guatemala to do this part of the work and also to supervise the serologic tests. It was deemed of special importance to study syphilis in Guatemala because of the unexpected results obtained in Yucatan.

RACE AND ENVIRONMENT

The Indians living near Lake Atitlan and at Santo Tomás, Chichicastenango, are closely allied racially to the Maya Indians of Yucatan and the population of mixed blood, the Indian-Spanish crosses or Ladinos, are very like the Mestizos of Yucatan; but the subjects of study in Yucatan lived in a tropical climate near sea-level and those of Guatemala lived at altitudes of from four to five thousand feet where the climate is temperate although the sun is hot. Most of the Indians of the two regions live in villages and subsist mainly by the cultivation of

*This expedition was organized by the Department of Tropical Medicine of the Harvard Medical School and was conducted under the auspices of the Carnegie Institution of Washington. The members of the expedition were George C. Shattuck, M.D., Clinician; William Curth, M.D., Specialist in Skin Diseases and Syphilis; Carlos Sanchez, Secretary and Interpreter; and Byron L. Bennett, Laboratory Technician.

9 Cutler, J.C. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000852.

maize. Many of them in Yucatan and also in Guatemala, however, are employed either temporarily or permanently as laborers. Those who labor for hire in Yucatan do not change their environment much but, in Guatemala, they often go for a season to distant coffee plantations at lower altitudes where the climate is subtropical, or even to the sugar plantations near sea-level where they are exposed to a tropical climate, to very unhygienic living conditions and to diseases not prevalent in the Highlands from which they come. Our clinical material included an uncertain number of Indians who had worked in the Lowlands.

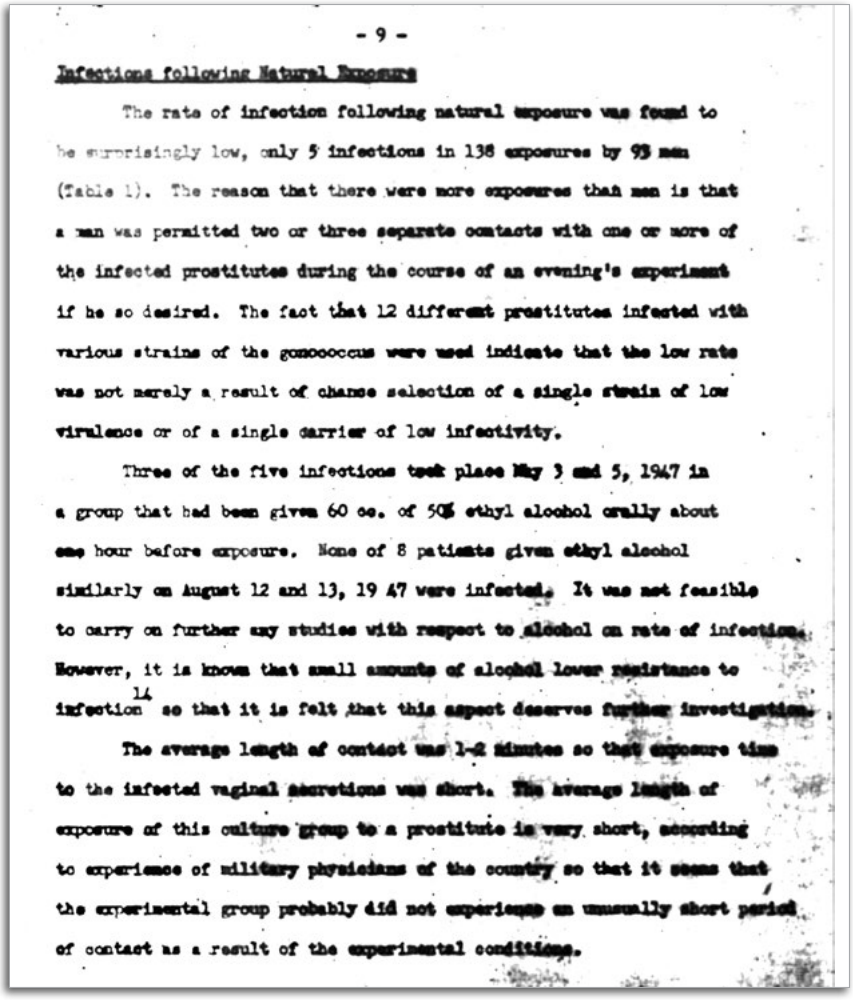
The Ladinos examined were residents of small towns or villages in some of which they were greatly outnumbered by the Indians. They were land owners, small tradesmen and the like.

Sanitation is primitive in these towns and villages and most of the Ladinos and Indians alike live in extreme simplicity. Over-indulgence in alcoholic liquors is common among the men of both races. Sexual promiscuity is said to be very prevalent among the Ladinos, whereas, we were informed on good authority that the Mayan Indians preserve a remarkably pure family life when at home but that their sexual life on the plantations is apt to be lax. Some Indians also serve in the Army. It appears from the foregoing that there is sufficient opportunity for the spread of syphilis in the communities studied but that, on the average, the Ladino is more often exposed to it than is the Indian.

Curth, W. (1933). Syphilis in the highlands of Guatemala. *American Journal of Syphilis*, 2(xvii), 164-65.

Race in the Guatemala STD Studies

Dr. Cutler discussed in his "Final Syphilis Report" that he did not have access to ethnological information regarding his subjects, although he believed Guatemala City to be "approximately 85% Indian [indigenous]." He added that "it was our observation too, that many of our patients had the classic, pure Indian features indicating little or no mixture [with other races]."[10] Dr. Cutler also discussed race-based presumptions about sexuality in his "Final Gonorrhea Report:"



- 9 -

Infections following Natural Exposure

The rate of infection following natural exposure was found to be surprisingly low, only 5 infections in 138 exposures by 93 men (Table 1). The reason that there were more exposures than men is that a man was permitted two or three separate contacts with one or more of the infected prostitutes during the course of an evening's experiment if he so desired. The fact that 12 different prostitutes infected with various strains of the gonococcus were used indicate that the low rate was not merely a result of chance selection of a single strain of low virulence or of a single carrier of low infectivity.

Three of the five infections took place May 3 and 5, 1947 in a group that had been given 60 cc. of 50% ethyl alcohol orally about one hour before exposure. None of 8 patients given ethyl alcohol similarly on August 12 and 13, 19 47 were infected. It was not feasible to carry on further any studies with respect to alcohol on rate of infection. However, it is known that small amounts of alcohol lower resistance to infection[14] so that it is felt that this aspect deserves further investigation.

The average length of contact was 1-2 minutes so that exposure time to the infested vaginal secretions was short. The average length of exposure of this culture group to a prostitute is very short, according to experience of military physicians of the country so that it seems that the experimental group probably did not experience an unusually short period of contact as a result of the experimental conditions.

-9-

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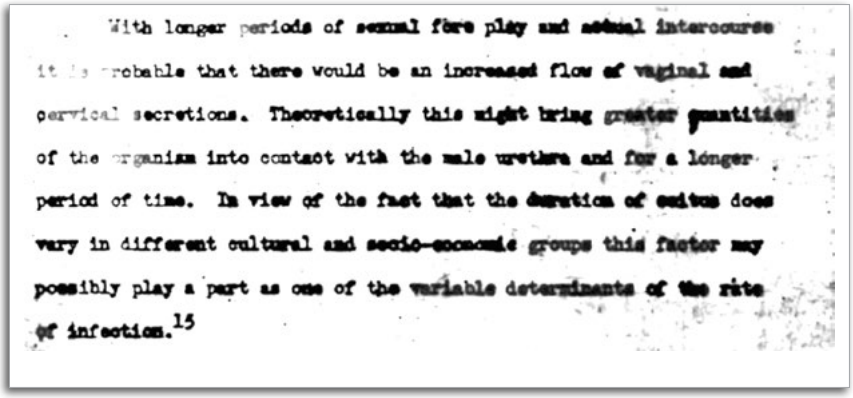
[10] PCSBI. (2011, September). *"Ethically Impossible" STD Research in Guatemala from 1946 to 1948*. Washington, DC: PCSBI, pp. 73-74.



With longer periods of sexual fore play and sexual intercourse it is probable that there would be an increased flow of vaginal and cervical secretions. Theoretically this might bring greater quantities of the organism into contact with the male urethra and for a longer period of time. In view of the fact that the duration of coitus does vary in different cultural and socio-economic groups this factor may possibly play a part as one of the variable determinants of the rate of infection.[15]

Cutler, J.C. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001287-88.

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Transcription of Cutler, J.C. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001287-88.

Comment

Clearly, the perceived differences of syphilis manifestations in different races played a role in the government's attempts at preventing syphilis throughout the beginning of the 20th century. These findings have since been discredited. How might racially biased assumptions affect the effort and resources invested in the treatment and prevention of disease? Assume the authorities at the time gave due consideration to the ethical justification for these studies, what ethical principles, in their minds, could have motivated the choices/decisions that were made? Should ethical frameworks used to justify research ever explicitly incorporate notions of race or ethnicity?

Misconceptions about syphilis and race also played a role in syphilis research in Guatemala before the Guatemala STD experiments began. Dr. Curth opened his article on syphilis in the Highlands of Guatemala with stereotyped observations of subjects' "sexual promiscuity" and excessive drinking. As sexual intercourse is usually seen as a choice, how might linking the spread of disease to sexual proclivities have influenced his approach to the diagnosis and treatment of syphilis in a certain population? How might the link between sexual intercourse and STDs affect their diagnosis and treatment today?

In the Guatemala STD experiments, Dr. Cutler also used "cultural or socio-economic"-based assumptions regarding sexuality in his research. He even blamed, in part, the ineffectiveness of disease transmission on the subjects' short period of sexual intercourse. It is interesting to note that while Dr. Curth blamed the spread of syphilis on the "sexual promiscuity" of his Guatemalan subjects, Dr. Cutler blamed the failure of his transmission experiments on the short duration of his subjects' sexual intercourse. Both of the two physicians used racial stereotypes of sexuality to support their conclusions. How might the precedent of Dr. Parran and Dr. Curth have influenced Dr. Cutlers' biased presumptions? How might race-based assumptions influence a researcher's approach to a study or presentation of data?

Recommended Reading

Clark Hine, D. (1994). 'In the Kingdom of Culture': Black Women and the Intersection of Race, Gender, and Class. In Early, G. (Ed.). *Lure and Loathing: Essays on Race, Identity, and the Ambivalence of Assimilation*. New York: Penguin Books.

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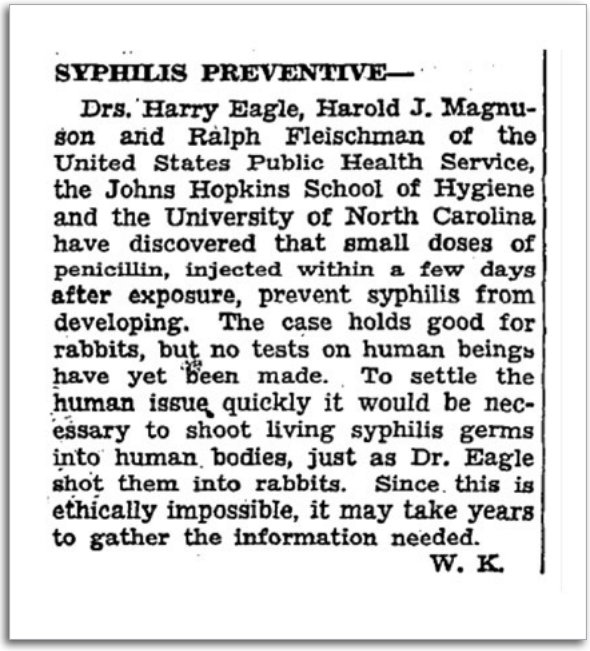
LaFleur, W.R., Böhme, G., and S. Shimazono, eds. (2007). *Dark Medicine: Rationalizing Unethical Medical Research*. Indiana University Press.

Shreeve, J. (1994). Terms of estrangement. *Discover*, 57-63.

Wills, C. (1994). The skin we're in. *Discover*, 77-81.

"Ethically Impossible:" Secrecy in the Guatemala Experiments

In April 1947, *New York Times* science editor Waldemar Kaempffert published a note describing an intentional exposure syphilis prevention experiment conducted in rabbits that offered great promise to reduce the spread of syphilis. The experiment found that penicillin injected into rabbits a few days after exposure to the disease could prevent syphilis infections. Dr. Harry Eagle, who also served on the Syphilis Study Section that recommended the Guatemala STD experiments for approval, worked as one of the rabbit study's investigators. Kaempffert observed that the next step could be to conduct similar research in humans, however, such research would be "ethically impossible:"



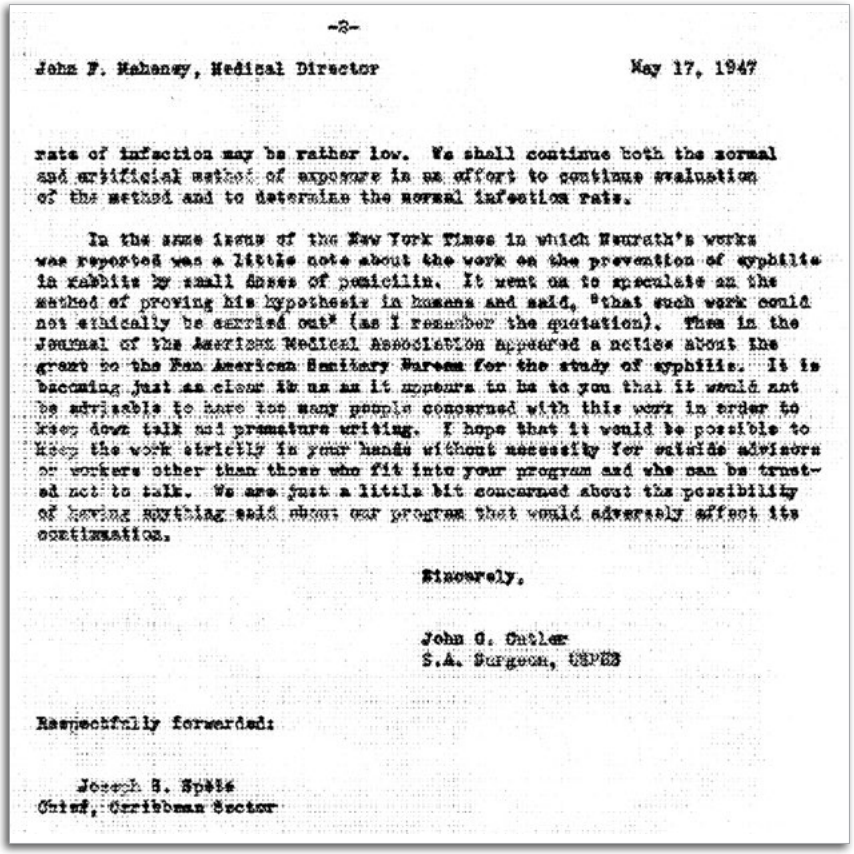
SYPHILIS PREVENTIVE—

Drs. Harry Eagle, Harold J. Magnuson and Ralph Fleischman of the United States Public Health Service, the Johns Hopkins School of Hygiene and the University of North Carolina have discovered that small doses of penicillin, injected within a few days after exposure, prevent syphilis from developing. The case holds good for rabbits, but no tests on human beings have yet been made. To settle the human issue quickly it would be necessary to shoot living syphilis germs into human bodies, just as Dr. Eagle shot them into rabbits. Since this is ethically impossible, it may take years to gather the information needed.

W. K.

Kaempffert, W. (1947). Notes on science: Syphilis prevention. *New York Times*. April 27.

Such human research, deemed "ethically impossible" by Kaempffert, is exactly what the investigators in Guatemala were planning. Dr. Cutler read the *New York Times* note and brought it to the attention of his superior, Dr. Mahoney, an excerpt of which is produced below:



-2-

John F. Mahoney, Medical Director May 17, 1947

rate of infection may be rather low. We shall continue both the normal and artificial method of exposure in an effort to continue evaluation of the method and to determine the normal infection rate.

In the same issue of the New York Times in which Neurath's works was 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, "that such work could not ethically be carried out" (as I remember the quotation). 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 would 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.

Sincerely,

John C. Cutler
S.A. Surgeon, USPHS

Respectfully forwarded:

Joseph S. Spoto
Chief, Caribbean Sector

John Cutler to John Mahoney. (1947, May 17). Correspondence. PCSBI HSPI Archives, CTLR_0001122.

John F. Mahoney, Medical Director

May 17, 1947

…rate of infection may be rather low. We shall continue both the normal and artificial method of exposure in an effort to continue evaluation of the method and to determine the normal infection rate.

In the same issue of the New York Times in which Neurath's works was 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, "that such work could not ethically be carried out" (as I remember the quotation). 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 would 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.

Sincerely,
John C. Cutler
S.A. Surgeon, USPHS

Respectfully forwarded:
Joseph S. Spoto
Chief, Caribbean Sector

Transcription of John Cutler to John Mahoney. (1947, May 17). Correspondence. PCSBI HSPI Archives, CTLR_0001122.

Comment

When analyzing Dr. Cutler's letter to Dr. Mahoney, take into consideration that:

1. Dr. Cutler read the "Ethically Impossible" *New York Times* note before the syphilis intentional exposures began in Guatemala;
2. In reading the article and writing his letter to Dr. Mahoney, Dr. Cutler demonstrated awareness that some scientific professionals would judge the work in Guatemala to be unethical;
3. Dr. Cutler believed the coinciding science note and the *Journal of the American Medical Association* publication to be important enough to bring to the attention of his superior; and
4. It is this potential comparison of the work that leads Dr. Cutler to suggest to Dr. Mahoney that they only discuss the work in Guatemala with people "who can be trusted not to talk."

How do these pieces of information inform an evaluation of what the researchers knew or should have known at the time about the ethics of the experiments that they were conducting?

Do you think the researchers addressed ethical concerns as outlined by Kaempffert? How might the researchers have justified a difference in opinion from Kaempffert? Why might the researchers have believed that their work should be excepted from the rules? If the researchers knew that they had to make their experiments and methods public either at the time or in the future, how might this have changed their actions? What ethical principles apply here?

Recommended Reading

Faunce, T.A., and S. Jefferys. (2007). Whistleblowing and scientific misconduct: Renewing legal and virtue ethics foundations. *Medical Law Review*, 26(3), 567-84.

Lombardo, P.A. (2003). "Of Utmost National Urgency:" The Lynchburg Colony Hepatitis Study, 1942. In Moreno, J.D. (Ed.). (2003). *In the Wake of Terror: Medicine and Morality in a Time of Crisis*. Cambridge: MIT Press.

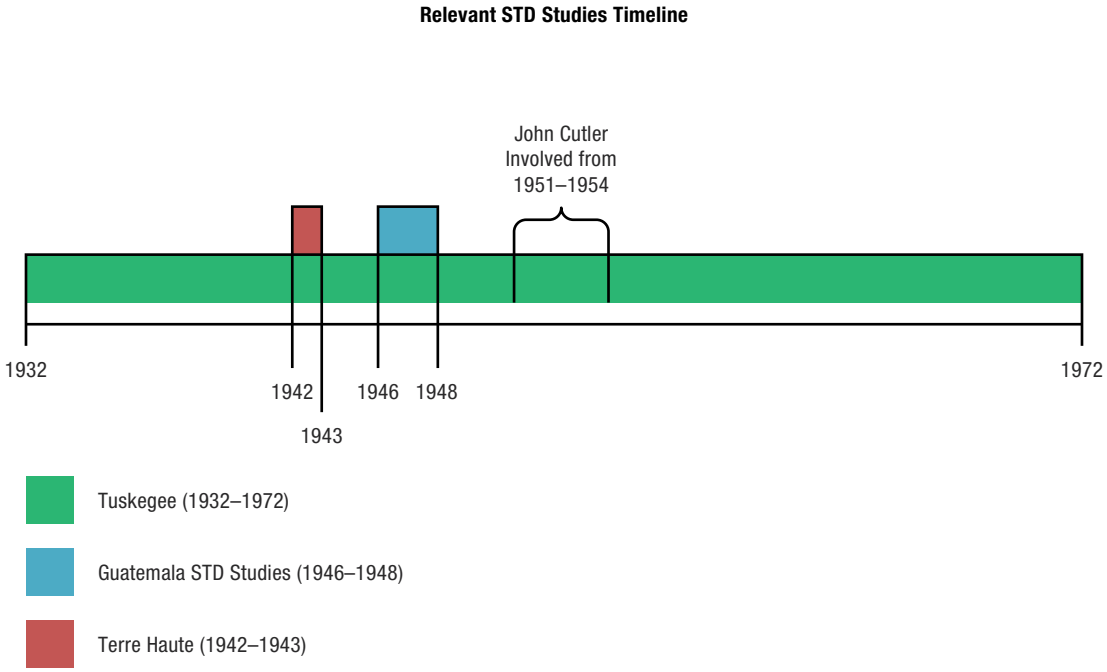
Moreno, J.D. (1999). *Undue Risk: Secret State Experiments on Humans*. New York: W.H. Freeman and Company.

Committee on Science, Engineering, and Public Policy, National Academies of Sciences. (2009). *On Being a Scientist: A Guide to Responsible Conduct in Research – Third Edition*. Washington, DC: National Academies Press, pp.19-23, 48-50.

Rhodes, R., and J.J. Strain. (2004). Whistleblowing in academic medicine. *Journal of Medical Ethics*, 30, 35-39.

Woloshin, S., and L.M. Schwartz. (2002). Press releases: Translating research into news. *Journal of the American Medical Association*, 287(21), 2856-2858.

Consent and Deception



As described above, in 1932 the PHS began an observational study of untreated syphilis in Tuskegee, Alabama that would last for 40 years. The investigators in Tuskegee did not expose any of the study subjects to syphilis; all of the subjects acquired syphilis on their own. However, investigators did not inform the subjects in Tuskegee of the true purpose of the research: the observation of the natural progression of the disease without treatment. In fact, researchers deceived the subjects and told them that they would treat the syphilis. Dr. Cutler, who led the Guatemala STD experiments, later played a role in the Tuskegee syphilis study in the 1950s.

After the Tuskegee study began, but before the Guatemala experiments began, Drs. Mahoney and Cutler also took part in the STD research conducted in a prison in Terre Haute, Indiana. In the Terre Haute experiments, conducted from 1942 to 1943, researchers provided each study subject with a "waiver" that detailed both the risks and procedures of the experiments.

STATEMENT OF EXPLANATION OF THE EXPERIMENT AND ITS
RISKS TO TENTATIVE VOLUNTEERS

The following is a suggested explanation to be given to volunteers solicited for the study. This should be reviewed and if necessary amended by counsel for CMR and by legal authority in the States in which experimentation is proposed.

"The study which we plan to carry on here, and for which we have asked your cooperation, is concerned with gonorrhea. You may also know this disease as the 'clap', 'strain', or the 'running ranges'. Some of you have had the infection at some time in the past, or perhaps several times, and you know that it did not make you seriously sick. Recently a simple, dependable treatment has been discovered which consists of a drug taken in the form of pills.

"What we propose to try now is to develop certain methods of <u>preventing</u> the disease in men who are exposed to it. Gonorrhea causes a great loss of time in the Army and Navy, and one of the important medical problems today is to discover how to prevent it in the armed forces. We believe that we have effective methods of doing this, but we cannot know for certain until they have been tested on men. It is not possible to use animals for this purpose because they are not susceptible to gonorrhea. Therefore, we are calling on you for your cooperation. This is one way in which you can specifically help in the war effort. The benefits will not be limited to the armed forces but will be applied to the civil population as well, and it is very likely that you and your families might later profit from them.

"In the first place, I want to assure you that so far as we are able to discover, there is no reason to expect any injury from this treatment, but one cannot predict with positiveness that the result in all cases will be the same. Certain of the men may develop signs of gonorrhea, but in almost every instance they will disappear within a few days after treatment. Most of you, however, will have no disease whatever.

"The general plan of the study is as follows:- First, you will be examined to be certain that you do not now have gonorrhea. Those of you who are now or have recently been infected will not be accepted for the study. Then we will test methods of prevention (prophylaxis) for use in the Army and Navy, in order to determine if they will prevent the disease after exposure to the infection.

"One group of men will be given the drug sulfathiazole in the form of pills as a preventive. This will be given at different times before and after exposure to the infection, which will be carried out by applying the germ to the end of the penis. Another group will first be exposed to the infection in the same manner and shortly after will be given a prophylactic treatment. This consists of applying an ointment to the inside and outside of the penis. A third group will be exposed to the infection and later treated with sulfathiazole, if signs of the disease should develop.

"All men exposed to the infection will be examined daily for at least 3 weeks. You will be under the supervision of a physician specially trained to treat gonorrhea and he will be available at all times throughout the study.

"Most patients with gonorrhea can be cured within 5 to 10 days with modern treatment without experiencing discomfort or complications. A few patients with gonorrhea do not respond to modern treatment methods (probably less than 1 in 10). These patients can usually be cured by the older methods which, however, require more time in which to get results. A few of the patients who are treated by these older methods develop certain complications in the lower genital tract which, in most instances, are ultimately cured. In very rare instances patients treated by the older methods develop complications which involve the joints, the eyes, and other organs.

"A very small percentage of patients treated by modern methods experience slight discomfort while taking the medicine. This may consist of a tired sensation or a slight headache, but these symptoms never become serious if the patient is observed daily by the physician. Fever, skin rash, nausea and vomiting rarely occur but disappear rapidly when the treatment is stopped. Other reactions have been reported which involved the blood, joints, kidneys, liver, and nervous system, but these reactions have been so rare that the possibility of their occurrence is extremely remote.

"Before we can accept you as part of our group, it is necessary to obtain written permission from you.

"_____(place)
_____(date)

"This is to certify that I have read, or have had read to me, and that I understand the above and foregoing statement.

Witness _____ _____(signature)_____ "

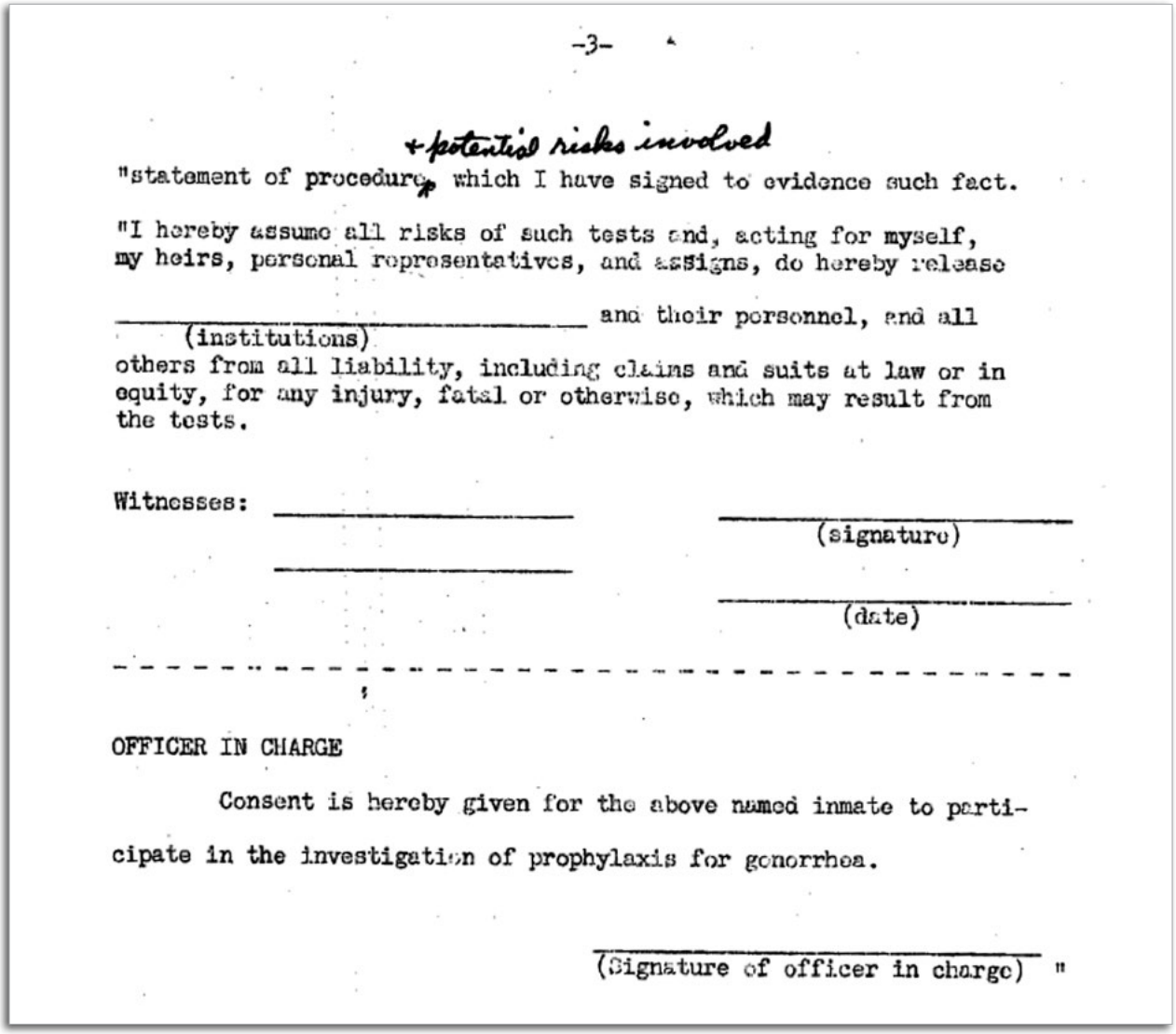
* * * * * * *

SUGGESTED PERMIT AND RELEASE

APPLICATION FOR INCLUSION IN STUDY ON
CHEMICAL PROPHYLAXIS FOR GONORRHEA

"I, _____ # _____, _____, hereby
(name) (age)
voluntarily make application to _____
(cooperating agencies)

for inclusion in the investigation on prophylaxis for gonorrhea.



-3-

+potential risks involved

"statement of procedure, which I have signed to evidence such fact.

"I hereby assume all risks of such tests and, acting for myself, my heirs, personal representatives, and assigns, do hereby release

_____ and their personnel, and all
(institutions)
others from all liability, including claims and suits at law or in equity, for any injury, fatal or otherwise, which may result from the tests.

Witnesses: _____ _____
(signature)

_____ _____
(date)

- -

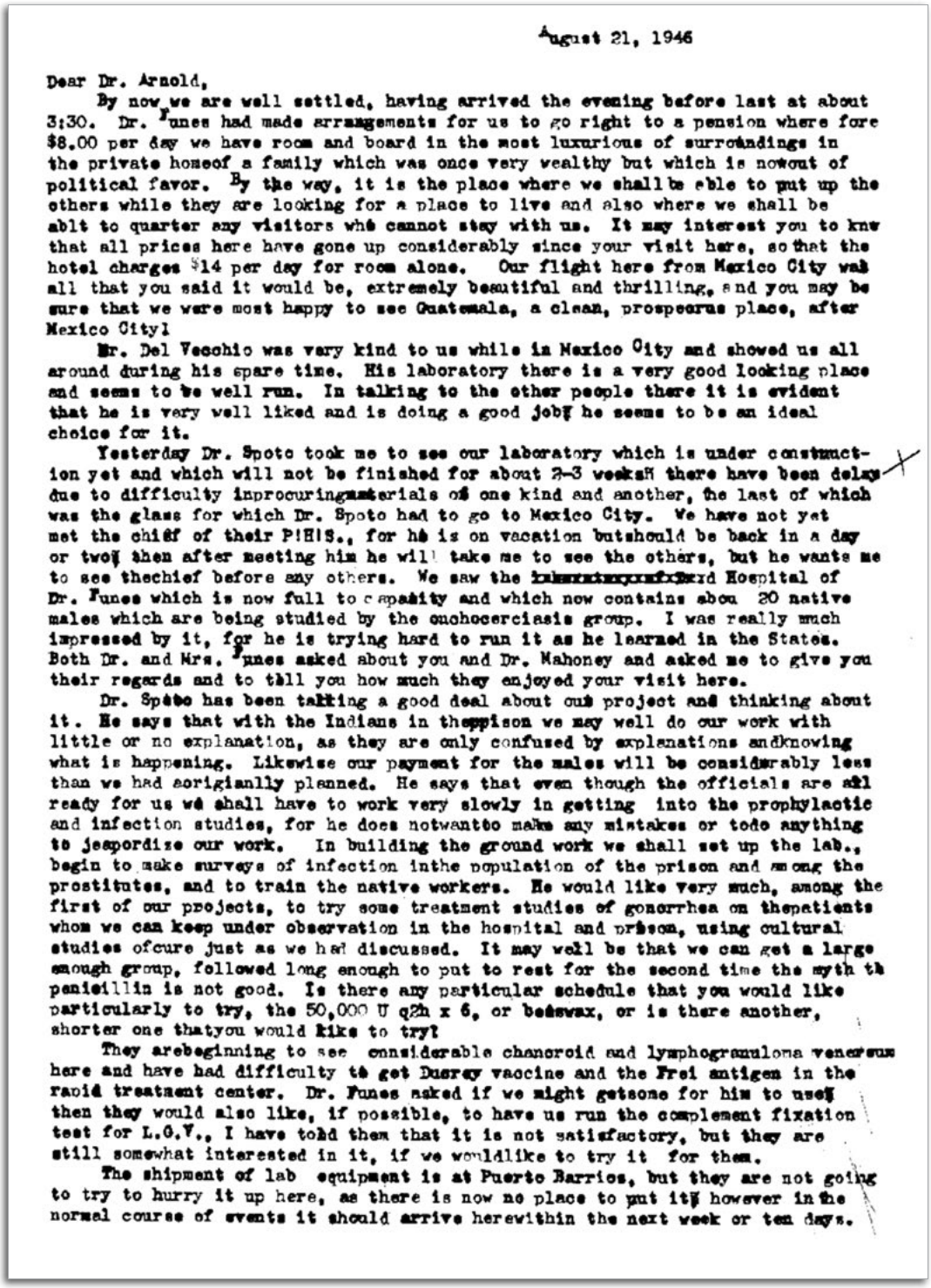
OFFICER IN CHARGE

Consent is hereby given for the above named inmate to participate in the investigation of prophylaxis for gonorrhea.

_____
(Signature of officer in charge) "

Statement of Explanation of the Experiment and its Risks to Tentative Volunteers. (n.d.) Reproduced in Minutes of a Conference on Human Experimentation in Gonorrhea Held Under the Auspices of the Subcommittee on Venereal Diseases. (1942, December 29). PCSBI HSPI Archives, NARA-II_0000173-76.

In Guatemala however, there is no evidence that the same researchers who used this form in Terre Haute sought or received any type of consent from their subjects. In fact, according to a letter by Dr. Cutler, Dr. Joseph Spoto, another PHS researcher working in Guatemala, suggested to Dr. Cutler that it would be better for the subjects if researchers did not inform them of the experiments:



August 21, 1946

Dear Dr. Arnold,

By now we are well settled, having arrived the evening before last at about 3:30. Dr. Funes had made arrangements for us to go right to a pension where fore $8.00 per day we have room and board in the most luxurious of surroundings in the private homeof a family which was once very wealthy but which is nowout of political favor. By the way, it is the place where we shall be able to put up the others while they are looking for a place to live and also where we shall be ablt to quarter any visitors who cannot stay with us. It may interest you to knw that all prices here have gone up considerably since your visit here, so that the hotel charges $14 per day for room alone. Our flight here from Mexico City was all that you said it would be, extremely beautiful and thrilling, and you may be sure that we were most happy to see Guatemala, a clean, prospeerus place, after Mexico City!

Mr. Del Vecchio was very kind to us while in Mexico City and showed us all around during his spare time. His laboratory there is a very good looking place and seems to be well run. In talking to the other people there it is evident that he is very well liked and is doing a good job; he seems to be an ideal choice for it.

Yesterday Dr. Spoto took me to see our laboratory which is under construction yet and which will not be finished for about 2-3 weeks; there have been delays due to difficulty inprocuringmaterials of one kind and another, the last of which was the glass for which Dr. Spoto had to go to Mexico City. We have not yet met the chief of their P.H.S., for he is on vacation butshould be back in a day or two; then after meeting him he will take me to see the others, but he wants me to see thechief before any others. We saw the [redacted] Hospital of Dr. Funes which is now full to capacity and which now contains abou 20 native males which are being studied by the onchocerciasis group. I was really much impressed by it, for he is trying hard to run it as he learned in the States. Both Dr. and Mrs. Funes asked about you and Dr. Mahoney and asked me to give you their regards and to tell you how much they enjoyed your visit here.

Dr. Spoto has been talking a good deal about our project and thinking about it. He says that with the Indians in theprison we may well do our work with little or no explanation, as they are only confused by explanations andknowing what is happening. Likewise our payment for the males will be considerably less than we had aorigianlly planned. He says that even though the officials are all ready for us we shall have to work very slowly in getting into the prophylactic and infection studies, for he does notwantto make any mistakes or todo anything to jeapordize our work. In building the ground work we shall set up the lab., begin to make surveys of infection inthe population of the prison and among the prostitutes, and to train the native workers. He would like very much, among the first of our projects, to try some treatment studies of gonorrhea on thepatients whom we can keep under observation in the hospital and prison, using cultural studies ofcure just as we had discussed. It may well be that we can get a large enough group, followed long enough to put to rest for the second time the myth th penicillin is not good. Is there any particular schedule that you would like particularly to try, the 50,000 U q2h x 6, or beeswax, or is there another, shorter one thatyou would like to try?

They arebeginning to see considerable chancroid and lymphogranuloma venereum here and have had difficulty to get Duergy vaccine and the Frei antigen in the rapid treatment center. Dr. Funes asked if we might getsome for him to use; then they would also like, if possible, to have us run the complement fixation test for L.G.V., I have told them that it is not satisfactory, but they are still somewhat interested in it, if we wouldlike to try it for them.

The shipment of lab equipment is at Puerto Barrios, but they are not going to try to hurry it up here, as there is now no place to put it; however in the normal course of events it should arrive herewithin the next week or ten days.

Unsigned [John Cutler] to Richard Arnold. (1946, August 21). Correspondence. PCSBI HSPI Archives, CTLR_0001215.

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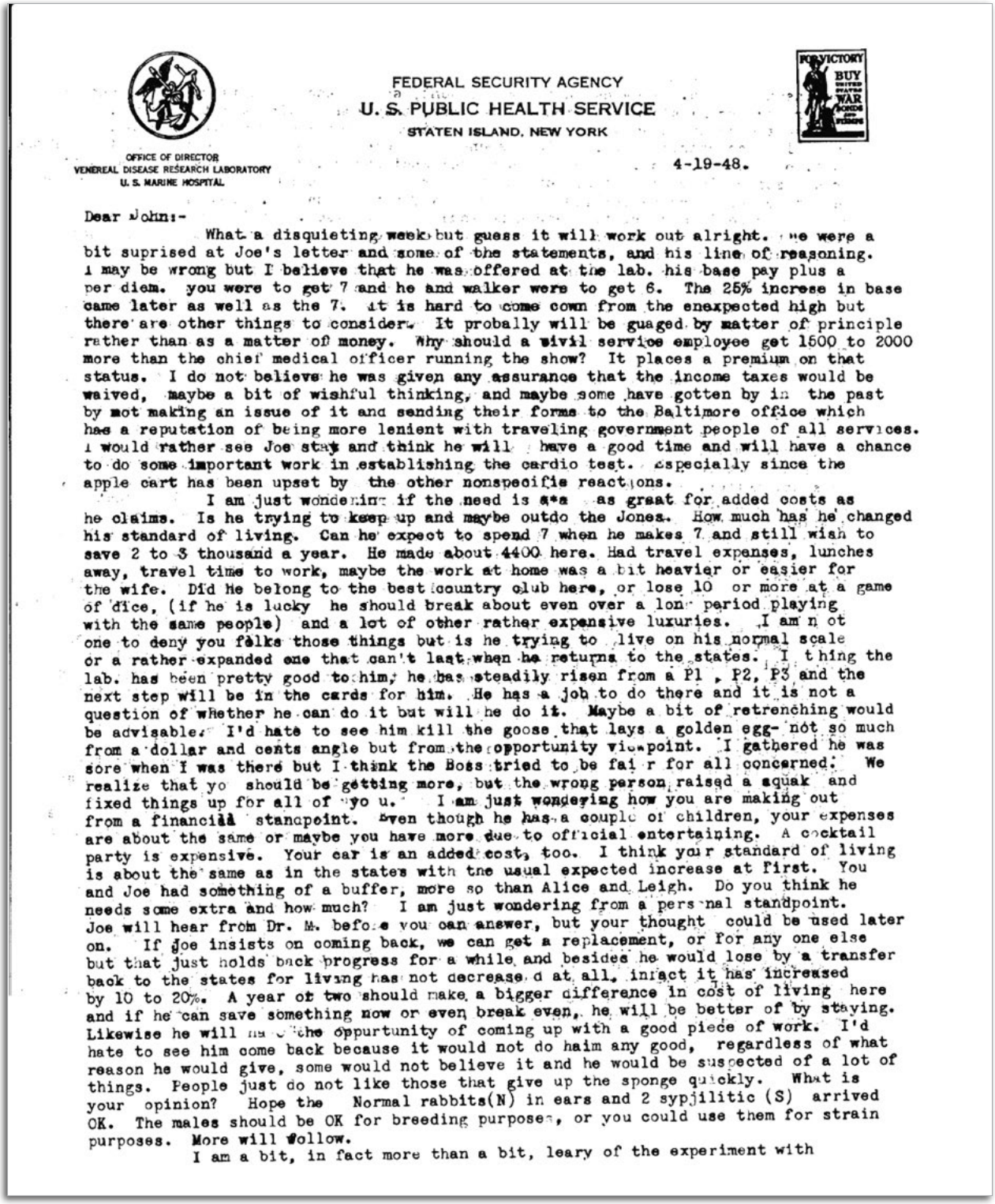
Transcription of Unsigned [John Cutler] to Richard Arnold. (1946, August 21). Correspondence. PCSBI HSPI Archives, CTLR_0001215.

At least one of Dr. Cutler's superiors in the United States, Dr. Arnold, at first expressed concern about the lack of consent, but later suggested deceiving the subjects and possibly the institution:



FEDERAL SECURITY AGENCY
U. S. PUBLIC HEALTH SERVICE
STATEN ISLAND, NEW YORK

FOR VICTORY BUY UNITED STATES WAR BONDS AND STAMPS

OFFICE OF DIRECTOR
VENEREAL DISEASE RESEARCH LABORATORY
U. S. MARINE HOSPITAL

4-19-48.

Dear John:-

What a disquieting week but guess it will work out alright. We were a bit suprised at Joe's letter and some of the statements, and his line of reasoning. I may be wrong but I believe that he was offered at the lab. his base pay plus a per diem. you were to get 7 and he and walker were to get 6. The 25% increse in base came later as well as the 7. it is hard to come down from the enexpected high but there are other things to consider. It probally will be guaged by matter of principle rather than as a matter of money. Why should a civil service employee get 1500 to 2000 more than the chief medical officer running the show? It places a premium on that status. I do not believe he was given any assurance that the income taxes would be waived, maybe a bit of wishful thinking, and maybe some have gotten by in the past by not making an issue of it and sending their forms to the Baltimore office which has a reputation of being more lenient with traveling government people of all services. I would rather see Joe stay and think he will have a good time and will have a chance to do some important work in establishing the cardio test. Especially since the apple cart has been upset by the other nonspecific reactions.

I am just wondering if the need is as great for added costs as he claims. Is he trying to keep up and maybe outdo the Jones. How much has he changed his standard of living. Can he expect to spend 7 when he makes 7 and still wish to save 2 to 3 thousand a year. He made about 4400 here. Had travel expenses, lunches away, travel time to work, maybe the work at home was a bit heavier or easier for the wife. Did he belong to the best country club here, or lose 10 or more at a game of dice, (if he is lucky he should break about even over a long period playing with the same people) and a lot of other rather expensive luxuries. I am not one to deny you folks those things but is he trying to live on his normal scale or a rather expanded one that can't last when he returns to the states. I think the lab. has been pretty good to him, he has steadily risen from a P1 , P2, P3 and the next step will be in the cards for him. He has a job to do there and it is not a question of whether he can do it but will he do it. Maybe a bit of retrenching would be advisable. I'd hate to see him kill the goose that lays a golden egg- not so much from a dollar and cents angle but from the opportunity viewpoint. I gathered he was sore when I was there but I think the Boss tried to be fair for all concerned. We realize that you should be getting more, but the wrong person raised a squak and fixed things up for all of you. I am just wondering how you are making out from a financial standpoint. Even though he has a couple of children, your expenses are about the same or maybe you have more due to official entertaining. A cocktail party is expensive. Your car is an added cost, too. I think your standard of living is about the same as in the states with the usual expected increase at first. You and Joe had something of a buffer, more so than Alice and Leigh. Do you think he needs some extra and how much? I am just wondering from a personal standpoint. Joe will hear from Dr. M. before you can answer, but your thought could be used later on. If Joe insists on coming back, we can get a replacement, or for any one else but that just holds back progress for a while and besides he would lose by a transfer back to the states for living has not decreased at all, infact it has increased by 10 to 20%. A year or two should make a bigger difference in cost of living here and if he can save something now or even break even, he will be better of by staying. Likewise he will miss the oppurtunity of coming up with a good piece of work. I'd hate to see him come back because it would not do haim any good, regardless of what reason he would give, some would not believe it and he would be suspected of a lot of things. People just do not like those that give up the sponge quickly. What is your opinion? Hope the Normal rabbits(N) in ears and 2 sypjilitic (S) arrived OK. The males should be OK for breeding purposes, or you could use them for strain purposes. More will follow.

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4-19-4[7]

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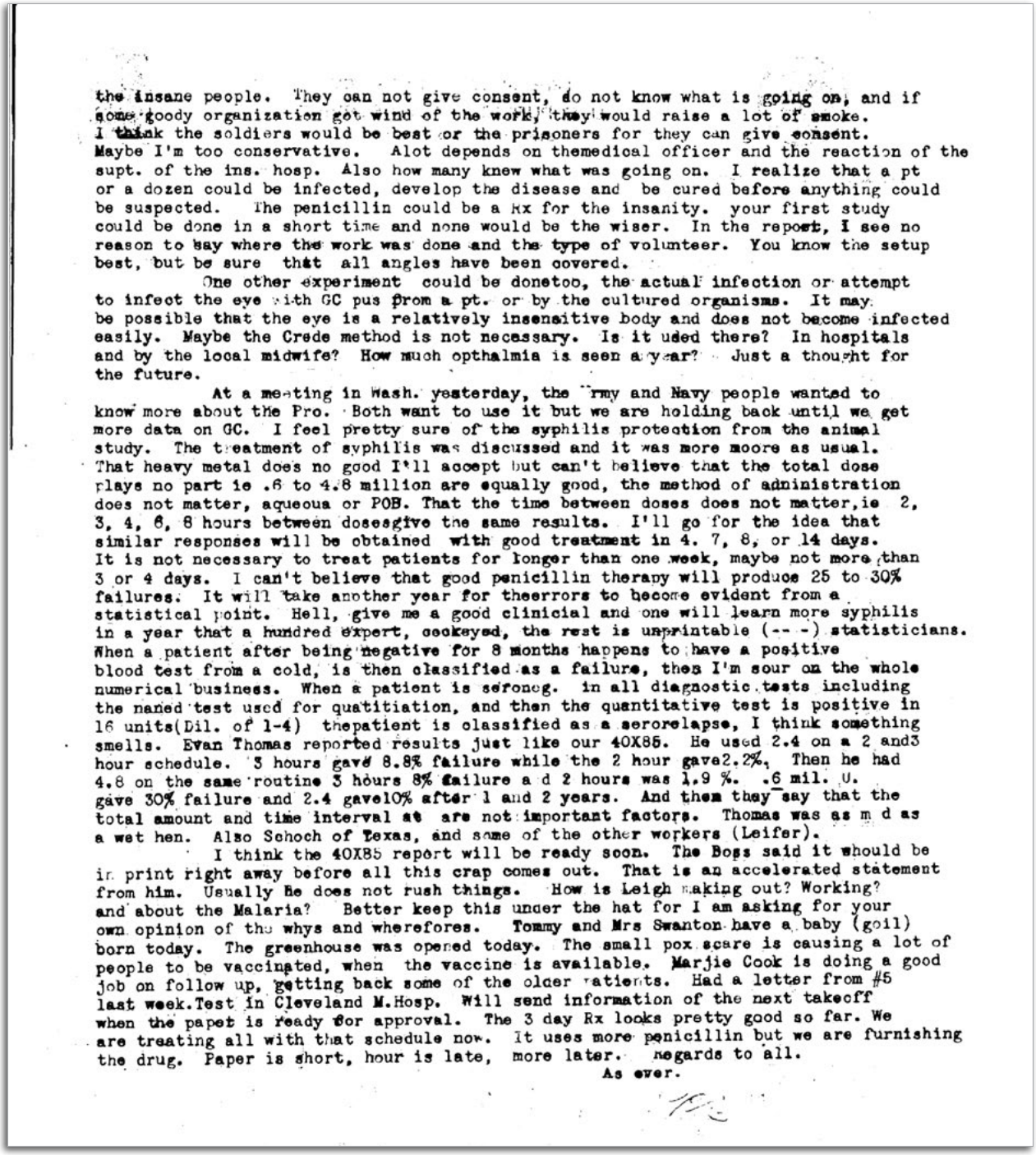

the insane people. They can not give consent, do not know what is going on, and if some goody organization got wind of the work, they would raise a lot of smoke. I think the soldiers would be best or the prisoners for they can give consent. Maybe I'm too conservative. Alot depends on themedical officer and the reaction of the supt. of the ins. hosp. Also how many knew what was going on. I realize that a pt or a dozen could be infected, develop the disease and be cured before anything could be suspected. The penicillin could be a Rx for the insanity. your first study could be done in a short time and none would be the wiser. In the report, I see no reason to say where the work was done and the type of volunteer. You know the setup best, but be sure that all angles have been covered.

One other experiment could be donetoo, the actual infection or attempt to infect the eye with GC pus from a pt. or by the cultured organisms. It may be possible that the eye is a relatively insensitive body and does not become infected easily. Maybe the Crede method is not necessary. Is it used there? In hospitals and by the local midwife? How much opthalmia is seen a year? Just a thought for the future.

At a meeting in Wash. yesterday, the Army and Navy people wanted to know more about the Pro. Both want to use it but we are holding back until we get more data on GC. I feel pretty sure of the syphilis protection from the animal study. The treatment of syphilis was discussed and it was more moore as usual. That heavy metal does no good I'll accept but can't believe that the total dose plays no part ie .6 to 4.8 million are equally good, the method of administration does not matter, aqueous or POB. That the time between doses does not matter, ie 2, 3, 4, 6, 8 hours between dosesgive the same results. I'll go for the idea that similar responses will be obtained with good treatment in 4. 7, 8, or 14 days. It is not necessary to treat patients for longer than one week, maybe not more than 3 or 4 days. I can't believe that good penicillin therapy will produce 25 to 30% failures. It will take another year for theerrors to become evident from a statistical point. Hell, give me a good clinicial and one will learn more syphilis in a year that a hundred expert, cockeyed, the rest is unprintable (-- -) statisticians. When a patient after being negative for 8 months happens to have a positive blood test from a cold, is then classified as a failure, then I'm sour on the whole numerical business. When a patient is seroneg. in all diagnostic tests including the naned test used for quatitiation, and then the quantitative test is positive in 16 units(Dil. of 1-4) thepatient is classified as a serorelapse, I think something smells. Evan Thomas reported results just like our 40X85. He used 2.4 on a 2 and3 hour schedule. 3 hours gave 8.8% failure while the 2 hour gave2.2%, Then he had 4.8 on the same routine 3 hours 8% failure a d 2 hours was 1.9 %. .6 mil. U. gave 30% failure and 2.4 gave10% after 1 and 2 years. And them they say that the total amount and time interval at are not important factors. Thomas was as m d as a wet hen. Also Schoch of Texas, and some of the other workers (Leifer).

I think the 40X85 report will be ready soon. The Boss said it should be in print right away before all this crap comes out. That is an accelerated statement from him. Usually he does not rush things. How is Leigh making out? Working? and about the Malaria? Better keep this under the hat for I am asking for your own opinion of the whys and wherefores. Tommy and Mrs Swanton have a baby (girl) born today. The greenhouse was opened today. The small pox scare is causing a lot of people to be vaccinated, when the vaccine is available. Marjie Cook is doing a good job on follow up, getting back some of the older patients. Had a letter from #5 last week.Test in Cleveland M.Hosp. Will send information of the next takeoff when the paper is ready for approval. The 3 day Rx looks pretty good so far. We are treating all with that schedule now. It uses more penicillin but we are furnishing the drug. Paper is short, hour is late, more later. Regards to all.

As ever.

Richard Arnold to John Cutler. (194[7], April 19). PCSBI HSPI Archives, CTLR_0001220. This letter is originally dated April 19, 1948, however it is clear that this was a typo from context (e.g., the discussion about Joseph Portnoy's salary in response to the letter that Dr. Cutler forwarded to them on April 10, 1947) that the letter should have been dated April 19, 1947.

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 best or the prisoners for they can give consent. Maybe I'm too conservative. A lot depends [on] the medical officer and the reaction of the [supervisor of the insane hospital]. Also how many know what was going on. I realize that a [patient] or a dozen could be infected, develop the disease and be cured before anything could be suspected. The penicillin could be a Rx [cure] for the insanity. Your first study could be done in a short time and none would be the wiser. In the report, I see no reason to say where the work was done and the type of volunteer. You know the setup best, but be sure that all angles have been covered.

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I think the 40X85 report will be ready soon. The Boss said it [would] be in print right away before all this crap comes out. That is an accelerated statement from him. Usually he does not rush things. How is Leigh making out? Working? And about the Malaria? Better keep this under the hat for I am asking for your own opinion of the whys and wherefores. Tommy and Mrs. Swanton have a baby [girl] born today. The greenhouse was opened today. The small pox scare is causing a lot of people to vaccinated, when the vaccine is available. Marji Cook is doing a good job on follow up, getting back some of the older patients. Had a letter from #5 last week. Test in Cleveland M.Hosp. Will send information of the next takeoff when the paper is ready for approval. The 3 day Rx looks pretty good so far. We are treating all with that schedule now. It uses more penicillin but we are furnishing the drug. Paper is short, hour is late, more later. Regards to all.

As ever,

[R.C.]

Transcription of Richard Arnold to John Cutler. (194[7], April 19). PCSBI HSPI Archives, CTLR_0001220.

Comment

Under current human subjects research standards, obtaining the "informed consent" of research participants is required. Informed consent must include, among other things:

- Descriptions of any reasonably foreseeable risks or discomforts to the subject;
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- An explanation of whom to contact for answers to pertinent questions; and
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits.[11]

Evaluate the Terre Haute waiver form under modern day standards enumerated above. In what ways does the waiver meet modern standards? In what ways might it fall short?

Drs. Mahoney and Cutler both played roles in the Terre Haute experiments. However, in Guatemala, the idea of consent seems to have been dismissed and active deception encouraged—similar to what was occurring in the then ongoing research in Tuskegee. What excuses were given for not getting consent from research subjects? If the subjects *had* given consent to the researchers, how would your feelings about the ethics of the experiments change?

Under current human subjects research standards, research protocols must be approved by an Institutional Review Board which is tasked with ensuring, among other things, that risks to participants are minimized and reasonable, and that additional safeguards are included for research involving participants "likely to be vulnerable to coercion or undue influence, such as children, prisoners…mentally disabled persons, or economically or educationally disadvantaged persons…"[11] In its report on the Guatemala STD experiments, the Commission concluded that no Institutional Review Board today would have approved them.[12] What types of things would need to be done for these studies to be considered ethical under current standards?

Current regulations also require informed consent by the participant or a participant's "legally authorized representative."[13] Dr. Cutler claimed that in Guatemala the researchers were often working at institutions such as the Penitentiary and the Psychiatric Hospital with permission of the directors of those institutions. Under what circumstances is it ethically appropriate for the directors of such institutions to provide legal consent for experimentation involving the persons under their charge?

[11] 45 C.F.R. § 46.111. (2009). *Protection of Human Research Subjects.*
[12] PCSBI. (2011, September). *"Ethically Impossible" STD Research in Guatemala from 1946- 1948*. Washington, DC: PCSBI, p. 92.
[13] 45 C.F.R. § 46.116. (2009). *Protection of Human Research Subjects.*

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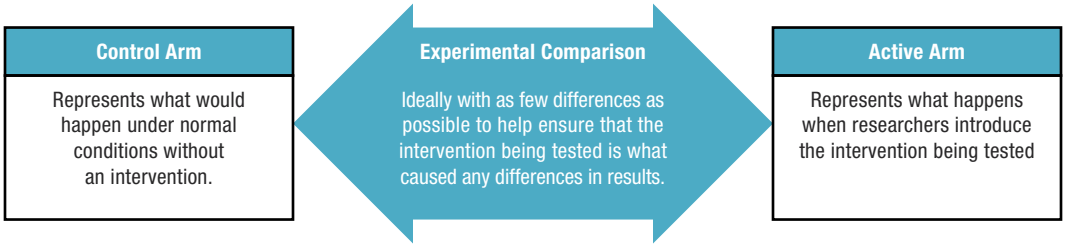
Scientific Method and Publication

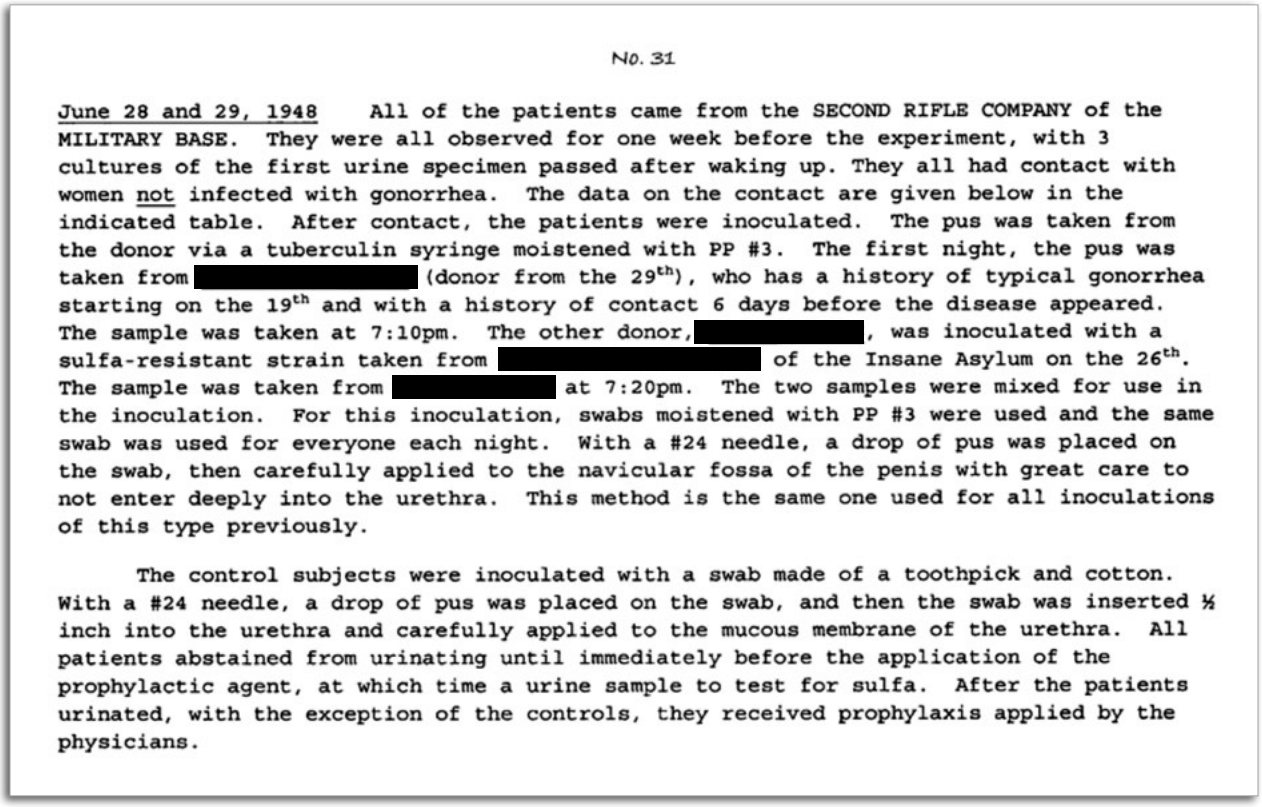
Scientific Method

Today, research involving human subjects must follow the "scientific method." The scientific method begins with defining a question to be answered, collecting already known observations on the topic, forming a hypothesis of a possible answer to be tested, performing an experiment to test the hypothesis (in a way that will be reproducible by other scientists), analyzing and interpreting the data to reach conclusions, and, finally, typically publishing the results in a journal that is vetted by fellow researchers ("peer-reviewed") to ensure quality.

During the experiment portion of the scientific method, many researchers employ a comparison "control arm" to help rule out factors (other than those being tested) that might affect the result of the experiment. The control arm is not subjected to the intervention being tested so that researchers can determine what would happen under non-experimental circumstances. The intervention being tested is used in the "active arm" of an experiment. Ideally, the only difference between the control and active arms of the experiment would be the intervention. This allows researchers to reliably compare what happens in a normal situation without the intervention to what happens with the intervention. A well-designed experiment with as few differences as possible between the active and control arms of the experiment helps ensure that the intervention being tested is what caused any differences in results.



The below translated excerpt comes from Dr. Cutler's "Clinical Notebook" during the Guatemala STD studies. Here Dr. Cutler describes his experimental design for a gonorrhea experiment with soldiers:



No. 31

June 28 and 29, 1948 All of the patients came from the SECOND RIFLE COMPANY of the MILITARY BASE. They were all observed for one week before the experiment, with 3 cultures of the first urine specimen passed after waking up. They all had contact with women not infected with gonorrhea. The data on the contact are given below in the indicated table. After contact, the patients were inoculated. The pus was taken from the donor via a tuberculin syringe moistened with PP #3. The first night, the pus was taken from [redacted] (donor from the 29th), who has a history of typical gonorrhea starting on the 19th and with a history of contact 6 days before the disease appeared. The sample was taken at 7:10pm. The other donor, [redacted], was inoculated with a sulfa-resistant strain taken from [redacted] of the Insane Asylum on the 26th. The sample was taken from [redacted] at 7:20pm. The two samples were mixed for use in the inoculation. For this inoculation, swabs moistened with PP #3 were used and the same swab was used for everyone each night. With a #24 needle, a drop of pus was placed on the swab, then carefully applied to the navicular fossa of the penis with great care to not enter deeply into the urethra. This method is the same one used for all inoculations of this type previously.

The control subjects were inoculated with a swab made of a toothpick and cotton. With a #24 needle, a drop of pus was placed on the swab, and then the swab was inserted ½ inch into the urethra and carefully applied to the mucous membrane of the urethra. All patients abstained from urinating until immediately before the application of the prophylactic agent, at which time a urine sample to test for sulfa. After the patients urinated, with the exception of the controls, they received prophylaxis applied by the physicians.

Cutler Documents. (1948, June 28-29). Translation of Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000602.

Publication

Despite the money, time, and resources spent during the three years the researchers worked in Guatemala, the team never published the results of the STD exposure and prophylaxis experiments. Thus they never subjected their experimental design, analysis, or results to scientific peer review or public scrutiny. Scientific peer-reviewed journals however, did publish the results of the serological experiments in several articles.

In the 1950s, Dr. Cutler wrote final reports in which he summarized all three types of STD experiments, but again, did not publish them or subject them to peer review. When the researchers wrote retrospective reviews of STD research in their future publications, they never overtly discussed the research they conducted in Guatemala.

Dr. Cutler donated more than 20 boxes of Guatemala documents, including his "Final Reports" and "Clinical Notebooks," to the University of Pittsburgh archives in 1990. These documents were made public in 2010. If Dr. Cutler had not donated these documents, it is likely that the public would never have known about the Guatemala STD experiments. These documents along with the documents that the Commission collected during its investigation, are now housed at the National Archives Southeast Region.

Comment

In Gonorrhea Experiment 31 (translated excerpt above) in the Guatemalan military, the researchers exposed all of the subjects to gonorrhea and used a post-exposure prophylaxis wash in the active arm to test whether it prevents infection. The researchers, however, exposed the active arm of the experiment to gonorrhea by placing gonorrhea pus on the outside of the subjects' penises. They exposed the control arm of the experiment to gonorrhea by inserting pus ½ inch into the subjects' penises. Why did this experimental protocol violate the modern scientific method? What affect might this violation have had on the conclusions that the researchers reached at the end of this experiment? Disregarding other issues (such as lack of consent and risks), why might using faulty experimental design, as described above, be unethical in and of itself?

What are the ethical concerns associated with the fact that the Guatemala STD research was never submitted for peer-reviewed publication? What might have been the result if it had been?

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Howard, J., and L. Friedman. (1981). Protecting the scientific integrity of a clinical trial: Some ethical dilemmas. *Clinical Pharmacology and Therapeutics*, 29, 561-569.

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REVIEWING ETHICAL STANDARDS IN CONTEXT

The Commission's Report

On November 24, 2010, President Barack Obama charged the Commission to "oversee a thorough fact-finding investigation into the specifics" of the Guatemala STD experiments.[14] The Commission began its work in January 2011. It published the results of its inquiry, *"Ethically Impossible:" STD Research in Guatemala from 1946 to 1948*, in September 2011.

Above and beyond its fact-finding investigation, the Commission also evaluated the ethics of the Guatemala STD experiments in its "Reviewing Ethical Standards in Context" section. On the following page is an excerpt from that section discussing the concept of retrospective moral judgment:

[14] PCSBI. (2011, September). *"Ethically Impossible" STD Research in Guatemala from 1946- 1948*. Washington, DC: PCSBI, p. 3.

REVIEWING ETHICAL STANDARDS IN CONTEXT VI

Contemporaneous Standards for Ethical Research in 1946-1948

The norms of medical ethics for a given era are often difficult to identify in detail. They are a complex mixture of written statements, practices, and attitudes. The era in which the research in Guatemala occurred was certainly one in which ethical standards were in flux. The medical experimenters of the years immediately following World War II were swimming in a sea of change that, several decades later, produced decisive shifts in the tides of moral awareness and regulation. Retrospective moral judgments can therefore be hazardous. With the passage of time, the accumulation of experience, and the luxury of reflection, it can be easy to feel morally superior to our predecessors.

Despite these challenges, it is possible to develop and apply a standard for moral judgments about past actions and, to some degree, to conclude that actions and actors were blameworthy. In the case of the Guatemala experiments, retrospective moral judgment is facilitated by a rich historical record of the experimenters' own words and behavior in the years prior to the onset of these studies, behavior that expressed and endorsed a self-imposed moral metric that can be held against their activities. What bears particular emphasis is that this historical record includes not only practices but also self-indicting statements by the researchers themselves.

To be sure, these investigators were operating within a culture of medical research that often treated moral norms pragmatically, primarily as defenses against meddling "do-gooders" who would impinge upon their all-important work, rather than as genuine moral imperatives based upon respect for persons. In 1947, such an attitude might have characterized the majority of medical researchers and, indeed, some researchers might still harbor such views today.

Nonetheless, during this period basic tenets bearing on informed consent and risk reduction were beginning to be widely recognized and followed in practice. Many researchers, especially public health investigators, were familiar with Walter Reed's yellow fever experiments at the turn of the century during which Spanish workers were recruited and agreed to be exposed to mosquitoes to test the theory that the insects carried yellow fever.[671] Legal standards articulated early in the 20th century included an individual's right to determine what shall be done with his or her body, although acceptance and application of these norms diffused slowly within the medical profession.[672]

Writing after a thorough historical review of practices during this time period, the President's Advisory Committee on Human Radiation Experiments (the "Radiation Experiments Committee") reached a set of equivocal conclusions. On one hand, the Radiation Experiments Committee found that, "as early as 1944 it was conventional for physicians and other biomedical scientists to obtain consent from healthy subjects of research."[673] However, the Committee also found that "physicians engaged in clinical research [i.e., research on sick patients, not healthy volunteers] generally did not obtain consent from patient-subjects" even when the experiment offered no prospect of direct benefit to the patient.[674] Nonetheless, it was "common for physicians to be concerned about risk in conducting research on patient-subjects and, in the absence of a prospect of offsetting medical benefit, to restrict research uses of patients to what were considered low- or minimal-risk interventions."[675] Subsequent concerns that physician-investigators underestimated risks to patient-subjects contributed to the establishment of independent review mechanisms.

By mid-century, these early examples of informed consent and risk-assessment practices, while not often phrased as such, were common for experiments involving healthy subjects like prisoners, soldiers, and conscientious objectors.[676] In particular, the Terre Haute researchers and their superiors—who included some of the same individuals as the experiments in Guatemala—carefully considered and adopted strict requirements for individual consent and voluntariness for the research they conducted in 1943 and 1944.[677] In 1946, VDRL researchers Drs. Mahoney, Cutler, Van Slyke, and Blum also recognized a need to use only "volunteers" as experimental subjects, and then only after providing adequate information about risks for a prospective participant to make an informed choice. Writing in the *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* about their work with prisoners at Terre Haute, the doctors insisted that participants must possess "a thorough understanding of the purpose underlying the study and the possible risks involved."[678] Other researchers engaged in intentional infection research expressed similar sentiments.[679] Of course, it is impossible to know whether these sentiments were largely intended to avert public disapproval.

The period between 1946 and 1948 was an especially important time in the development of human research ethics. During these years, the Nuremberg

REVIEWING ETHICAL STANDARDS IN CONTEXT VI

Medical Tribunal considered charges against 23 physicians and bureaucrats accused of complicity in concentration camp experiments, many of which were geared to support the Third Reich's war effort.[680] A key witness for the prosecution was Dr. Andrew C. Ivy, a leading U.S. medical researcher who served as a vice president at the University of Illinois and as former scientific director of the Naval Medical Research Institute in Bethesda, Maryland. Dr. Ivy was a consultant designated by the American Medical Association to assist the prosecutors.[681] Around the time the trial began in 1946, Dr. Ivy prepared a report to articulate ethical and legal conventions, or "rules," for human experimentation. Historians have argued that the preparation of this report was prompted by the Nazis' defense lawyers' surprisingly disconcerting arguments regarding questionable conduct of human research in the United States, particularly research conducted in prisons.[682]

The American Medical Association accepted the report of Dr. Ivy and his collaborator, Dr. Leo Alexander, and its House of Delegates adopted it in December 1946. The *Journal of the American Medical Association* published the statement in early January 1947.[683] The rules emphasized voluntary and informed consent, as well as avoidance of inappropriate risk. First:

> "Consent of the human subject must be obtained. All subjects must have been volunteers in the absence of coercion in any form. Before volunteering the subjects have been informed of the hazards, if any…"[684]

And, second:

> "The experiment must be conducted…so as to avoid all unnecessary physical and mental suffering and injury, and…there is no *a priori* reason to believe that death or disabling injury will occur, except in such experiments as those on Yellow Fever where the experimenters serve as subjects along with non-scientific personnel."[685]

In May 1947, Dr. Ivy, describing his assessment of the Nazi doctors' medical experiments in the newsletter of the Federation of State Medical Boards, concluded that the activities "were crimes because they were performed on prisoners without their consent and in complete disregard for their human rights. They were not conducted so as to avoid unnecessary pain and suffering,

death being the premeditated outcome in a number of these experiments."[686] In fact, however, those who were later convicted in the Nazi doctors' trial were found guilty of participation in mass slaughter, not for violations of medical ethics.

Writing in *The New York Times* in April 1947 about syphilis research, journalist Waldemar Kaempffert, reported that any plan to "shoot living syphilis germs into human bodies" to advance science would be "ethically impossible." Yet human testing of the very kind described in the note as "ethically impossible" was about to begin in Guatemala. Upon reading the *New York Times* article, Dr. Cutler called it to the attention of his superior Dr. Mahoney, VDRL Director. In his letter to Dr. Mahoney, Dr. Cutler expressed his concern that, in light of the unqualified ethical statement made in Kaempffert's article, a recent public notice regarding the Guatemala research would draw undesirable criticism. Dr. Cutler also emphasized the need to increase secrecy and limit information about the program to those "who can be trusted not to talk."[687]

Kaempffert's *New York Times* article and the concern it engendered on Dr. Cutler's part illustrate the tensions that were created as a result of evolving research ethics standards in the period immediately following World War II. The rules subsequently issued by the Nuremberg court in its judgment on the Nazi doctors' case in August 1947, now famously called "The Nuremberg Code," largely echo Drs. Ivy and Alexander's original formulation.[688] First, the court found that "the voluntary consent of the human subject is absolutely essential."[689] The court emphasized the need for careful attention to risks and rigorous commitment to individual participant welfare. Experiments should be conducted "so as to avoid all unnecessary physical and mental suffering and injury," the court ruled, and be "not random and unnecessary in nature."[690] Furthermore, "[n]o experiments should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur, except, perhaps, in those experiments where the experimental physicians also serve as subjects."

Like Dr. Ivy and the American Medical Association, the tribunal asserted that its rules were already understood and followed by all ethical medical researchers everywhere in the world.[691] However, more recent scholarship has disclosed that these assertions were at the very least highly exaggerated.[692] It would be more accurate to state that these rules were available in the culture

of medicine, as is clear from the fact that Dr. Ivy was able to identify them and the American Medical Association promulgated them, although they were not understood and appreciated as fully as they are today. Certainly, the evidence suggests that the physicians and officials responsible for the Guatemala experiments recognized that these rules were in circulation and had some appreciation of their implications for research, as Dr. Cutler's reaction to the Kaempffert article shows. As medical professionals and public officials, they had a moral and professional duty to recognize these rules and to appreciate their implications for research practices.

Yet the physicians and officials responsible for the Guatemala experiments violated all of these requirements. Not only was there no evidence of voluntary consent by the subjects, but also they were clearly exposed to the risk of serious physical harm posed by contracting various diseases. Specific correspondence and other records show that some subjects were exposed to, and sometimes suffered, significant injury when treatment and available medicines could have prevented such harms.[693] Compounding these issues was the fact that even had risks been reasonable, there was no proportionate humanitarian benefit to be gained, as the experiments were not designed in a scientifically or morally responsible fashion. There is no evidence that any of the researchers volunteered to subject themselves to the experiments, a condition that we might today view as quaint and irrelevant but which was not uncommon at the time and would at least have established that they were willing to consent to the risks to which they exposed others without seeking their consent.

Comment

The Commission discussed some of the potential complications with retrospective moral judgment in the above excerpt, but concluded that it was comfortable doing so on the basis of the researchers' past involvement in clinical trials and their writings at that time. What specific aspects of the Guatemala STD experiments lend support to the appropriateness of retrospective moral judgment? What aspects of these experiments might suggest that retrospective moral judgment is inappropriate?

As discussed above, the Nuremburg Code was published in August 1947, while the Guatemala STD experiments were occurring. There is no record in the Guatemala archives that the researchers ever read or discussed the Nuremburg Code. To what extent do you think researchers have a moral obligation to ensure that they are updated on contemporary ethical thinking? Today, human subjects researchers are required to follow many regulations and institutional policies to be knowledgeable about and in compliance with current ethical standards. What, if any, moral obligations do you think human subjects researchers have above and beyond that which is required of them by law?

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Presidential Commission for the Study of Bioethical Issues
1425 New York Avenue NW, Suite C-100
Washington, D.C. 20005
(202) 233-3960
www.bioethics.gov