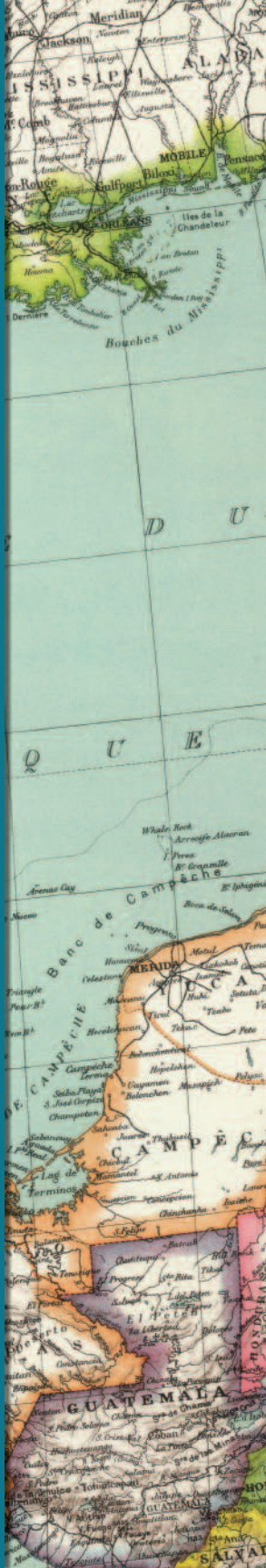
"ETHICALLY IMPOSSIBLE"
STD Research in Guatemala from 1946 to 1948



Presidential Commission
***for the* Study of Bioethical Issues**

September 2011

ABOUT THE COVER:
Detail taken from historical map
Complete map shown above

Author: Schrader; Vivien St Martin, L.
Date: 1937
Short Title: Mexique
Publisher: Librairie Hachette, Paris
Type: Atlas Map

"ETHICALLY IMPOSSIBLE"
STD Research in Guatemala from 1946 to 1948

Presidential Commission
for the Study of Bioethical Issues

Washington, D.C.
September 2011

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.

For more information about the Commission, please see www.bioethics.gov.

CONTENTS

Presidential Commission for the Study of Bioethical Issues

President Barack Obama
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Dear Mr. President:

On behalf of the Presidential Commission for the Study of Bioethical Issues, we present to you this report, *"Ethically Impossible": STD Research in Guatemala from 1946 to 1948*. In response to your request of November 24, 2010, the Commission oversaw a thorough fact-finding investigation into the specifics of the U.S. Public Health Service-led studies in Guatemala involving the intentional exposure and infection of vulnerable populations.

Following a nine-month intensive investigation, the Commission has concluded that the Guatemala experiments involved gross violations of ethics as judged against both the standards of today and the researchers' own understanding of applicable contemporaneous practices. It is the Commission's firm belief that many of the actions undertaken in Guatemala were especially egregious moral wrongs because many of the individuals involved held positions of public institutional responsibility.

The best thing we can do as a country when faced with a dark chapter is to bring it to light. The Commission has worked hard to provide an unvarnished ethical analysis to both honor the victims and make sure events such as these never happen again.

The Commission is also working to fulfill your other charge on human subjects research—a review of domestic and international contemporary human subjects protection rules and standards, to ensure federally funded scientific studies are conducted ethically—and will submit a report to you in December.

The Commission is honored by the trust you have placed in us and grateful for the opportunity to serve you and the nation in this way.

Sincerely,

Amy Gutmann, Ph.D.
Chair

James Wagner, Ph.D.
Vice-Chair

1425 New York Avenue, NW, Suite C-100, Washington, DC 20005
Phone 202-233-3960 Fax 202-233-3990 www.bioethics.gov

THE WHITE HOUSE
WASHINGTON

November 24, 2010

MEMORANDUM FOR DR. AMY GUTMANN
Chair, Presidential Commission for the Study of Bioethical Issues

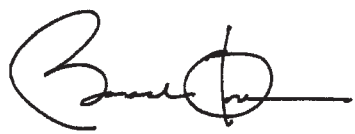
SUBJECT: Review of Human Subjects Protection

Recently, we discovered that the U.S. Public Health Service conducted research on sexually transmitted diseases in Guatemala from 1946 to 1948 involving the intentional infection of vulnerable human populations. The research was clearly unethical. In light of this revelation, I want to be assured that current rules for research participants protect people from harm or unethical treatment, domestically as well as internationally.

I ask you, as the Chair of the Presidential Commission for the Study of Bioethical Issues, to convene a panel to conduct, beginning in January 2011, a thorough review of human subjects protection to determine if Federal regulations and international standards adequately guard the health and well-being of participants in scientific studies supported by the Federal Government. I also request that the Commission oversee a thorough fact-finding investigation into the specifics of the U.S. Public Health Service Sexually Transmitted Diseases Inoculation Study.

In fulfilling this charge, the Commission should seek the insights and perspective of international experts, including from Guatemala; consult with its counterparts in the global community; and convene at least one meeting outside the United States. I expect the Commission to complete its work within 9 months and provide me with a report of its findings and recommendations.

While I believe the research community has made tremendous progress in the area of human subjects protection, what took place in Guatemala is a sobering reminder of past abuses. It is especially important for the Commission to use its vast expertise spanning the fields of science, policy, ethics, and religious values to carry out this mission. We owe it to the people of Guatemala and future generations of volunteers who participate in medical research.



PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

AMY GUTMANN, PH.D., CHAIR
President and Christopher H. Browne
Distinguished Professor of Political Science, University of Pennsylvania

JAMES W. WAGNER, PH.D., VICE CHAIR
President, Emory University

YOLANDA ALI, M.B.A.
Michael J. Fox Foundation
Founder's Council;
Emory Neurosciences
Community Advisory Board

ANITA L. ALLEN, J.D., PH.D.
Henry R. Silverman Professor of Law
and Professor of Philosophy
University of Pennsylvania Law School

JOHN D. ARRAS, PH.D.
Porterfield Professor of Biomedical
Ethics, Professor of Philosophy,
University of Virginia

BARBARA F. ATKINSON, M.D.
Executive Vice Chancellor,
University of Kansas Medical Center;
Executive Dean, University of
Kansas School of Medicine

NITA A. FARAHANY, J.D., PH.D.
Leah Kaplan Visiting Professor in
Human Rights, Stanford Law School
Associate Professor of Law;
Associate Professor of Philosophy
Vanderbilt University

ALEXANDER G. GARZA, M.D., M.P.H.
Assistant Secretary, Office of Health
Affairs; Chief Medical Officer,
Department of Homeland Security

CHRISTINE GRADY, R.N., PH.D.
Acting Chief of the Department of
Bioethics, National Institutes of
Health Clinical Center

STEPHEN L. HAUSER, M.D.
Robert A. Fishman Distinguished
Professor and Chair of the Department
of Neurology, University of California,
San Francisco

RAJU S. KUCHERLAPATI, PH.D.
Paul C. Cabot Professor, Department
of Genetics, Harvard Medical School;
Professor, Department of Medicine,
Brigham and Women's Hospital

NELSON L. MICHAEL, M.D., PH.D.
Colonel, Medical Corps, U.S. Army;
Director, Division of Retrovirology;
Walter Reed Army Institute of Research;
U.S. Military HIV Research Program

DANIEL P. SULMASY, M.D., PH.D., FACP
Kilbride-Clinton Professor of Medicine
and Ethics, Department of Medicine
and Divinity School; Associate Director,
The MacLean Center for Clinical Medical
Ethics, University of Chicago

PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

STAFF* AND CONSULTANTS

Executive Director
Valerie H. Bonham, J.D.

Deputy Director
Debbie Banks Forrest, M.P.P.

Communications Director
Hillary Wicai Viers, M.S.J.

Senior Advisors
Paul Lombardo, Ph.D., J.D.
Jonathan D. Moreno, Ph.D.
Jeremy Sugarman, M.D., M.P.H., M.A.

Research Staff
Eleanor Celeste, B.A.
Tom Cinq-Mars, B.A.
Brian C. Eiler, J.D.
Michelle Groman, J.D.
Chris Havasy, Sc.B.
Holly Fernandez Lynch, J.D., M. Bioethics
Debra Mathews, Ph.D.
Eleanor E. Mayer, J.D., M. Bioethics
David G. Miller, Ph.D.
Anne Pierson, J.D.
Jason L. Schwartz, A.M., M. Bioethics
Kayte Spector-Bagdady, J.D., M. Bioethics
Victoria Wilbur, B.A.

Consultants
Burness Communications
Kathi E. Hanna, M.S., Ph.D.
Jonathan Zenilman, M.D.

Committee and Staff Affairs
Judith E. Crawford
Esther Yoo, B.A.

Fellows and Interns
Laura Biron, Ph.D.
Michael Grippaldi, B.S.
Magdalina Gugucheva, B.A.
Casey Nicol, B.S.
Tuua Ruutiainen, B.A.
Michael Tennison, M.A.
David Tester, Ph.D.
Ilana Yurkiewicz, B.S.

**Includes former and part-time staff*

ACKNOWLEDGEMENTS

The Commission is grateful to the many individuals who contributed their time, energy, and insight to this investigation. The Commission extends its thanks to the historians, scholars, archivists, and agency officials who helped it find and synthesize the records and documents necessary to fully describe these events.

It is impossible to name each person here, but the Commission offers its particular thanks to Suzanne Junod, Susan Lederer, Richard Mandel, Robert F. Moore, Betty Murgolo, John Parascandola, Richard Peuser, Andrew Pope, Martin Rangel, John Rees, Susan Reverby, Rob Richards, Nancy Terry, Paul Theerman, and Wanda Williams. The Commission also extends a special thanks to Jonathan Zenilman, Epidemiology Director at the Johns Hopkins Center for Sexually Transmitted Infections Research and Prevention, for his assistance in interpreting the research records.

Finally, the Commission is enormously indebted to its talented staff for their unwavering dedication to conducting a thorough and comprehensive investigation into this complex set of events in a short period of time. The Commission extends a special thanks to Executive Director Valerie Bonham, for her passion and tireless commitment to bringing the truth to light, Senior Advisors Paul Lombardo and Jonathan Moreno, for their wisdom and expertise, and lead staff on the investigation Brian Eiler, Eleanor Mayer, and Kayte Spector-Bagdady, whose drive for excellence inspired us all.

PREFACE

On October 1, 2010, President Barack Obama telephoned President Álvaro Colom of Guatemala to extend an apology to the people of Guatemala for medical research supported by the United States and conducted in Guatemala between 1946 and 1948. Some of the research involved deliberate infection of people with sexually transmitted diseases ("STDs")[1] without their consent. Subjects were exposed to syphilis, gonorrhea, and chancroid, and included prisoners, soldiers from several parts of the army, patients in a state-run psychiatric hospital, and commercial sex workers. Serology experiments that did not involve intentional exposure to infection, which continued through 1953, also were performed in these groups, as well as with children from state-run schools, an orphanage, and several rural towns. President Obama expressed "deep regret" for the research and affirmed the U.S. government's "unwavering commitment to ensure that all human medical studies conducted today meet exacting" standards for the protection of human subjects.[2]

Kathleen Sebelius, Secretary of the U.S. Department of Health and Human Services (DHHS), and Hillary Rodham Clinton, Secretary of the Department of State, immediately issued a joint apology to the government of Guatemala and the survivors and descendants of those affected. Calling the experiments "clearly unethical," Secretaries Sebelius and Clinton amplified the President's statements of regret and apologized "to all the individuals who were affected by such abhorrent research practices."[3] In the spirit of openness and freedom of inquiry needed to restore trust and repair the damage created by these revelations, the Secretaries indicated that the U.S. government would launch an independent inquiry into the events. They also announced plans for the Presidential Commission for the Study of Bioethical Issues (the "Commission"), with input from international experts, to undertake a thorough review of human subjects protections to "ensure that all [U.S.-sponsored] human medical research conducted around the globe today meets rigorous ethical standards."[4]

The outrage that the U.S. government registered with these announcements echoed around the globe. For some, the story was reminiscent of the infamous U.S. Public Health Service (PHS) Study of Untreated Syphilis (also known as the "Tuskegee Syphilis Study"), in which nearly 400 African American men with syphilis in Alabama were left untreated for nearly 30 years while

U.S. government researchers observed the progress of their infections.[5] The similarities between the two cases were stark. The cases arose from the same laboratory of the Public Health Service, the Venereal Disease Research Laboratory (VDRL), involved some of the same researchers, and focused, in part, on the same disease. Both cases also involved deliberate efforts to deceive experimental subjects and the wider community that might have objected to the work. But other factors distinguished the research in Guatemala from that conducted in Tuskegee. The research in Guatemala ended long before the work in Tuskegee stopped and took place over a much shorter period. Subjects in Guatemala were deliberately exposed to infections, were members of different populations, and were citizens of a foreign country.

As additional details about the research emerged, President Obama directed the Commission to undertake both a forward-looking assessment of research ethics and an historical review of events that occurred in Guatemala between 1946 and 1948.[6] On November 24, 2010, he charged the Commission, beginning in January 2011, to "oversee a thorough fact-finding investigation into the specifics" of the Guatemala research.[7] The President also charged the Commission to undertake "…a thorough review of [current] human subjects protection to determine if federal regulations and international standards adequately guard the health and well-being of participants in scientific studies supported by the federal government."[8]

The Commission began its work in January 2011. It held three public meetings addressing the President's requests. During these meetings, the Commission heard from experts in law, history, medicine, and ethics, and received testimony from members of the public. With dual responsibilities to give a full and fair accounting of events largely hidden from history for nearly 65 years and also provide an assessment of the current system, the Commission decided to publish two reports. This is the first report, a historical account and ethical assessment of the Guatemala experiments. It aims to uncover and contextualize as much as can be known at this time about the experiments that took place nearly 65 years ago. It also aims to inform current and continuing efforts to protect the rights and welfare of the subjects of U.S.-sponsored or -conducted research. The second report on this topic, to be published in late 2011, will address contemporary standards for protecting human research subjects around the world.

Many unanswered questions drove the Commission's work at the outset of its historical review and throughout the investigation process. Among the overarching questions to be examined were:

- What occurred in Guatemala between 1946 and 1948 involving a series of STD exposure studies funded by the U.S. PHS?
- To what extent were U.S. government officials and others in the medical research establishment at that time aware of the research protocols and to what extent did they actively facilitate or assist in them?
- What was the historical context in which these studies were done?
- How did the studies comport with or diverge from the relevant medical and ethical standards and conventions of the time?[9]

In seeking to answer these questions, the Commission cast a wide net. It began with the original records documenting the Guatemala activities found by Wellesley College professor Dr. Susan M. Reverby at the University of Pittsburgh in June 2003.[10] Dr. John C. Cutler, who directed the studies in Guatemala and later served as a faculty member at the University of Pittsburgh, donated the records to the university in 1990. Dr. Reverby had presented her findings from these records at a May 2010 meeting of the American Association for the History of Medicine.[11] Thereafter, she contacted Dr. David Sencer, former Director of the Centers for Disease Control and Prevention (CDC), who notified the CDC of this information. Upon learning of these records, the CDC immediately undertook a review of them at the university. In September 2010, the university contacted the CDC to request the transfer of the material to the federal government, and the documents were subsequently transferred to the U.S. National Archives and Records Administration.[12] The National Archives provided the Commission with copies of these records in December 2010.

The Commission also sought information from other government and nongovernmental sources. Staff independently reviewed documents in nine archives, including the National Archives and the University of Pittsburgh Archives, and three libraries, including the library of the Pan American Health Organization (PAHO) headquarters. PAHO's predecessor organization, the Pan American Sanitary Bureau (PASB), sponsored the research

in Guatemala through a National Institute of Health grant funded by the PHS Venereal Disease Division and its VDRL, which later became part of the CDC.[13] The Commission sought documents from several government agencies, including the U.S. Departments of Defense and Veterans Affairs. Documents were requested from the government of Guatemala as well, though none were received.[14]

In total, the Commission reviewed more than 125,000 pages of original records. It collected tens of thousands of pages of relevant archival records and examined more than 550 published sources. The Commission focused its review on the period between 1935 and 1956, starting 10 years before the first known planning for the Guatemala experiments began and continuing through the year after Dr. Cutler finalized his last retrospective report on the experiments. Collected documents and publications are maintained in the Commission's archives. These records will be provided to the National Archives for future researchers.

With the passage of over six decades, the evidence available to document the events is limited. Moreover, much of the available information was written retrospectively by Dr. Cutler years after the experiments were actually conducted. Some of these retrospective accounts include inaccurate data or incomplete descriptions of experiments. The documentary evidence is in some cases scattered and incomplete. This Commission report was prepared, and should be read, with an awareness of the inherent limitations of fact finding based in large part on one person's recollections, particularly those of one who played a primary role in the research.[15]

At the outset of the Commission's investigation, Commission Chair Amy Gutmann and Commission Executive Director Valerie Bonham met with Vice President Rafael Espada of Guatemala, and they shared their respective plans to lose no time in undertaking thorough investigations to be made public.[16] Several Commission staff members later traveled to Guatemala in May 2011 to meet with the separate commission charged by the government of Guatemala to investigate the experiments and to visit the Central American Archives in Guatemala City and relevant historical sites.[17]

When the Commission began its inquiry, all agreed that—judging from what they had learned to date—the intentional exposure research conducted in

Guatemala between 1946 and 1948 was clearly and grievously wrong. The Commission's aim in conducting a more comprehensive historical investigation was to fully uncover the facts surrounding the experiments and offer a fair-minded and unvarnished ethical assessment.

In sum, the PASB[18] and VDRL activities in Guatemala led by Dr. Cutler took place from approximately July 1946 to December 1948, with follow-up work continuing through 1953.[19] PASB built and supplied a venereal disease research laboratory in Guatemala City to support the work and negotiated agreements that gave the researchers authority to work with officials and institutions across the Guatemalan government, including public health service treatment centers for venereal diseases, government hospitals, medical installations and officers of the military, institutions caring for orphans and the insane, and the penal system. Many aspects of the research were collaborative. Costs were borne by the PASB (for administration, travel, construction, and supplies), the U.S. Public Health Service Venereal Disease Division (providing and paying directly for staff and supplies as well as funding the grant issued from the Research Grants Office of the then U.S. National Institute of Health), and the government of Guatemala (directly funding staff and supplying facilities).

The studies encompassed research on three STDs—syphilis, gonorrhea, and chancroid—and involved the intentional exposure[20] to STDs of 1,308 research subjects from three populations: prisoners, soldiers, and psychiatric patients.[21] Of the 1,308 subjects exposed to an STD, the researchers documented some form of treatment for 678 subjects.[22] Commercial sex workers,[23] who in most cases were also intentionally infected with STDs, were used to transmit disease. In addition, to improve diagnostics, the researchers conducted diagnostic testing of 5,128 subjects[24] including soldiers, prisoners, psychiatric patients, children,[25] leprosy patients,[26] and Air Force personnel at the U.S. base in Guatemala.[27] This diagnostic testing, which included blood draws as well as lumbar and cisternal punctures,[28] continued through 1953.[29]

Most of the information about the experiments in Guatemala available to the Commission comes from the records Dr. Cutler donated to the University of Pittsburgh Archives Service Center (the Cutler Documents). The documents include several final reports on the STD experiments authored in the 1950s

(see Table 1). Institutional leaders of the PHS, the National Research Council (NRC), the National Institute of Health, and the Director and Assistant Director of the VDRL, as well as leading academic scientists encouraged and supported the work. Research staff for the Guatemala experiments included leaders and senior medical personnel of the government of Guatemala, for example, directors of the national Public Health Service Venereal Disease Section, the national psychiatric hospital, the national orphanage, and the Army medical department (see Table 2). The records show that these events involved many officials and researchers in the United States as well as Guatemala. The records reveal the unconscionable ways in which the researchers sometimes used people as a mere means to advance what Dr. Cutler sometimes called "pure science,"[30] hidden from public scrutiny in the United States.

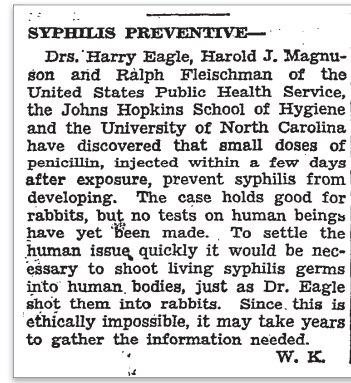
The history of U.S.-supported experimentation undertaken to advance medical knowledge and protect national security is complex with evolving ethical standards and norms.[31] Nonetheless, the experiments in Guatemala starkly reveal that, despite awareness on the part of government officials and independent medical experts of then existing basic ethical standards to protect against using individuals as a mere means to serve scientific and government ends, those standards were violated. The events in Guatemala serve as a cautionary tale of how the quest for scientific knowledge without regard to relevant ethical standards can blind researchers to the humanity of the people they enlist into research.

Arising in response to cases such as these, today's requirements for the protection of human subjects in U.S.-funded research are expressed in the medical ethics literature and through government regulations and international covenants and declarations, all of which share certain standards and principles. Obtaining informed consent of subjects is a cornerstone ethical requirement. So too are requirements for minimization of risks, a reasonable balance of risks and benefits, sound scientific justification, protection of privacy and confidentiality, and special protections for those who are especially vulnerable, including minors and those with impaired decision making.[32] While research *is* sometimes still done with vulnerable populations, using deliberate exposure and infection, and without informed consent, such studies have to be carefully justified, reviewed, and approved often with additional protections added.[33]

None of the principles and requirements reflected in the standards noted above were satisfied in the Guatemala experiments. And several—if not all—of these principles were known by the researchers in Guatemala at the time. Their behavior in a similar case—just two years earlier in the United States—and contemporaneous correspondence shows understanding of, and disregard for, generally accepted moral principles such as respect for human dignity in the course of their work in Guatemala. For these reasons, the Commission finds that many of the actions of the researchers were morally wrong and the individual researchers and institutional officials were morally blameworthy.

BACKGROUND

In April 1947, *New York Times* science editor Waldemar Kaempffert published a note describing an intentional exposure syphilis prophylaxis (prevention) experiment in rabbits that offered great promise to reduce spread of the disease, if only similar research could be conducted in humans.[34] The investigators that conducted that experiment, which included colleagues of Dr. John C. Cutler from the relatively small world of venereal disease researchers, had shown that penicillin injected within a few days after exposure could prevent syphilis infections.[35] But, Kaempffert observed, it would be "ethically impossible" to undertake such research and "shoot living syphilis germs into human bodies."[36] Therefore, it might be years before similar conclusions could be drawn for human beings.[37] Kaempffert's article was of particular interest to Dr. Cutler and his colleagues, who had been planning precisely the same type of experiment for months, and were about to begin doing just what Kaempffert described as being ethically impossible with prisoners and psychiatric patients in Guatemala.[38]



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.

Waldemar Kaempffert. Notes on Science: Syphilis Preventive. *New York Times.* April 27, 1947.

Thomas Parran
From the National Library of Medicine

STDs were long a concern of the U.S. government. In 1938, U.S. Surgeon General Thomas Parran testified before Congress in support of proposed legislation to expand funding for public health prevention efforts and scientific research in this field.[39] "Men and munitions" were needed in the battle against syphilis and other STDs, such as gonorrhea.[40] Dr. Parran sought support for the PHS to complete "studies, investigations and demonstrations which are necessary to develop more effective measures of prevention, treatment and control of venereal diseases… [so that] science will

STD TREATMENT OPTIONS

The modern era for the treatment of syphilis began in 1909 when Dr. Paul Ehrlich developed salvarsan, an arsenic-based compound. Bismuth used in combination with either mercury or arsenic-based compounds became a popular treatment for syphilis in the early 1920s, though patients found it complicated, time consuming, and even toxic. Arsenical therapy remained the primary treatment for syphilis until after 1943 when the effectiveness of penicillin was demonstrated. In 1938, sulfanilamide became the first reliable method of curing gonorrhea. Sulfonamides were still being used to treat gonorrhea when the U.S. involvement in the Second World War began in 1941.

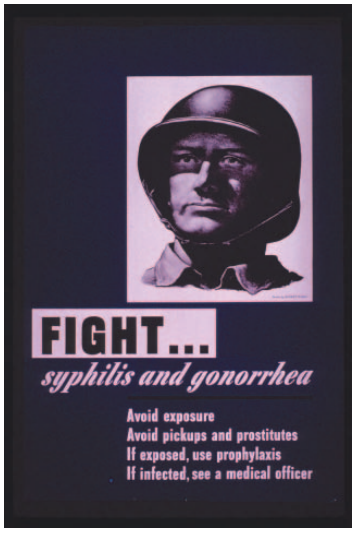
John F. Mahoney
From the Lasker Foundation

give us a much more effective method of treatment than we now have."[41]

Dr. Parran also emphasized the need for more funds to train the doctors who would man the front lines against STDs, which posed a major threat to members of the military, as well as the general population. Operating without such funding "would be like sending a battleship to sea with untrained officers and crew aboard," said Dr. Parran.[42]

New developments in STD treatment and prophylaxis were overdue. At the beginning of World War II the same system of chemical prophylaxis had been in use in the U.S. Army and Navy for about 30 years.[43] The procedure required men to begin by urinating and washing with soap and water. They then injected a silver proteinate into their penises to prevent gonorrhea and rubbed a calomel ointment over their penis and pubic region to prevent syphilis.[44] These methods had been adopted based on "poorly controlled and relatively unconvincing statistical studies carried out in the field."[45] Speaking of the need to re-evaluate the regimen of prophylaxis followed by the armed services, STD expert Dr. John F. Mahoney, then head of PHS/VDRL in Staten Island, New York, said, "[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."[46]

When World War II began, scientists, physicians, and public health officials considered the steps needed to address STDs occurring in troops in wartime. Dr. Joseph Earle Moore, Chairman of the NRC[47] Subcommittee on Venereal Diseases, wrote that he expected, "approximately 350,000 fresh infections with gonorrhea [in the Armed Forces], [which] 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."[48] Dr. Moore estimated that the cost of treating the anticipated infections would be $34 million (approximately $440 million today, adjusted for inflation).[49]



President Franklin D. Roosevelt's newly established Office of Scientific Research and Development (OSRD) (see Figure 1) and its Committee on Medical Research (CMR)[50] provided STD researchers an unprecedented opportunity to mobilize federal funds to mitigate these threats.[51] The OSRD served "to initiate and support a research program [to] utilize the scientific personnel and resources of the nation" and "to aid and coordinate the research activities carried on by other governmental Departments and Agencies."[52] Within the Office, the CMR's primary charge was to focus on "medical problems affecting national defense."[53] Through these new entities, the U.S. government substantially increased the amount of money available for medical research in a short period of time.[54]

Above and Above Right: Venereal Disease Posters
From the National Library of Medicine

In addition to chairing the NRC Subcommittee on Venereal Diseases (see Figure 2), Dr. Moore directed the Venereal Disease Division at Johns Hopkins University and served as advisor to the

Surgeons General of the U.S. Army, Navy, and PHS on STD control.[55] NRC committees provided initial screening of proposals submitted to the CMR, which recommended approval or disapproval to Dr. Vannevar Bush, the OSRD Director.[56] Later, Moore chaired the 1946 study section that approved the Guatemala research. Dr. Moore's comments were made in support of a proposal to the CMR for a new program of clinical research to study chemical prophylaxis for gonorrhea. The study would be carried out with "human volunteers" and would occur in a prison. While initially proposed by university-based researchers, PHS researchers, including Dr. Cutler, conducted the research in 1943 and 1944.

Top: Cassius Van Slyke
From the National Library of Medicine
Bottom: Joseph Moore
From Louis Fabian Bachrach

Terre Haute Prison Experiments, 1943-1944

The Terre Haute Experiments, which were done at the U.S. Penitentiary in Terre Haute, Indiana, provide important comparisons and contrasts with the experiments conducted several years later in Guatemala. The Terre Haute experiments were conducted and supported by many of the same people involved in the Guatemala experiments, including Dr. Cutler, Dr. John F. Mahoney, Dr. Thomas Parran, Dr. Joseph Earle Moore, and Dr. Cassius J. Van Slyke. The Terre Haute experiments had the same goals as the Guatemala experiments (i.e., to find a suitable STD prophylaxis) and had a similar study design.

Planning for the experiments began in October 1942,[57] when Dr. Charles M. Carpenter, a researcher at the University of Rochester School of Medicine and Dentistry, contacted Dr. Moore to ask about possible support for conducting gonorrhea prophylaxis

research in humans following intentional exposure to *Neisseria gonorrhoeae*, the bacterium that causes gonorrhea. Dr. Moore forwarded the question to Dr. A.N. Richards, CMR Chair.[58] Dr. Richards promptly responded that human experimentation was "not only desirable but necessary in the study of many of the problems of war medicine which confront us."[59] Dr. Richards emphasized strict constraints for informed consent:

> "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 were described."[60]

Dr. Moore subsequently organized a meeting of the NRC Subcommittee on Venereal Diseases,[61] at which Dr. Carpenter and his fellow researcher Dr. Alfred M. Cohn, from the New York City Department of Health, discussed their ideas. The NRC Subcommittee[62] agreed that Dr. Moore, as Chairman, should "attempt to obtain official government backing…through the Surgeons General of the Army, Navy, and Public Health Service, the Committee on Medical Research, and OSRD."[63]

Dr. Moore succeeded in his efforts. In November and early December 1942, leaders from the PHS, the Army, and the Navy endorsed the proposal that Dr. Carpenter had initiated, so long as "volunteers" only were exposed to infection. Dr. Thomas Parran, PHS Surgeon General, explained his support:

> "Because 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."[64]

Colonel John A. Rogers, Executive Officer of the U.S. Army Medical Corps agreed "that the National Research Council [should] undertake an investigation in search of an effective prophylaxis and improved treatment for gonorrheal infections, using selected human volunteers."[65] "Any progress in this field," he explained, "will have a direct bearing on the conservation of manpower engaged

in war work of any character and it is hoped it will be possible for the [National Research] Council to undertake such an investigation." The Surgeon General of the U.S. Navy, Dr. Ross T. McIntire, also concurred, emphasizing that "the incidence of gonorrhea in the armed forces and the lost manpower resulting therefrom constitutes a problem of major military importance."[66] Consequently, he observed, "[t]he crucial experiment in the development of new prophylactic agents against gonorrhea lies in the experimental inoculation of human volunteers."[67]

Dr. Moore's Subcommittee on Venereal Diseases, this time with CMR head Dr. A.N. Richards,[68] met again in early December 1942.[69] It approved the proposal and recommended that Moore organize a conference with members he selected to further specify details of the experiment and the accompanying risks.[70] Dr. Richards urged Dr. Moore to convene the conference group "immediately."[71]

Dr. Moore's conference group met promptly at the end of December to formulate specific plans.[72] Its proposal included a detailed research protocol, a clear set of goals, and a participant waiver form that outlined the procedures and the risks associated with the experiments.[73] The project would "study the effectiveness of two types of prophylaxis against gonorrhea: (1) the protective action of sulfonamide compounds taken by mouth before exposure to the disease, and (2) the prophylactic action of chemical agents applied locally to the genital tract after exposure to the disease."[74]

Consistent with the opinions of the Surgeons General, Dr. Carpenter stated that "[o]nly volunteers are acceptable."[75] The proposed waiver form explicitly described the procedures involved and risks associated with the experiment.[76] It used colloquial terms ("clap," "strain," and "running ranges") for gonorrhea in addition to medical language, and stated that individuals would be exposed to infection by "applying the germ to the end of the penis."[77] The form included an explanation of risks, including the fact that not all subjects would respond to "modern treatment methods" and that complications could arise from being treated with older methods. It also detailed the side effects of the "modern treatment."[78] According to the form, an inmate had to waive liability and the officer in charge had to give permission before the inmate could volunteer for the experiment.[79]

The issue of the ethical and legal permissibility of intentionally exposing humans to STDs remained unsettled. Dr. O.H. Perry Pepper, Chairman of the NRC Committee on Medicine,[80] asked members about the experiment. Dr. James E. Paullin, President of the American Medical Association[81] and one of the committee members, argued that eventually the details of the experiment would "fall in the hands of a very unscrupulous lawyer" and the waivers signed by the subjects would not constitute sufficient legal protection for those involved.[82] As a result, he voted not to approve the experiment, despite the fact that he supported its scientific value. Another member that endorsed the scientific merit of the experiments, Dr. Arthur Bloomfield, questioned "the public relations" aspect of the research.[83]

With NRC members raising doubts about the work, Dr. Moore met in January 1943 with another group that included CMR head Richards and OSRD attorney James B. Donovan.[84] At that conference, Dr. Richards reported that he had discussed the matter with Dr. Vannevar Bush, OSRD Director, who also questioned the legality of the experiments and the potential for adverse public reaction.[85] Among other issues, New York State law constraints raised concerns about the original plan to proceed in a state prison.[86] Donovan suggested the possibility of using federal prisoners, Army prisoners, or conscientious objectors as an alternative.[87] The group agreed that if OSRD approved the experiments on scientific grounds, it would contact the U.S. Solicitor General to seek additional legal advice.[88]

With the groundwork thus laid, Dr. Moore's subcommittee finalized a proposal for OSRD in February 1943. The proposal emphasized the importance of the research to the war effort and outlined the prophylactic methods then used in the U.S. Armed Forces.[89] The subcommittee noted that the chemical prophylaxis administered at the time was highly unsatisfactory for the men[90] because it was "embarrassing, revelatory to fellow soldiers and sailors, mildly uncomfortable, time-consuming, and messy."[91]

The subcommittee recommended that the experiments be conducted in men in state prisons and city jails for several reasons.[92] First, they were isolated from women. The subcommittee emphasized that the volunteers needed to live "under conditions which prevent sexual intercourse for approximately 6 months."[93] In addition, prisoners would be under medical supervision for

the required time period.[94] The subcommittee speculated that prisoners also wanted to help win the war and so would participate out of patriotism.[95] The prison environment also provided readily available medical facilities.[96] Finally, the subcommittee observed that because many prisoners had previously contracted gonorrhea, they might be less concerned about the risks associated with the experiment.[97]

In describing the subcommittee's proposal, Dr. Moore explained that the group rejected other potential populations for several reasons.[98] Both soldiers and people living in psychiatric institutions were considered unacceptable experimental populations. According to the subcommittee, military personnel could not be used because they could not be subjected to sexual isolation, and the U.S. Armed Forces would not want military personnel to take time from training or combat in order to participate in the experiment.[99] Individuals housed in psychiatric institutions were also deemed unacceptable. Dr. Moore explained: "[t]his population group has never been seriously considered, since it is clearly undesirable to subject to any experimental procedure persons incapable of providing voluntary consent."[100]

The subcommittee asked CMR to address two issues about the experiments: (1) "legality" and (2) "expediency," which seems to have been a reference to potentially adverse public opinion.[101] Despite these questions, Moore relayed the subcommittee's view that stated that the experiment was legal, despite some potentially contrary state statutes,[102] and that public opinion would likely be on the side of "any sound scientific proposal" combating STDs.[103] It also noted that an experiment involving infected men and non-infected commercial sex workers had been reported in 1939 both in the popular press (by journalist Paul de Kruif) and in the *Journal of the Oklahoma State Medical Association*,[104] without ensuing public outcry.[105] In that experiment, commercial sex workers who were not infected with gonorrhea were given a pre-exposure prophylaxis and then had sexual intercourse with men infected with gonorrhea (at the request of the researchers—the experiment was not purely observational).[106] The subcommittee recommended that the CMR approve the proposal.[107]

Later that month, OSRD investigated the legality of the experiments. Dr. Bush contacted Assistant Solicitor General Oscar Cox, who discussed the matter with Attorney General Francis Biddle.[108] Cox and Biddle agreed that:

> "The problem is not a legal one, but political in nature. There should be no question of the legality of the experiments, in the absence of specific provisions of law to the contrary. While the experiments might be held to be technical violations of law in a particular jurisdiction, any criminal prosecution should be easily defended."[109]

Cox furthermore dismissed the political risks; he argued that the experiments should not be hampered by such criticism in a "time of war."[110]

A little more than two weeks after submitting the NRC subcommittee proposal to OSRD, Dr. Moore contacted James Bennett, Director of the Bureau of Prisons, because Dr. Bush favored the use of federal, rather than state, prisoners in the experiment.[111] After receiving Dr. Moore's "detailed statement of the proposed plan of procedure,"[112] Bennett endorsed the proposal with a few conditions.[113] Researchers should not promise pardons or commutations of sentences as an incentive to volunteer,[114] though he agreed that the parole board would probably consider their involvement in the research when the inmates were eligible for parole.[115] The volunteers could be paid $100 each for participation,[116] but Bennett questioned the effect of some receiving these benefits on prisoners not selected for participation. He told Dr. Moore to conduct the experiments in secret "to protect the general morale of the several [prison] institutions."[117]

With the Bureau of Prisons on board, the leadership of the National Academy of Sciences (NAS) and NRC, its operating agency, responded to questioning from Dr. Bush about the legality and ethics of the experiment. In March 1943, Dr. Frank B. Jewett, NAS President and head of Bell Telephone Laboratories, and Dr. Ross G. Harrison, NRC Chairman and Professor Emeritus at Yale University, wrote to Dr. Bush, who had asked the scientists "whether the Academy and Council, having considered the possibility of public reaction, are willing to encounter the risk in view of the results attainable."[118] Drs. Jewett and Harrison declined to speak for either NAS or NRC, but they offered Dr. Bush their "personal opinions in [their] official capacities."[119] With that qualification, both men endorsed the experiments, noting that attitudes toward STDs had become more progressive and that the public had an interest in protecting men in the armed services.[120] These facts, they suggested, could help explain the experiment if questions about intentionally infecting prisoners were raised later.[121]

With collective support from the highest echelons of the nation's medical establishment, and with the concurrence of the Attorney General, Dr. Bush approved the experiment in early March.[122] Only four federal prisons had appropriate medical facilities.[123] The federal penitentiaries in Terre Haute, Atlanta, New York State, and Leavenworth were all considered, but Terre Haute had the best medical facilities.[124] Dr. Parran had already identified the high-quality medical facilities available as one of the benefits of conducting the experiment in a federal prison,[125] and Terre Haute offered the best option for capitalizing on that benefit.

Dr. Bush directed that PHS conduct the experiment rather than the university-based research team of Drs. Carpenter and Cohn.[126] Where previously the PHS role was limited, like that of the U.S. Army and Navy, to simply endorsing the scientific merit and opining on ethical and legal limitations of Moore's NRC proposal and the university-based research, it now became the lead for the work. In April 1943, Dr. R.A. Vonderlehr, a PHS Assistant Surgeon General, wrote to Dr. Moore regarding PHS's new role.[127] A PHS investigator leading the experiments would also assure support from the Bureau of Prisons. He explained:

> "Mr. James Bennett of the Bureau of Prisons has lost interest in the proposed project…Mr. Bennett thinks a great deal of the Public Health Service and if we assure him that the investigation will be done by regular officers in our Service I believe he will show much more interest than he has evinced in recent weeks."[128]

Within PHS, responsibility for conducting the research fell to the VDRL. The VDRL arose in 1927 under the PHS Venereal Disease Division, led by Dr. Thomas Parran, who later became the Surgeon General.[129] A small laboratory was set up within the U.S. Marine Hospital in Staten Island, New York, that conducted laboratory experiments for the purpose of studying methods of treating syphilis, and gonorrhea.[130] Clinical studies were also undertaken with the cooperation of the hospital staff.[131]

Dr. John F. Mahoney led the laboratory, with Dr. Cassius J. Van Slyke serving as the Associate Director.[132] Dr. Mahoney, a 1914 graduate of Marquette University School of Medicine, had joined PHS in 1917 as a scientific assistant.[133] In 1918, he was commissioned as an Assistant Surgeon in the PHS Commissioned

Staten Island Marine Hospital *From the National Library of Medicine*

Corps.[134] Dr. Mahoney was assigned to the Staten Island Marine Hospital and became director of VDRL in 1929.[135]

Dr. Van Slyke, a 1928 graduate of the University of Minnesota medical school, joined the VDRL at Staten Island in 1936, after eight years of practicing general medicine. He served in Staten Island until August 1944, when he moved to be the Assistant Chief of the PHS Venereal Disease Division in Washington, D.C.

Dr. Mahoney submitted a formal proposal to OSRD/CMR in June 1943.[136] Dr. Mahoney's proposal indicates that OSRD and PHS split the costs of the experiments.[137] The budget requested for the first year of the experiment was $45,200,[138] which included salary support for one physician and two bacteriologists in addition to "two medical officers and one bacteriologist to be assigned" from the PHS.[139]

Implementing the Experiments

Work at Terre Haute began in September 1943 under Dr. Mahoney's leadership in Staten Island, and his young associate, Dr. Cutler, at the prison.[140] Dr. Cutler, age 28, was relatively new to PHS, having joined in 1942, the year after his graduation from Western Reserve University Medical School in Cleveland.[141] After serving a year as a medical officer with the U.S. Coast Guard, Dr. Cutler moved to the VDRL in Staten Island in early 1943.[142] Dr. Henrik Blum, another junior PHS officer assigned to the VDRL, went with Dr. Cutler to Terre Haute to help conduct the experiments.[143]

The investigators required that participants be at least 21 years old and provide "[a]ssurance that the volunteer possessed a thorough understanding of the purpose underlying the study and the possible risks involved."[144] At the conclusion of the experiments, participants received $100, a certificate of merit, and a letter of commendation to the parole board.[145] The documents do not indicate whether the prisoners were told ahead of time that they would

receive a letter of commendation for the parole board, but Bennett's disapproval of such inducements suggests they were not.[146]

In total, 241 prisoners participated in the experiments, which ended in 1944.[147] The first stage of the experiment required the investigators to develop a consistent technique for producing gonorrhea in subjects. Dr. Mahoney, Dr. Cutler, and their staff began efforts to infect subjects through artificial exposure in October 1943, a year after Dr. Carpenter first proposed the work to Dr. Moore.[148] All subjects were inoculated with bacteria deposited into the end of the penis.[149] The researchers tried a variety of strains and concentrations of gonorrhea.[150] At least some of the strains were gathered from local commercial sex workers who were examined by Dr. Blum after they had been arrested in Terre Haute by local police.[151]

Five months after beginning work to intentionally induce gonorrhea infection, the researchers faced serious challenges. Dr. Mahoney, as project leader, reported to Dr. Moore's NRC subcommittee, which retained at least indirect, if not direct, oversight responsibility for the work.[152] He explained that the researchers were unable to consistently produce infection in the prison volunteers and opined that further research was not likely to succeed.[153] He asked whether the experiments should be discontinued, and if not, whether they should be recalibrated to focus on other issues.[154]

Despite Dr. Mahoney's concerns, the NRC subcommittee favored continuing the experiments. At its February 1944 meeting, the group concluded:

> "The opportunity for a study of experimental gonococcal infection in human volunteers and its relationship to the chemical prophylaxis of gonorrhea has never previously arisen on the present scale and with the termination of this experiment is unlikely to arise again unless under the impetus of a future war."[155]

With the exigency of war, and after a year and a half of intense effort, the scientific establishment represented at NRC directed Dr. Mahoney and PHS to continue the work. Under Dr. Mahoney's guidance, Dr. Cutler set about finding a reliable method to infect the prisoners. Results continued to be poor. A conference group convened again, this time in Terre Haute, in April 1944, to "review all circumstances in connection with the study of prophylaxis in gonorrhea…in progress in the Terre Haute institution."[156] The attendees[157] of

the conference agreed that the investigators should try one more approach, involving particular "colony types" of gonorrhea, and decided that if that did not work it was probably time to discontinue the study.[158] Each infection method yielded unsatisfactory results.

In June 1944, Dr. Mahoney reported to Dr. Moore's subcommittee that he would not be continuing the work.[159] Describing his feelings about this decision later, Dr. Cutler referred to what a "blow" it had been "to discontinue the Terre Haute project."[160] The experiments ended a month later in July 1944, 10 months after they began. Dr. Mahoney attributed this decision to the inability to reliably induce infection. In his final report, he concluded: "In spite of the use of different strains of *Neisseria gonorrhea*, modifications in methods of cultivating the organism and of inoculation, it was found impossible to infect with a degree of regularity which would be required in the testing of prophylactic agents."[161]

A draft of a history of the OSRD, written in 1946, explains, "[e]fforts were made to produce experimental gonorrhea in these volunteers by almost every conceivable expedient *except by the intraurethral inoculation of pus taken directly from the cervix or urethra of infected females or by the natural method of infection – sexual intercourse*" (emphasis added).[162] OSRD's document includes no comment on whether the "natural method of infection," which was pursued in Guatemala in 1947, would be an appropriate next step. But it did observe that the scientific questions pursued in Terre Haute remained unanswered. "It is still unknown," the document states, "whether any prophylactic agent, including the silver proteinate the armed forces have used for thirty-five years, [has] any value in the prevention of this disease."[163]

Drs. Mahoney, Van Slyke, Cutler, and Blum published the results of the experiments in the *American Journal of Syphilis and Gonorrhea* in January 1946, around the same time that plans for work in Guatemala were developing.[164] The researchers concluded that "[n]one of the exposure techniques employed proved capable of producing disease with a consistency considered to be adequate for a study of experimental prophylaxis."[165] They did, however, note "the most effective method of conveying infection to volunteers was… the direct transference of secretions from the infected patient to the urethra of normal volunteers."[166] They also observed "a significantly lower rate of

experimental infections in those patients with a history of previous gonorrheal infection."[167]

The experiments in Terre Haute presaged the work in Guatemala in a number of ways. They demonstrated how military and science leaders actively sought improved methods to combat STDs and their willingness to endorse experiments using human volunteers to improve STD prophylaxis.[168] They also provided a scientific impetus for the experiments in Guatemala; the inability to develop a reliable method for gonorrheal infection in Terre Haute left the researchers unable to address their primary research goal, more effective prophylaxis, and wondering about alternative infection strategies. The investigators and reviewing committee viewed the Terre Haute experiments as a rare opportunity, and both Dr. Cutler and Dr. Mahoney viewed the work as unfinished. The chance to do additional experiments in Guatemala presented an unexpected and welcome opportunity.

The Terre Haute research offered an important precedent for exploring and applying ethical constraints related to individual consent. These considerations did not constrain the later research in Guatemala. Conducting the experiments in Guatemala provided an opportunity to work with reduced concern for some of the key obstacles associated with the Terre Haute experiments: fear of adverse legal consequences and bad publicity.[169]

Richard C. Arnold
From the National Library of Medicine

Developments in the Science and Prevention of Sexually Transmitted Diseases

In June 1943, as he submitted plans for the Terre Haute experiments to OSRD/CMR, VDRL chief Dr. John Mahoney began studying the effects of penicillin on syphilis in human subjects.[170] Through a limited four-person human trial with colleagues Drs. R.C. Arnold and Ad Harris, both of whom worked at the VDRL, the researchers showed that eight days of penicillin use caused "a more or less rapid and complete disappearance" of the

disease.[171] The conventional arsenic therapy generally required 18 months to complete and had many unpredictable side effects.[172]

As Dr. Cutler was beginning research in Terre Haute in October 1943, Dr. Mahoney announced these results to a "jam-packed session" at the American Public Health Association's annual meeting. The initial results were so promising that one researcher called the work "probably the most significant paper ever presented in the medical field."[173] Dr. Mahoney, in collaboration with Dr. Moore and several others comprising the newly established NRC Penicillin Panel, quickly began a much larger clinical trial involving 1,400 subjects.[174] Eight months later, in June 1944, the U.S. Army adopted penicillin as its standard treatment for syphilis.[175] In September 1944, Drs. Moore and Mahoney and their colleagues published results for the larger trial that confirmed their earlier findings.[176]

Despite this success, many questions remained. Researchers wondered whether penicillin therapy left subjects immune to further infection or at risk of re-infection with the same or a different strain of the disease.[177] Uncertainty lingered too about penicillin's long-term effectiveness. Blood tests showed that penicillin eliminated syphilis spirochetes (a type of bacterium) in the short term, but could not confirm whether the disease disappeared entirely.[178]

Researchers and policy makers alike were also seeking to improve methods to *prevent* syphilis with post-exposure prophylaxis. Describing these facts in his 1955 "Final Syphilis Report," Dr. Cutler reported that Drs. Mahoney and Arnold felt that a prophylaxis consisting of a simple orvus-mapharsen wash might meet with more acceptance than the calomel ointment, which at the time was routinely prescribed. Animal studies conducted in the laboratory repeatedly showed orvus-mapharsen's effectiveness.[179] Furthermore, Drs. Arnold, Cutler, and another researcher, Dr. Sacha Levitan, a PHS Senior Surgeon, conducted "small scale studies" of the orvus-mapharsen solution on "ships where relatively high rate [sic] of venereal infection was expected among the crews."[180] But these results were inconclusive.[181] Consequently, Dr. Cutler later reported, they felt that small controlled experiments on individuals "exposed to a high risk of infection" were required to determine if orvus-mapharsen could be effective, "particularly in the Armed Services."[182]

STD PROPHYLAXIS OPTIONS

Orvus-mapharsen: a substance made up of 1 percent orvus [alkyl aryl sulfate] and 0.15 percent mapharsen in aqueous solution and was supposed to be applied after sexual intercourse to prevent infection.

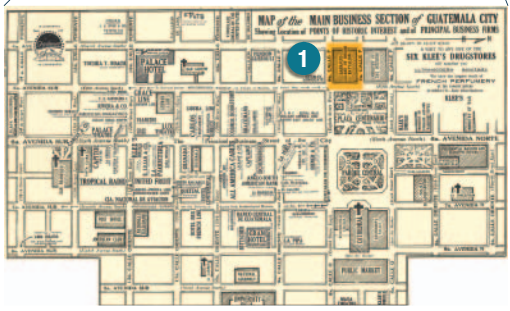
Calomel: a substance used by the U.S. Army and Navy as a post-exposure prophylaxis for syphilis.

Silver proteinate: the active ingredient in one of the post-exposure prophylaxis regimens used for gonorrhea.

Similarly, as Dr. Cutler wrote in his 1952 Experimental Studies in Gonorrhea report, Drs. Mahoney and Arnold hoped that the orvus-mapharsen prophylaxis would also prove effective for gonorrhea.[183] Post-exposure prophylaxis regimens to prevent gonorrhea during WWII involved a solution of silver proteinate injected directly into the urethra that, like the calomel solution for syphilis prophylaxis, did not appeal to servicemen.[184] Furthermore, animal testing was unhelpful because gonorrhea produced in a rabbit's eye or chick embryo lacked appropriate comparability to the male urethra. Drs. Mahoney and Arnold, Dr. Cutler said, wanted to test orvus-mapharsen's effectiveness in man.[185] Dr. Cutler later explained that a large-scale field study of orvus-mapharsen would have included many men and a long period of observation, and therefore a carefully controlled study in a small group was deemed advisable.[186] The VDRL found an opportunity to undertake this work in 1946 in Guatemala.

KEY

1 Honor Guard Barracks
2 Psychiatric Hospital
3 Orphanage
4 Venereal Disease and Sexual Prophylaxis Hospital (VDSPH)
5 Penitentiary
6 Military Hospital



Map of Guatemala City and
Map of Guatemala City Center
The original map is held at the University of Chicago Library's Map Collection

● Serology Experiments

GUATEMALA EXPERIMENTS 1946-1948

This section contains graphic medical descriptions of artificially inoculating humans with STDs. It may not be appropriate for all readers. This information has been included for completeness of the historical record.

Initial Experiment Design

The Terre Haute experiments had shown the difficulty of reliably producing infection, at least for gonorrhea, through artificial inoculation. Dr. Mahoney later observed in the *Journal of Venereal Disease Information* (July 1947) that undertaking research in Guatemala offered new opportunities unavailable in the United States:

> "It has been considered impractical to work out, under postwar conditions in the United States, the solution of certain phases concerned with the prevention and treatment of syphilis. These problems are largely concerned with the development of an effective prophylactic agent for both gonorrhea and syphilis and the prolonged observation of patients treated with penicillin for early syphilis. Because of the relatively fixed character of the population and because of the highly cooperative attitude of the officials, both civil and military, an experimental laboratory in Guatemala City has been established…"[187]

John C. Cutler
From the National Library of Medicine

Dr. Cutler, who was 31 years old when he traveled to Guatemala to lead the work in August 1946, emphasized the scientific merit of working where "normal exposure" could be easily replicated.[188] Dr. Cutler wrote later that the idea for the research in Guatemala originated with Dr. Juan Funes, a Guatemalan physician who worked as a one-year fellow with Drs. Mahoney, Arnold, and Cutler at the VDRL in Staten Island in 1945.[189] In Guatemala, the legality of commercial sex work and the requirement for sex workers to undergo health inspection at medical clinics, the main one of which was supervised by Dr. Funes, presented "the possibility of carrying out carefully controlled studies

there."[190] The researchers decided to study orvus-mapharsen prophylaxis (an aqueous solution made up of 1-percent orvus [alkyl aryl sulfate] and 0.15-percent mapharsen that was supposed to be applied after sexual intercourse to prevent infection)[191] in cooperation with the Guatemalan Venereal Disease Control Department (which Dr. Funes directed) and the Penitenciaría Central (Penitentiary) "where exposure of volunteers to infected prostitutes would provide the testing opportunities."[192] Following prisoners, a contained and restricted population, after they had sexual intercourse with commercial sex workers known to be infected with STDs, promised to establish a "rapid and unequivocal answer as to the value of various prophylactic techniques" through the preferred technique of "normal exposure."[193]

Other factors may have also influenced the decision to locate the research in Guatemala. The pre-existing relationship between the United States and Guatemala included aid for the provision of medical services and development of public health services. The Office of Inter-American Affairs, which brought fellows like Dr. Funes to the United States to study, and its predecessor, the Office of the Coordinator of Inter-American Affairs,[194] supported construction of a 300-bed general hospital in Guatemala City in 1944.[195] In addition, the presence of other U.S. medical researchers working in Guatemala ensured that the researchers would not be alone in their efforts.

With Guatemala identified as a research location, the VDRL needed a way to pay for the research. During the war, OSRD and CMR had served to coordinate and fund an expanded system to support scientific and biomedical research.[196] As these war-time activities began winding down, federal policymakers, spurred in part by Surgeon General Thomas Parran and NIH Director R.E. Dyer, shifted authority to PHS and NIH, whose Congressional mandates changed considerably in 1944[197] (see Figure 3.) The enactment of the Public Health Service Act, on July 1, 1944, created a PHS grant system under the Surgeon General and authorized the National Advisory Health Council (NAHC) (see Figure 4) to recommend projects to be funded.[198] The NAHC was a longstanding government committee of federal and nonfederal scientific advisors established in 1902 as the Advisory Board for the Hygienic Laboratory of the Public Health Service,[199] the precursor to the NIH.[200]

NAHC had served since at least 1930 to advise the government on both field and laboratory research activities of the PHS.[201] In September 1944, CMR accepted a proposal by NIH Director Dyer to transfer control of CMR and its NRC reviewing committees to PHS.[202] In 1945, OSRD medical research contracts began transferring to the PHS grant system.[203] A new system for federally funded biomedical research emerged, housed at NIH, in which OSRD contracts were converted into PHS grants.[204] The Assistant Chief of the Venereal Disease Division, and former VDRL Associate Director, Dr. Cassius J. Van Slyke, became chief of the new NIH Research Grants Office.[205]

PHS leadership established a dual-review structure for evaluating funding applications, borrowed in part from the war-time structure of OSRD/CMR and its advisory NRC committees.[206] Study sections (serving a similar function as the NRC committees), composed of independent, usually civilian, peer scientists and representatives from the Army, Navy, Veterans Administration, and PHS, made recommendations about the applications' scientific merit and an advisory council, also comprised of independent scientists, considered policy implications in addition to evaluating questions of scientific merit.[207] The Surgeon General made final funding decisions.[208]

Syphilis Study Section, 1947
From the National Institutes of Health, Department of Health and Human Services

The first study section established under this new structure was the Syphilis Study Section (see Figure 5), formerly the Penicillin Panel of the NRC Subcommittee on Venereal Diseases and renamed by Dr. Parran in December 1945.[209] It began work in early 1946 and reviewed the proposal for research in Guatemala as one of 30 projects considered at its first meeting on February 7-8, 1946.[210] Dr. Joseph Moore, from Johns Hopkins University and chair of the NRC Subcommittee on Venereal Diseases, chaired the group, which included 11 other members.

They were:

- Dr. David E. Price, U.S. PHS Venereal Disease Division;
- Dr. Harry Eagle, U.S. PHS Hospital in Baltimore and the Venereal Disease Research Laboratory at Johns Hopkins University;
- Dr. John R. Heller, chief of the PHS Venereal Disease Division and Dr. Van Slyke's most recent former supervisor;
- Dr. John F. Mahoney, who continued to direct the VRDL in Staten Island;[211]
- Dr. Lowell J. Reed, Johns Hopkins University;
- Dr. John H. Stokes, University of Pennsylvania;
- Dr. Harry C. Solomon, Harvard University;
- Dr. Thomas B. Turner, Johns Hopkins University;
- Major L.N. Altshuler, U.S. Army;
- Cdr. George W. Mast, U.S. Navy; and
- Dr. Bascom Johnson, Veterans Administration.[212]

The study section approved the proposal for "the Guatemala study dealing with the experimental transmission of syphilis to human volunteers and improved methods of prophylaxis,"[213] and recommended it to the NAHC for funding.[214] On March 8-9, 1946, PHS Deputy Surgeon General Warren Draper presided over the NAHC meeting that recommended funding the proposal.[215] Funded shortly thereafter as "Research Grant No. 65 (RG-65)" for "a grant to the Pan American Sanitary Bureau for investigation into venereal disease to be held in Guatemala," the funding recommendation of $110,450 "was different from others in that funds were provided by the Venereal Disease Division with mechanics of processing to be handled by the [NIH] Research Grants Office." [216] In other words, the funding for this research came not from general NIH Research Grants Office monies but specifically from VDRL funds.[217]

Following the NAHC meeting, Surgeon General Thomas Parran approved the grant, and the funds were transferred to the PASB, which started work in Guatemala in April 1946 (see Table 3).[218] Construction began on a new "Venereal Disease Research Laboratory" to support the work.[219] Dr. Cutler arrived in August 1946.[220] Dr. Joseph Spoto, Assistant Chief of the Venereal Disease Division, also on assignment to PASB for research,[221] met him on

arrival and briefed him on the construction efforts to date.[222] Dr. Spoto also introduced Dr. Cutler to many Guatemalan officials who would facilitate the work.[223] The two met with officials at Guatemala's Dirección General de Sanidad Pública (Ministry of Public Health), as well as with the "chiefs" of the Ejército Nacional de la Revolución (National Army of the Revolution) (Guatemalan Army).[224] Dr. Cutler also met with the Minister in charge of the Penitentiary and reported that "[a]ll of those concerned" at the Penitentiary were indeed "very anxious" for the research to begin.[225] Additional PHS staff soon joined Dr. Cutler in Guatemala, including Dr. Sacha Levitan, a Senior Surgeon who served as the Assistant Director of the Guatemala project, Dr. Elliot Harlow, an Assistant Surgeon, Joseph Portnoy, a serologist, and Alice Walker and Virginia Lee Harding, bacteriologists.[226]

To facilitate the work, PASB officials signed agreements for "cooperative working arrangements"[227] with the Ministers of Health, War, and "Gobernación" [Interior] under whose jurisdiction the Penitenciaría Central (the Penitentiary) fell.[228] According to Dr. Cutler, these agreements gave the researchers authority to work with officials and institutions across the Guatemalan government, 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."[229] Writing in 1955, Dr. Cutler explained that many different activities were contemplated, including: assessing the prevalence of STDs in the country; developing an improved system of STD control through personnel training; establishing prophylactic, diagnostic, and treatment facilities; investigating and refining diagnosis and treatment; and prophylactic experiments.[230] The researchers were to train local personnel to take over the new PASB VDRL-constructed research laboratory as a Guatemalan government facility in the future.[231]

Treatment Programs and Goodwill Efforts

After Dr. Cutler met with leaders of the Guatemalan Army in August, they asked the researchers to set up a "treatment program" for the Hospital Militar (Military Hospital).[232] With the support of Dr. Spoto, in whom Dr. Mahoney vested great confidence,[233] and Dr. Funes, the former VDRL fellow, Dr. Cutler argued to Dr. Mahoney that treatment programs should start in order

to earn "complete cooperation" for the future inoculation work.[234] While Dr. Mahoney expressed some doubts, both Drs. Cutler and Spoto were anxious to provide a treatment program to the Guatemalan Army.[235] The program began and, eventually, approximately 309 soldiers received some form of STD treatment, such as penicillin or salvarsan. Of these 309, 242 were soldiers whom the researchers intentionally exposed to infection during the STD experiments at one point or another.[236]

In October, Dr. Mahoney wrote to Dr. Cutler:

> "Your show is already attracting rather wide and favorable attention up here. We are frequently asked as to the progress of your work. Doctor T.B. Turner of Johns Hopkins wants us to check on the pathogenicity in man of the rabbit spirochete; Doctor Neurath of Duke would like to have us follow patients with his verification procedure; [Surgeon General] Doctor Parran and probably Doctor Moore might drop in for a visit after the first of the year."[237]

While supervisors and colleagues in the United States were awaiting opportunities to do additional research, Dr. Cutler was continuing to develop relations with the Guatemalan authorities. In November, Dr. Cutler asked Dr. Mahoney to provide the Guatemalan Army with penicillin, which was in short supply, for its own needs on a reimbursable basis. Dr. Mahoney rejected this request, warning against "entering into a too comprehensive program which may involve the use of more of the drug than we are able to procure."[238] Dr. Cutler agreed and promised to use the penicillin sparingly so as to leave it available for "demonstration programs and to build goodwill."[239]

TREATMENT DURING DIAGNOSTIC TESTING

The researchers conducted diagnostic testing for syphilis, gonorrhea, and chancroid among 5,128 subjects including sex workers, soldiers, prisoners, orphans, schoolchildren, leprosarium patients, and U.S. servicemen.

Out of the subjects involved in the Guatemala experiments, the researchers provided some form of STD treatment for 820 of them. While some of the subjects involved in the diagnostic testing were also involved in the intentional exposure experiments, at least 142 subjects who were not exposed to an STD by the researchers were given some form of treatment.

By December, Dr. Constantino Alvarez B., Division Chief at the Guatemalan Ministry of Health, requested that Dr. Cutler "inform us in great detail of the penicillin treatment for syphilis; given that many chief physicians of the departmental health units have been directing their enquiries for more information to this Division."[240] Dr. Cutler replied with a "general treatment plan for each syphilis stage" in which penicillin had been shown to be "truly valuable."[241] Dr. Carlos E. Tejeda, Chief of the Guatemalan Army Medical Department, later wrote a letter to Dr. Cutler in June 1947 "beseeching you to draw up an Emergency Venereal Disease Prophylaxis Plan for [the Military Medical Department], which would be implemented in the National Army as soon as possible."[242] Dr. Cutler complied with a "Prophylactic Plan for the Guatemalan Army," which included an educational program; a prophylactic program of condoms, silver proteinate solution, and ointment; and methods for implementation of the prophylactic program.[243] In July, an article of Dr. Cutler lecturing the First Convention of Military Doctors on the "prophylactic venerological emergency plan for the Army of the Revolution" appeared in one of the local papers.[244]

Dr. Cutler lecturing the First Convention of Military Doctors in July 1947
From the Diario de Centro America

In the Penitentiary, Dr. Cutler reported that "ready acceptance of our group" followed from the establishment of diagnostic and treatment programs ("a program of care for venereal disease which they have lacked in the past").[245] The treatment program, he said in January 1947, was "worthwhile" and "fully justified" to promote the prophylaxis experiments.[246]

While Dr. Cutler planned to start a "program of prophylaxis for all contacts that took place at the penitentiary," he suggested to Dr. Mahoney that they would only "use placebo." The intent of the placebo program was to "accustom[] the inmates to the use of prophylaxis so there will be no difficulty

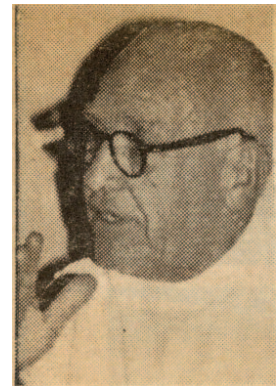
in carrying on with our own compound [orvus-mapharsen] at the proper time."[247] While further specifics of the Penitentiary program are unclear, records show that 139 prisoners received some form of treatment for an STD. Of these, 92 were prisoners whom the researchers intentionally exposed.[248] Later, when Dr. Cutler departed from Guatemala in 1948, the Director of Medical Services for the Penitentiary, Dr. Roberto Robles Chinchilla, wrote to give Dr. Cutler "our everlasting gratitude which will remain for ever [sic] in our hearts, because of your noble and gentlemanly way with which you have alleviated the sufferings of the guards and prisoners of this penitentiary."[249]

While Dr. Cutler did not discuss the treatment program in the Asilo de Alienados (Psychiatric Hospital) in his final reports, records show that the researchers treated a total of 334 psychiatric subjects for an STD. Of them, 328 were subjects whom the researchers intentionally exposed at one point or another.[250]

The researchers fostered goodwill and cooperation in other ways as well. In January 1947, Dr. Cutler arranged for serology testing supplies to be sent from the VDRL on Staten Island to the Ministry of Public Health in Guatemala.[251] The researchers also provided training for Guatemalan laboratory personnel and established collaborative and mutually beneficial professional relationships with many Guatemalan medical personnel. Among these, the researchers developed a particularly close rapport with Dr. Carlos E. Tejeda, Colonel and Chief of the Guatemalan Army Medical Department. Dr. Tejeda visited Dr. Mahoney on Staten Island in October 1946, shortly after Dr. Cutler arrived, and later worked with the researchers on all three of the inoculation experiments.[252] After Dr. Tejeda's visit to New York, Dr. Cutler confided to Dr. Mahoney that Dr. Tejeda "appreciated [Dr. Mahoney's] attention" and was "very much interested in our study."[253] Consequently, the researchers were "counting on real cooperation from the [Guatemalan] Army."[254] When Dr. Tejeda's wife fell ill that autumn, Dr. Cutler relayed his and Dr. Spoto's opinion that "it [would] be a very good move" for PHS to supply Dr. Tejeda with the scarce medication his wife needed, which they did, "although it did arrive too late."[255]

In addition, in the Psychiatric Hospital, the researchers developed a close relationship with the director, Dr. Carlos Salvado. He later received an offer to work as a fellow in the United States, and also became a paid employee of the Venereal Disease Division to facilitate "continuing observations" of

the experimental subjects.[256] Dr. Hector Aragon, the director of the Hospicio Nacional de Guatemala (the Orphanage), who in addition worked in the Psychiatric Hospital,[257] also developed a relationship with the researchers. He published with the researchers and gave a speech on the diagnostic experiments in the orphanage at the Second Congress of Venereal Diseases in Central America held in Guatemala City in 1948.[258]



Hector Aragon
"Tribute to Dr. Aragon on his Golden Anniversary in the Profession" Published in the Prensa Libre newspaper on December 4, 1971. The Daily Journal Archive, Historical Archives, CIRMA

Serological Experiments

To ensure reliable syphilis diagnoses and to assist their colleagues in the Guatemalan government to improve public health, the researchers began serology testing (a diagnostic tool to detect antibodies indicative of infection) in November 1946. The investigators focused primarily on the effectiveness of four specific blood tests: the Kahn, Mazzini, Kolmer, and VDRL slide tests.[259] For these serology tests, blood was drawn and subjected to one or more different syphilis testing methods that would indicate whether the blood contained antibodies against syphilis. If antibodies were present, the conclusion was that a subject had either an active syphilitic infection or a previous infection.[260] Lumbar punctures were sometimes conducted 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.[261]

The Venereal Disease and Sexual Prophylaxis Hospital, Guatemala City, 2011

Serology testing began in the Penitentiary on November 7, 1946.[262] The researchers also conducted serological research in the Guatemalan Army and Psychiatric Hospital. Efforts to develop reliable serological testing would confound the group for several years and their serology work in Guatemala

SUBJECT PROFILE: CARLOS

Carlos, a male prisoner at Guatemala City's Penitenciaría Central in 1947, contracted syphilis before he was enrolled in the PHS experiments. He noticed a chancre during the summer of the preceding year, and a blood test confirmed that he had syphilis.

In September 1946, Carlos was treated with injections of Neosalvarsan, as well as 11 injections of bismuth (standard of care for the time). Although Carlos was asymptomatic when he arrived at the Penitentiary, dark-field microscopy showed that he still had syphilis.

Carlos was treated by the researchers with 3,400,000 units of penicillin over the course of a week, and his blood tests showed dramatic improvement during the following two months.

continued through 1953, well after Dr. Cutler left the country in 1948.[263]

Several days after beginning the work in the Penitentiary, Dr. Cutler reported traveling to the "lowlands" for a "preliminary venereal disease survey" in children.[264] In December, he described doing small-scale serologic work in the Hospital de Profilaxis (Venereal Disease and Sexual Prophylaxis Hospital) (VDSPH), a hospital directed by Dr. Funes, Dr. Cutler's colleague who originally suggested the research in Guatemala.[265]

In total, the researchers, including cooperating Guatemalan officials, conducted syphilis serology experiments on Guatemalan prisoners, children, psychiatric patients, and leprosy patients. Blood specimens from U.S. Air Force personnel stationed in Guatemala were also used to compare results between Guatemalan and U.S. populations.[266] There is no record of any of the subjects involved in the serology experiments consenting to any of the procedures performed by investigators.[267]

Penitentiary

Overall, 842 prisoners were involved in diagnostic testing for STDs, which included gonorrhea and chancroid, and the researchers discovered high rates of false positives for syphilis.[268] Dr. Cutler concluded that either syphilis affected a much higher portion of the Guatemalan population than expected, or that other "factors…operative in the population different from those experienced in the United States or in Northern Europe" explained the results.[269] A high base rate of syphilis in the population would have limited the researchers' ability to conduct planned prophylaxis experiments.[270] Dr. Cutler later explained "[t]he serologic findings posed a real problem."[271]

The researchers also soon encountered problems obtaining cooperation from the prisoners. The "Indians," Dr. Cutler reported to Dr. Mahoney in January 1947, had "very widespread prejudice against frequent withdrawals of blood," which Dr. Cutler attributed to them being "uneducated and superstitious."[272] As Dr. Cutler later explained:

> "Most of [the prisoners] believed that they were being weakened by the weekly or biweekly withdrawals of 10 cc. of blood and complained that they were getting insufficient food to replace it. The fear of what they saw was much more important to them than the potential damage which might be done by syphilis years later and could not be countered by promises of or actual administration of penicillin for syphilis and iron tablets to replace blood. In their minds there was no connection between the loss of a 'large tube of blood' and the possible benefits of a small pill."[273]

The prisoners' lack of cooperation also threatened the researchers' ability to proceed with the project.[274] The researchers' plan for prophylaxis research "as originally conceived at the prison could not be carried out," Dr. Cutler later wrote.[275]

Children

Serology testing in children began sometime before June 1947[276] and ended in summer 1949.[277] The researchers conducted physical examinations, blood draws, and, in some cases, lumbar punctures, on 1,384 Guatemalan children between 1 and 18 years of age.[278] Children came from the Orphanage, a school at Port of San José, Totonicapan, and the "highlands" of Guatemala.[279] Testing children below the age of sexual maturity, Dr. Cutler later explained, ensured the opportunity for conclusive evidence of false positivity for any testing regimen, because subjects presumably would have acquired the disease congenitally rather than sexually, and congenital syphilis was distinguishable.[280]

There is no record of any of these children being inoculated or exposed to any STD. There is also no record that the children knew that they were a part of an experiment or had an individual parent or guardian consent on their behalf. Guatemalan government officials were aware of, and supported, the research.[281] At the Orphanage, the director, Dr. Aragon, collaborated as a

researcher and co-author on the publication later describing the work.[282] The Ministry of Public Health also supported the research.

Serological testing began with schoolchildren in Port of San José, Guatemala, followed closely by children in the Orphanage.[283] Many of the 151 children tested in Port of San José exhibited symptoms of malaria. Indeed, Dr. Cutler later sent blood and blood smears from approximately 300 children to Dr. Willard Wright, Chief of the Division of Tropical Diseases at NIH, for the laboratory's ongoing malaria study in Guatemala.[284] To Dr. Mahoney, Dr. Cutler relayed that treating the children for malaria was "to [the researchers'] advantage":

> "In drawing blood from these children it is to our advantage to give them some medicine, for that reason we are planning to give them Aralen [an antimalarial drug] to treat the group found infected with malaria and at the same time we shall arrange for all of the children to receive a weekly prophylactic dose."[285]

The researchers conducted clinical exams of the children's mouths, skin, lymph nodes, and, in boys, the genitals.[286] Two children in the Port of San José were identified with congenital syphilis, one symptomatic and one asymptomatic. Other children with clear or ambiguous seropositive reactions never manifested further clinical symptoms.[287] Several months later, after compiling preliminary results on the children in the Port of San José, Dr. Cutler reported that "it is very evident to us that the cardiolipin test [i.e. the VDRL or Kolmer test] is much more nearly specific than the Kahn or Mazzini techniques [which utilized lipoidal antigens]."[288]

Serology research, including clinical examinations, in the Orphanage involved significantly more children, approximately 515.[289] In April 1948, the researchers presented preliminary serological findings at the Second Congress of Venereal Diseases in Central America held in Guatemala City, which Dr. Arnold also attended.[290] The Director of the Orphanage reviewed results and described the efforts taken within the institution to care for the children.[291] To the researchers, the children in the Orphanage made an ideal study population for many reasons. Most of the children had never had sexual contact, thereby preventing the sexual spreading of syphilis, the facility was in excellent condition, and the children were accustomed to routine medical examinations and treatment. The Orphanage also had a large, stable, and

easily accessible population. The Orphanage generated and meticulously maintained medical records for each child from the moment of admittance, facilitating screening for previous infection or other complicating factors.[292]

Three children showed serologic patterns highly suggestive of syphilis. The researchers treated all three with penicillin and the children showed a slight decline in serologic titer the following year, though none became seronegative.[293] Eighty-nine children demonstrated some level of serologically positive reaction, but only 55 received a clinical work-up.[294] Forty-nine children then underwent lumbar punctures for further diagnosis.[295]

Additional experiments involving 441 "Ladino" children between the ages of 5 and 14 years from the highlands of Guatemala, and 277 "Indian" children between the ages of 6 and 14 years from Totonicapan, Guatemala were also undertaken.[296] These children were involved in blood serology testing only; no lumbar punctures were reported.[297]

Although Dr. Cutler's rationale—at least in part—for testing children appeared to be to validate serological methods for prophylaxis research, the exposure experiments in the Penitentiary in May 1947 began *before* the research in children started,[298] and was over in September 1948,[299] long before the testing in children ended in 1949.[300] Furthermore, Dr. Cutler later changed his mind about the utility of the experiments in children. In 1955 he concluded that effective validation of the serological test methods needed to come from comparisons with better matched populations to the prophylaxis experiments, that is, "an adult group coming from the same society as the prisoners."[301]

Leprosarium

The researchers conducted serological experiments with 51 leprosy patients, nearly the entire population of a leprosarium just outside of Guatemala City.[302] Given the high rates of false positive serologic tests for syphilis seen in other Guatemalan populations, along with published reports of false positive reactions in leprosy patients, the investigators sought to examine serologic tests for syphilis when both factors—disease state and nationality—were combined.[303] The researchers did not find any clinical evidence of syphilis, but positive serologic results appeared higher than in other Guatemalan

populations. The researchers attributed this finding to the leprosy itself causing false positive results for syphilis.[304]

Psychiatric Hospital

The researchers also conducted serologic research in the Psychiatric Hospital of Guatemala.[305] Dr. Carlos Salvado, the director of the Psychiatric Hospital (whom the U.S. government later paid to complete follow-up work after Dr. Cutler left) invited the group to begin serologic screening of patients and new admissions. Dr. Cutler later explained that this presented an opportunity for the researchers to do regular and repeated serologic screening in a defined population of adults over time.[306] A total of 642 psychiatric subjects were involved in STD (syphilis, gonorrhea, and chancroid) diagnostic research, many of whom were engaged repeatedly for different interventions.[307] In addition to blood testing and lumbar punctures, the researchers performed hundreds of cisternal punctures on psychiatric patients for serological purposes.[308] Writing in 1955, Dr. Cutler claimed to need these data from the Psychiatric Hospital because of failure in the children experiments.[309]

The serological testing in the Psychiatric Hospital continued after Dr. Cutler left Guatemala. Drs. Funes and Salvado managed continuing observations for PHS and shipped samples back to the United States for analysis. Blood draws and lumbar punctures continued in approximately 250 subjects from the institution,[310] several of whom tested positive for syphilis.[311] Treatment was not documented. These observations continued through at least 1953.[312]

Intentional Exposure Experiments

Overview

Six months after Dr. Cutler arrived in Guatemala, the intentional exposure and prophylaxis experiments began. They continued from February 1947 through October 1948.[313] In total, Dr. Cutler reported 32 gonorrhea experiments,[314] 17 syphilis experiments,[315] and one chancroid experiment[316] (see Table 4).[317] A total of 1,308 people including commercial sex workers, soldiers, prisoners, and psychiatric patients were involved in the exposure experiments.[318] The ages of subjects involved in the exposure experiments ranged from 10 to 72 years, with the average subject being in his/her 20s.[319] Of that group, 678 individuals can be documented as receiving some form of treatment.[320]

The original plan for the Guatemala experiments—what Dr. Cutler argued brought them to Guatemala initially—was to test the orvus-mapharsen prophylaxis wash as a prophylaxis for syphilis in prisoners exposed to infected commercial sex workers. The purpose was to develop more effective preventative tools for U.S. military personnel. This experiment never happened.[321] Instead, the researchers faced difficulties in diagnosing syphilis, reliably inducing infection (through the use of commercial sex workers), and procuring a compliant subject population. The experiments, upon review, appear to lack logical progression: baseline experiments for background infection rates were conducted after prophylaxis experiments began and new experiments were started before the results for pilot experiments were known (see Figure 6).[322] Intentional exposure experiments began in the Guatemalan Army and focused almost equally on efforts to infect as efforts to test a prophylaxis for gonorrhea. As in Terre Haute, the researchers never mastered a technique with which to infect subjects.

The majority of the intentional exposure experiments took place in the Guatemalan Army on 60 different days and involved gonorrhea and chancroid. The researchers conducted gonorrhea, chancroid, and syphilis experiments at the Psychiatric Hospital on 33 different days. Intentional exposures in the Penitentiary were relatively few, occurring on 24 different days, and were limited to syphilis.[323] While Dr. Cutler's retrospective reports suggest a logical progression in the experiments from one population to the next, and from one type of experiment to another, this step-wise progression is often absent from the contemporaneous records and the aggregate data he collected (see Figure 7).

Dr. Cutler's contemporaneous records note 83 deaths during the course of the experiments.[324] The exact relationship between the experimental procedures and the subject deaths is unclear. When Dr. Cutler wrote his 1955 Final Syphilis Report, he noted a "steady loss of patients by death" that he attributed primarily to tuberculosis and to the fact that "both acute and chronically ill patients" were used.[325] The researchers planned "to perform autopsies on all patients so that special spirochetal and histologic experiments could be made."[326]

Gonorrhea is a contagious disease caused by the bacterium *Neisseria gonorrhoeae*. Similar to syphilis, gonorrhea is transmitted largely through sexual contact and can also be spread from mother to fetus during pregnancy. Symptoms may vary depending on the gender of the individual infected. Signs of infection in men include a burning sensation during urination, or a white, yellow, or green discharge from the penis. Women on the other hand, exhibit either mild or no symptoms at all. Gonorrhea can be cured by antibiotics, but there are currently an increasing number of drug-resistant strains that are difficult to treat.

Gonorrhea Experiments

Overview

Intentional exposure gonorrhea experiments involved approximately 582 people including at least four commercial sex workers and 518 soldiers from February 1947 to July 1948, psychiatric patients from June 1948 through September 1948, and ten additional subjects during the same period whose background is unknown. Of the subjects exposed to gonorrhea (an STD caused by the bacterium *Neisseria gonorrhoeae*), available records document only 237 receiving any form of treatment.[327] The primary purpose of the gonorrhea experiments in the Guatemalan Army was to test the effectiveness of different prophylaxis measures including the orvus-mapharsen solution, a 10-percent argyrol (i.e., silver) intra-urethral instillation, the U.S. Army "pro kit," and oral penicillin.[328] The experiments in the Psychiatric Hospital appear to have been primarily observational (i.e., no prophylaxis or treatment was tested).

The researchers required "ample supplies of pus" carrying the gonorrhea bacteria for their gonorrhea experiments. To obtain such samples, they turned to patients "under arsenical treatment for syphilis" at the Military Hospital.[329] There, the researchers sought to infect the syphilis patients with gonorrhea in order to create a "reservoir of infect[i]on" from which to draw.[330]

In his 1952 retrospective summary of their work, the Experimental Studies in Gonorrhea report, Dr. Cutler wrote that all experimental infections were treated with penicillin in the form of injections of 300,000 units of a repository delayed-absorption preparation.[331] However, the researchers' contemporaneous records reveal that some of the subjects they infected received treatment with a bismuth-arsenic combination,[332] and many of the subjects were never treated at all.[333]

Guatemalan Army and Commercial Sex Workers

On February 15, 1947, the researchers began intentional exposure experiments with gonorrhea.[334] Unlike serological testing for syphilis, with its associated false-positive complications, diagnostic testing for gonorrhea was more straightforward and reliable.[335] In total, 518 soldiers were exposed to gonorrhea, 202 of whom received some form of treatment.[336]

The research in the Guatemalan Army began, Dr. Cutler later explained, as a "result of the interest of the medical department" of the Guatemalan Army.[337] The researchers established relationships with local physicians in the military to support their work. Some of these Guatemalan researchers were involved in the syphilis work as well. Dr. Raul Maza of the Military Hospital was involved in both the syphilis and gonorrhea experiments,[338] and Col. Juan Oliva of the Guardia de Honor (Honor Guard) worked on the syphilis experiments.[339]

Gonorrhea experiments among the Guatemalan Army continued through July 1948.[340] Methods of infection included sexual exposure, superficial inoculation into the penis, deep inoculation into the penis, and superficial inoculation following sexual exposure. Subjects included men in the Military Hospital, the Honor Guard,[341] and the Second Army Company of Riflemen.[342] The average age of the soldiers involved was 22 years old.[343] Many also held the lowest rank of private.[344]

Often, the soldiers involved in the experiments were isolated under careful control and supervision during the experiment.[345] No discussion of compensation for the soldiers is included in Dr. Cutler's reports, beyond some purchasing of clothing by PHS Senior Surgeon Dr. Levitan for the "volunteers."[346] Many of the soldiers were also noted as having been given Arginol (a herbal supplement designed to facilitate erections) in conjunction with the sexual intercourse experiments.[347]

There is no evidence that the soldiers gave consent for the experiments. Indirect evidence from June 1947 shows that the subjects at the time were not, in fact, "volunteers."[348] As Dr. Mahoney explained to Dr. Cutler: "[t]he use of volunteer groups *rather than the type which is being employed* would be more than satisfactory. Our budget will stand for almost any fee for volunteers which you consider to be advisable" (emphasis added).[349]

Dr. Luis Galich
"Gallery of future Presidential contenders: We now offer readers the Mayor of the capital, Luis Fernando Galich."
Published in Diario La Hora on May 11, 1962.
The Daily Journal, Historical Archives, CIRMA

Normal Exposure

Dr. Cutler's contemporaneous notes identify four commercial sex workers who were used in "normal exposure" gonorrhea experiments on two different days in which they had sexual intercourse with soldiers (Dr. Cutler did not include the first two days experiments in his final gonorrhea report and also reported that 12 sex workers were involved).[350] Commercial sex workers were also involved in artificial inoculation exposure experiments after sexual intercourse (discussed below) on 13 different days.[351] Both Dr. Luis Galich, the head of the Ministry of Public Health, and Dr. Juan Funes, by that time the Chief of Medicine at VDSPH, referred infected commercial sex workers from VDSPH to Dr. Cutler.[352] Their assistance was advantageous because, Dr. Cutler reported in 1952, "[c]ontrary to what might be expected, it proved extremely difficult to obtain prostitutes willing to serve under experimental conditions."[353]

Dr. Funes was the physician responsible for the medical supervision of the commercial sex workers and the STD rapid treatment centers "where all venereal disease patients could be hospitalized for free treatment."[354] Detailed Guatemalan regulations, a copy of which Dr. Cutler retained in his personal papers,[355] required commercial sex workers be at least 18 years old, register with the Sexual Prophylaxis and Venereal Diseases Section[356] of the government, and report twice weekly for an examination at a local Venereal Disease Control Clinic.[357] Women infected with syphilis, gonorrhea, or chancroid were prohibited from working as commercial sex workers, but treatment, which was based primarily on arsenical drugs, was provided at no cost.[358]

There is no record in any of the available documents that the women consented to being a part of the experiments or had any idea that they were infected with STDs by the researchers.[359] Medical records reflect that at least one commercial sex worker used in these prophylaxis experiments was 16 years old, contrary to applicable law.[360] Several of the women were also given alcohol before the experiments. While documents stated that men

occasionally received alcohol to "lower resistance to infection,"[361] no reason is stated for giving alcohol to the commercial sex workers.

At least four of the sex workers presented with naturally occurring gonorrhea, but Dr. Cutler concluded that it was "impossible to wait for chance of infection with gonorrhea."[362] The researchers artificially inoculated four commercial sex workers several times.[363] Some contemporaneous notes for gonorrhea experiments show $25 payments to commercial sex workers for particular experiments,[364] although the majority of the notes do not document any compensation.[365]

SUBJECT PROFILE: MARIA LUISA

Maria Luisa was a commercial sex worker who went to the VDSPH, directed by Dr. Funes, on March 13, 1947. She tested positive for gonorrhea when she arrived at the hospital and was subsequently referred by Dr. Funes to Dr. Cutler.

On March 15, 1947, Maria Luisa was paid $25 and had sexual contact with seven men. During the following year, Maria Luisa was inoculated 11 different times with many different strains of gonorrhea. While infected with gonorrhea she had 105 sexual contacts.

There is no evidence that Maria Luisa received any treatment for her acute gonorrhea during the experiments.

The researchers artificially inoculated commercial sex workers with gonorrhea by moistening a cotton-tipped swab with pus from an acute case of gonorrheal urethritis in the male, inserting the swab into the woman's cervix and "swabb[ing] it around…with considerable vigor."[366] All of the commercial sex workers infected in this manner reportedly contracted the disease. None "showed evidence of acute infection such as a rich outpouring of thick yellow pus from the cervix or by signs of pelvic inflammatory disease…[but] all of them showed evidence of infection by cervical discharge and excessive accumulation of secretion in the vagina," and all were culture-positive.[367] Dr. Cutler later made at least one note saying that two of the women involved in the experiments "were eventually treated,"[368] but detailed treatment records, like those that exist for the other subject populations, do not exist for the commercial sex workers.

The first gonorrhea experiment, on February 15, 1947, tested the effectiveness of Dr. Arnold's penicillin/POB (a preparation of penicillin in a medium of peanut oil and beeswax to ensure a slow steady release prophylaxis) in a placebo-controlled trial of 15 men who were exposed to commercial sex

workers known to be infected.[369] As Dr. Cutler later wrote "ideally, a prophylactic should be tested under normal conditions."[370] Dr. Arnold was there to oversee this work. He had arrived in Guatemala sometime before February 10, and left approximately 10 days later, arriving home in time to write Dr. Cutler on February 27.

Before the experiment began, Dr. Cutler specifically designated which soldiers were to receive the prophylaxis and which were to receive the placebo, but several men's roles were reversed on the day of the trial.[371] The commercial sex workers were instructed not to douche on the day of the experiment and were not permitted to wash between episodes of sexual intercourse with the men.[372] In later experiments, the researchers confirmed that the commercial sex workers were infected before the prophylaxis tests began, but in the first experiment, Dr. Cutler was unable to confirm infection status at the time of exposure because "the girls were quite apprehensive."[373]

For this first intentional exposure experiment, Dr. Cutler recorded the length of time the soldiers engaged in sexual intercourse, and he examined each man afterward for "evidence of vaginal secretion and ejaculation" to "assure that contact had actually taken place."[374] Dr. Cutler also recorded when the subject did not ejaculate.[375] While the goal of this first experiment was to "permit the exposure of a large group of men to infected prostitutes to determine the normal rate of infection with gonorrhea,"[376] none of the men involved in the experiment contracted gonorrhea. Dr. Cutler did not report this first experiment in his 1952 Experimental Studies in Gonorrhea report summary.[377]

After Dr. Arnold's visit in February,[378] Drs. Heller, Van Slyke, and Mahoney traveled to Guatemala in April 1947.[379] Dr. Cutler worked hard to entice and impress these senior PHS leaders. In January, Dr. Cutler had written Dr. Mahoney to tell him about eight cases of Pinto (a skin disease caused by a spirochete indistinguishable from *Treponema pallidum*) that Dr. Mahoney could review on his visit for use in rabbit experiments.[380] Dr. Cutler withheld treatment for three months so Dr. Mahoney would have such an opportunity: "we hope to be able to take you to the finca [estate] to see the cases of Pinto and then to give them Penicillin after having taken biopsies for rabbit inoculations. The cases were most interesting and I am sure that you will enjoy the trip."[381]

The visiting physicians observed the intentional exposure experiments. Dr. Van Slyke complained that Dr. Cutler had not confirmed that the commercial sex workers were in fact infected with gonorrhea at the time of exposure.[382] Discussing these concerns later, Dr. Arnold suggested that Dr. Cutler not "put on any more shows unless you are sure of everything" so as to avoid "an unfavorable impression." Alternatively, Dr. Arnold suggested that Dr. Cutler "do a little blanket stretching."[383]

In addition, the volume and frequency of exposures to the commercial sex workers raised some concern. Dr. Cutler's superiors advised that the commercial sex workers should have sexual intercourse with men several hours apart[384] or just several times a day[385] to maximize transmission rates. But the sex workers involved in the experiments had intercourse with different men sometimes less than a minute apart, seeing a large number of men in a very short time.[386] For example, one commercial sex worker whom the researchers infected with gonorrhea had contact with eight soldiers[387] in 71 minutes.[388] Transmission rates remained low. According to Dr. Cutler's final report, in total in the Guatemalan Army, only five infections resulted from 138 exposures of 93 men (5.4 percent) to 12 commercial sex workers over the course of the normal exposure experiments which ended in July 1948.[389]

Artificial Inoculation

Shortly after beginning the sexual intercourse experiments to induce gonorrhea infection, the researchers also began "artificial inoculation" experiments, mirroring techniques employed in Terre Haute (see Figure 8). The researchers conducted these artificial inoculation gonorrhea experiments in the Guatemalan Army beginning in April 1947 (two months after they started the sexual intercourse experiments).[390] They employed two procedures for artificial inoculation: "superficial" and "deep" inoculation. The swabs used in superficial inoculation were from the bacterial laboratory. For deep inoculation, the researchers used toothpicks wrapped in a small amount of cotton. For both procedures, the swab was moistened with pus from an "acute case of gonorrhea in the male."[391] In a superficial inoculation:

> "[T]he penis was grasped just distal to the sulcus between the left thumb and forefinger of the physician so that the mucosa of the fossa navicularis was averted and so that the urethra distal to a point 2-4 mm. from the meatus was occluded. With the right hand the physician carefully, and with some force, rolled the large inoculating swab over the mucosa so as to try to contaminate the entire fossa navicularis."[392]

For the deep inoculation method, "the toothpick swab was…inserted about ½ [inch] into the urethra, and carefully rubbed over the mucous membrane, so much so as to cause pain."[393]

Describing early results to Dr. Mahoney on May 17, 1947, Dr. Cutler explained:

> "On Friday, May the 9th, we performed another experiment inoculating six patients with pus and treating three of them. As of May 15, one of the controls showed positive culture, the second showed considerable discharge with extra-cellular organisms, while the third shows considerabl[e] discharge which is microscopically negative thus far. That reminds me of the patients at Terre Haute some of whom showed such a discharge for a few days before we were able to make the diagnosis, while others might show for a few days after inoculation extra or intra cellular organisms but remain culturally negative and not develope [sic] the infection. None of the treated patients thus far shows any evidence of a take."[394]

In the same letter, Dr. Cutler also described the researchers' first success using commercial sex workers for "normal exposure" from the months prior ("[w]e have had the first success with the normal exposure with one patient of six showing positive results"). But, Dr. Cutler continued to voice concerns about the effectiveness of that method of transmission.[395]

Writing to Dr. Arnold on June 5, 1947, following eight sexual intercourse experiments, Dr. Cutler observed that infection by "natural exposure with these men is rather low."[396] On June 22, after one additional sexual intercourse experiment, Dr. Cutler reported to Dr. Mahoney on his continued findings:

> "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 during the evening so that the tota[l] time of exposure averaged over ten minutes with most men having two and some three exposures. There was no 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 alcohol prior to exposure. It seems that clandestine affairs, with respect to gonorrhea, are far safer than ever before imagined."[397]

In response, Dr. Mahoney, whose doubts about the feasibility of intentional infection contributed to the decision to terminate the Terre Haute work,[398] advised his junior colleague on June 30 to follow a contact only (i.e., sexual intercourse) regimen: "we are anxiously awaiting your report of the transmission experiments utilizing contact only. This is of vital importance if we are to carry out the studies outlined."[399] By August, Dr. Mahoney had advised Dr. Cutler that "[i]t is becoming obvious also that experimental infection cannot be produced with sufficient frequency to assure an adequate background for a study of prophylaxis. Because of the circumstances your opinion as to the advisability of discontinuing the gonorrhea phase of the project for the time being would be appreciated."[400] Dr. Cutler responded that "we might well continue [the experiments] a while longer to get as much information as possible now that we have a set up here."[401]

Despite Dr. Mahoney's concerns, the researchers increased the number of artificial inoculation experiments relative to the sexual intercourse experiments beginning in August. While the researchers conducted 13 sexual intercourse experiments and eight artificial inoculation experiments between February and July 1947, they conducted nine sexual intercourse experiments and 32 artificial inoculation experiments between August 1947 and July 1948.[402]

Explaining his choice to begin artificial inoculation methods later in 1952, Dr. Cutler noted, "[a]s a result of the experience of several authors, it was decided to carry out an evaluation of prophylactic methods using artificial means of inoculation."[403] Dr. Cutler pointed out that Dr. Tejeda had many patients in the Guatemalan Army who had artificially inoculated themselves in order to get out of official duties: "[t]he technique commonly used was to take by the end of a match from an acute case and to insert the contaminated end of the match into the urethra of the solider desiring to infect himself."[404] Dr. Cutler also cited the Terre Haute experiments in his 1952 report as evidence that the method "could cause infection,"[405] despite concerns about the effectiveness of this form of inoculation research raised in 1944.[406]

In the control groups, Dr. Cutler reported rates of approximately 50 percent infection with the superficial inoculation method, and 97.8 percent with the deep inoculation method.[407] He concluded that these numbers showed that a prophylactic agent tested against a superficially inoculated subject was "subjected to a very severe test indeed."[408] If a prophylactic agent could withstand an otherwise 54-percent rate of infection, he argued, it "should be expected to show up well" when subjected to the "less-severe test of routine risk of infection."[409]

By September 1947, Dr. Cutler also decided to conduct several experiments using artificial inoculation after sexual intercourse. With this method, the men had sexual intercourse with a commercial sex worker, and immediately following intercourse, "while the penis was still partially engorged and while the fluid of the ejaculate was at the meatus," the inoculation was performed to "simulate more nearly the natural conditions."[410] This type of experiment occurred on 13 different days, but the results did not differ significantly to artificial inoculation without sexual intercourse.[411] The researchers completed their gonorrhea experiments with subjects in the Guatemalan Army in July 1948.[412]

Psychiatric Hospital

The researchers conducted gonorrhea intentional exposure experiments in the Psychiatric Hospital from June to September 1948.[413] These experiments involved a total of approximately 50 subjects, 32 of whom received some form of treatment.[414] They included inoculation in the subjects' rectum, urethra, and/or eyes.[415] One female subject who was identified as having a terminal

SUBJECT PROFILE: BERTA

Berta was a female patient in the Psychiatric Hospital. Her age and the illness that brought her to the hospital are unknown.

In February 1948, Berta was injected in her left arm with syphilis. A month later, she developed scabies (an itchy skin infection caused by a mite). Several weeks later, Dr. Cutler noted that she had also developed red bumps where he had injected her arm, lesions on her arms and legs, and her skin was beginning to waste away from her body. Berta was not treated for syphilis until three months after her injection.

Soon after, on August 23, Dr. Cutler wrote that Berta appeared as if she was going to die, but he did not specify why. That same day he put gonorrheal pus from another male subject into both of Berta's eyes, as well as in her urethra and rectum. He also re-infected her with syphilis. Several days later, Berta's eyes were filled with pus from the gonorrhea, and she was bleeding from her urethra.

On August 27, Berta died.

illness died four days after the researchers inoculated her, without receiving any treatment for the gonorrhea or syphilis with which the researchers had infected her.[416]

Syphilis Experiments

Overview

The researchers conducted intentional exposure experiments involving syphilis, the STD caused by the bacterium *Treponema pallidum*, with 688 subjects, including commercial sex workers, prisoners, and psychiatric patients from May 1947 through October 1948.[417] The primary purpose of these experiments was to study the clinical effectiveness of the orvus-mapharsen prophylaxis that Drs. Arnold and Mahoney proved effective in rabbits.[418] Other types of prophylaxis tested were the Army "pro kit" (a topical preparation containing calomel, sulfathiazole, white petrolatum, light mineral oil, and cetyl alcohol), parenterally administered preparations (e.g., POB), and oral penicillin in pill or liquid form.[419]

The researchers used several different strains of infectious material for the syphilis experiments.[420] They used rabbits as the source of most of the strains,[421] but they also tested strains taken directly from humans ("human passage material") because of questions about the impact of rabbit passage on the pathogenicity of *Treponema pallidum* and conviction that "the ultimate value of a prophylactic agent depended upon the ability to protect man against the infection in man."[422] These methods exposed subjects to additional health risks for human-to-human pathogens in addition to the syphilis and any number of zoonotic pathogens from the rabbit strains.

Syphilis is a contagious disease caused by the bacterium *Treponema pallidum*. Although it is mainly transmitted through sexual contact, syphilis can also be transmitted from mother to fetus during pregnancy. The disease is mainly characterized by sores, but can also cause a wide variety of symptoms that vary depending on the state of the disease (primary, secondary, latent, and tertiary). Syphilis can be diagnosed through a blood test or an examination of the bacteria found in the infectious sore. If caught early, syphilis can easily be treated with an antibiotic, such as penicillin.

To harvest the human passage material, Dr. Cutler used exudate (infectious fluid) from selected subjects with previously infected penile or skin chancres, some of which was obtained from patients in the local hospitals, including the Military Hospital where Dr. Raul Maza worked. Dr. Cutler then excised the cutaneous chancres, sometimes by full "circumcision," under local anesthesia.[423] He explained in his Final Syphilis Report that treatment for the donor's syphilis was sometimes provided immediately after removal of the chancre but that at other times "treatment was delayed to study the healing of operative wounds in syphilitic patients."[424] The material was then ground up and made into an emulsion. The "street strain" inoculum was a mixture of material collected from three different soldiers.[425]

The researchers used three types of intramuscular penicillin injections for treatment: an aqueous solution of the sodium or potassium salt of penicillin G; POB; or Duracillin, the procaine salt of penicillin in a peanut oil base.[426] While some of the subjects exposed to syphilis were not treated absent clinical evidence of disease (e.g., the development of a chancre), 388 out of 688 subjects exposed were treated in some fashion.[427] These treatment practices varied, however, and the efficacy of the different approaches was not fully known at the time. The researchers recorded few adverse events related directly to the penicillin treatment, but they noted that at least one subject died after receiving penicillin.[428]

Penitentiary

When the researchers began work in the Penitentiary in early fall 1946, they limited their work to "good will" screening and treatment, plus serology and placebo prophylaxis, until May 10, 1947, when the group began intentional exposure experiments.[429] In total, 219 prisoners were included in these experiments through exposure to infected commercial sex workers and/or artificial

inoculations with infectious material, between May 1947 and September 1948.[430] Only 92 of the 219 people exposed received some form of treatment.[431] In contrast to the experiments with soldiers and psychiatric patients, the prisoners were exposed to commercial sex workers and artificial inoculation with relatively less invasive injection methods.[432]

Prison inmates were viewed as an isolated population that could be used for "normal exposure" to STDs (i.e., sexual intercourse). There is no record of the men in the Penitentiary either consenting to be involved in an experiment or understanding that an experiment was taking place. Moreover, evidence suggests that some prisoners objected to participation. As Dr. Cutler later explained, "relationships between prisoners and experimenters" made it impossible to secure serum from dry lesions due to the prisoners' "strenuous objection to the pain."[433]

A large portion of the prison population consisted of indigenous Guatemalans, referred to in correspondence as "Indians." Writing to Dr. Arnold about this group shortly after he arrived in August 1946, Dr. Cutler relayed Dr. Spoto's view that the experiments need not be explained to the "Indians."[434] "Likewise," Dr. Cutler continued, "our payment for the males will be considerably less than we had originally planned."[435] Still, the researchers undertook various methods to deceive the prisoners about their research aims during, and possibly after, the experiments. In January 1947, Dr. Cutler advised Dr. Mahoney of several steps planned with "all concerned" to "allay fears and suspicions" about the research:

> "So far as the work in the prison goes, it appears that it will have to be carried out as a scheme of prophylaxis for everyone, using a placebo where indicated. To increase the number of exposures we shall bring in the sourcs [sic] of infection [the commercial sex workers] as indicated along with some not infected so as to allay fears and suspicion. In that way, we shall be able to avoid political repercussions which are even now in the air as the papers are complaining about conditions in the prison now. It is quite probable that we shall pay the men either nothing or a pack of cigarettes or some soap or other items for each extraction of blood. We have had many conferences about this matter and the scheme

> mentioned above seems to be the one acceptable to all concerned and is one which offers the least risk of any trouble."[436]

Notwithstanding these plans, Dr. Cutler's records reflect that only 13 of the 23 experiments involved sexual intercourse—the rest involved injection as an artificial exposure technique.[437] Writing in 1955 about the goals of the Penitentiary inoculation work, Dr. Cutler explained the purpose as seeking to identify an effective serologic test and answer several additional questions (only one of which concerned prophylaxis, and none of which involved orvus-mapharsen):

- What types of clinical and serologic changes might result from the injection of rabbit testicular syphilomata (versus human);[438]
- Whether superinfection was possible;[439]
- Whether virulence of the disease could be lost due to length of infection in the rabbit donor;[440]
- Whether animal passage material "so attenuated or altered the bacterium that it [] lost the ability to penetrate the human mucus membrane," leading the researchers to design an experiment to "pass the material through man";[441]
- What was the effectiveness of "abortive penicillin therapy"[442] and intramuscular penicillin prophylaxis;[443] and
- Whether treated subjects with early or late latent syphilis could be reinfected.[444]

The individual reports of the injection experiments, later found in the final 1955 report, include research data collected for addressing each of these questions.

Despite ongoing concern about serological testing and its reliability as an indicator of infection, the researchers began syphilis experiments with commercial sex workers and prisoners in May 1947 shortly after Drs. Mahoney, Heller and Van Slyke visited.[445] Writing in 1955, Dr. Cutler described the commercial sex workers who served the penitentiary populations as the "lowest in the social scale of local prostitutes and most frequently infected with syphilis and gonorrhea,"[446] but Dr. Cutler inoculated some of the commercial sex workers directly through intra-cervical injection of rabbit testicular syphilomata.[447] Shortly thereafter, these women had sexual contact with 12 inmates. None of the prisoners developed clinical symptoms of infection, but complete serologic follow-up was impossible due to the prisoners' objections to the collection of blood.[448] As in the first two gonorrhea experiments, this first syphilis

experiment in the Penitentiary was not included in the summary chronology in Dr. Cutler's Final Syphilis Report. Dr. Cutler later wrote that the commercial sex workers were to be paid by the researchers for their services,[449] but no contemporaneous records document compensation.

Dr. Cutler argued in his final report that "it became necessary to develop a different mode of attack" from the sexual intercourse exposure for inoculating the prisoners due to the small number of men available for the experiment and the scientific difficulties they were facing.[450] But researchers began intracutaneous inoculation of prisoners on May 14,[451] just days after the first failed "normal exposure" experiment. Prisoners were given intracutaneous injections of syphilitic material into the distal border of the foreskin and/or anterior aspect of the right forearm.[452]

The researchers achieved a 96.8-percent transmission rate in the first artificial inoculation prison experiment via injection.[453] But, "[i]n view of the importance of gaining information as rapidly as possible," the researchers decided to begin the next experiment "without waiting to determine the outcome" of the first.[454] The researchers also used the same needle "repeatedly" and "without sterilization of any kind from one patient to the next."[455] The practices significantly raised the risk of infection and other adverse health effects for individual subjects.

The original plan to test orvus-mapharsen prophylaxis through the "normal exposure" of sexual intercourse between an infected woman and an uninfected man in the Penitentiary was never implemented.

Psychiatric Hospital

In January 1947, four months before beginning any intentional exposure experiments in the Penitentiary, and a month before beginning intentional exposure experiments in the Guatemalan Army, Dr. Cutler advised Dr. Mahoney about supplementing the original research design to include experiments "such as inoculation" at the National Psychiatric Hospital of Guatemala.[456] The decision to undertake intentional exposure experiments there met with some resistance from Dr. Cutler's supervisors, who raised concern about possible adverse public reaction. In April 1947, before any intentional syphilis exposure experiments began in either the Penitentiary or

Psychiatric Hospital, Dr. Arnold wrote to Dr. Cutler that he was "a bit, in fact more than a bit, leary [sic] of the experiment with the insane people" as they "cannot give consent" and "do not know what is going on…"[457] Dr. Arnold appeared primarily concerned about exposure to criticism, because if "some goody organization got wind of the work, they would raise a lot of smoke."[458] He continued that:

> "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 supt. of the ins. hosp. [sic] Also how many knew what was going on [sic]. I realize that a [subject] or a dozen could be infected, develop the disease and be cured before anything could be suspected. The penicillin could be a Rx [treatment] 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."[459]

Writing in 1955 in his Final Syphilis Report, Dr. Cutler cast the choice to move to the Psychiatric Hospital as a reaction to problems in the Penitentiary, particularly the prisoners' objections to the blood draws that were critical to assessing infection.[460] "As work in the penitentiary grew less attractive," he wrote, the researchers "shifted [their] major activity to the asylum."[461] However, the first intentional exposure experiments in the Psychiatric Hospital occurred only three days after the first intentional exposure experiment in the Penitentiary (May 10 and 13, respectively).[462] And, the Penitentiary work continued for almost a year and a half after the work in the Psychiatric Hospital began. A total of 446 psychiatric patients were involved in the intentional syphilis exposure experiments, 294 of whom received some form of treatment.[463]

The syphilitic rash of a 22-year-old female psychiatric subject who was exposed to syphilis twice and received some treatment. *From the National Archives and Records Administration*

Dr. Cutler said they chose subjects in the Psychiatric Hospital based on "custodial considerations" such as expected date of release and absence of homosexual behavior, but there are several examples of the researchers intentionally exposing men they also noted to be "active homosexuals."[464] It is possible that the subjects involved in the experiment spread syphilis beyond the experimental boundaries through homosexual contact,[465] but Dr. Cutler dismissed this possibility in his 1955 Final Syphilis Report. He reported observing no clinical evidence of syphilis spread in this manner.[466]

Dr. Carlos Salvado, the Director of the Psychiatric Hospital, collaborated on the syphilis and gonorrhea experiments and made staff available to assist the researchers.[467] Dr. Cutler credited Dr. Salvado with suggesting use of the psychiatric patients in experiments "since we had available a certain and sure cure for syphilis…."[468] Dr. Cutler added that "[r]esponsible medical officials representing all groups concerned" together decided to undertake the syphilis inoculation experiments at the Psychiatric Hospital. Dr. Cutler justified this decision by pointing out that "[m]embers representing the VDRL had previous experience in inoculation of volunteers both with gonorrhea and syphilis," after which he cited the Terre Haute experiments as well as an "unpublished observation" he made with Dr. Arnold "on inoculation of volunteers with Nichols strain *T. pallidum* obtained from rabbit testicular syphilomata quick frozen and maintained in solid carbon dioxide refrigeration."[469] Dr. Cutler argued that "organizations concerned" had been involved in malaria[470] and infectious hepatitis inoculation experiments,[471] "so that there was a large background of experiences in the methods of working in human inoculation and with the safeguards for the individuals concerned."[472]

Such an opportunity, the researchers believed, would "provide conclusive answers to a large number of questions of great importance, not only in the matter of prophylaxis but also concerning progress of national and international control of venereal disease then in action or proposed for the future."[473] Once in the Psychiatric Hospital, questions to which "conclusive answers could be expected to be found," Dr. Cutler later wrote, included the following:

- Whether the orvus-mapharsen prophylaxis was effective in the prevention of syphilis;
- How the orvus-mapharsen prophylaxis compared with those in use at the time;

- Whether oral penicillin was effective as a prophylaxis;
- Whether reinfection could take place following treatment and its clinical course; and
- Whether reinfection or superinfection could take place in treated or untreated latent or late syphilis.[474]

Psychiatric Hospital staff assisted during the experiments on an "irregular yet constant" basis.[475] Dr. Salvado objected to having the researchers make supplementary payments to compensate Psychiatric Hospital staff, but he permitted the researchers to share the occasional pack of American cigarettes or a few extra dollars.[476] Workers at the hospital notified the researchers of deaths, helped at autopsies, and aided experiments with large groups of subjects.[477]

When the researchers began at the Psychiatric Hospital, Dr. Cutler proposed to shift the $1,500 originally intended to pay prison volunteers[478] to provide "for the benefit of the institution rather than for the individual."[479] At the direction of Dr. Salvado and "the Sister in charge," a refrigerator in which to store drugs, a sound projector, and some metal plates and cups were provided.[480] Dr. Cutler confirms in his report that these items were purchased for the hospital, but it appears from correspondence that the items were later sold to the hospital at cost.[481] As compensation to subjects, the researchers provided cigarettes for "patient management."[482]

The researchers also provided medication for psychiatric patients for the specific purpose of aiding their own serological testing needs. In a February 6, 1948 letter to Dr. Mahoney, Dr. Cutler explained:

> "We are having to order large quantities of [d]ilantin in order to protect ourselves. They had started treating the epileptics at the asylum with intravenous magnesium sulfate which caused thrombosis of the veins so that we are beginning to be unable to get blood samples. Out of self interest we agreed to furnish Dilantin to treat all of the patients in whom we are interested."[483]

Dr. Cutler's Final Syphilis Report makes no mention of this rationale but instead notes "the project provided much-needed anticonvulsant drugs, particularly Dilantin, for the large part of the patient population which was epileptic and for which funds previously had been insufficient to provide drugs."[484]

No evidence indicates that the psychiatric subjects gave consent or understood that they were involved in an experiment. Indeed, when writing about the first experiment in the Psychiatric Hospital Dr. Cutler wrote to Dr. Mahoney that

This female patient in the Psychiatric Hospital was exposed to syphilis twice and was treated with penicillin. She also was involved in the serological testing for syphilis. Her age and original diagnosis, and reason for hospital treatment, are unknown.

This female patient in the Psychiatric Hospital was exposed to syphilis twice and was treated with penicillin. She also was involved in the serological testing for syphilis. Her age and original diagnosis, and reason for hospital treatment, are unknown.

This 25-year-old female patient in the Psychiatric Hospital was exposed to syphilis once with no record of treatment. She also was involved in the serological testing for syphilis. Her original diagnosis, and reason for hospital treatment, are unknown. Records indicate that she was released.

This 16-year-old female patient in the Psychiatric Hospital was exposed to syphilis twice and was treated with penicillin. She also was involved in the serological testing for syphilis. Her original diagnosis, and reason for hospital treatment, are unknown. Records indicate that the patient was "uncooperative."
From the National Archives and Records Administration

"[a]s you can imagine we are all holding our breaths, and we are explaining to the patients and others concerned with but a few key exceptions that the treatment is a new one utilizing serum followed by penicillin. This double talk keeps me hopping at times."[485]

There are also several noted examples of psychiatric patients actively objecting to the experiments. For example, one subject "fled the room" after being subjected to scarification of the penis, and he was not found for several hours.[486] Dr. Cutler reported further that it was difficult to examine the women's abdomens, breasts, or backs "as a result of local prejudices against male viewing of the body, even by physicians…"[487] Dr. Cutler also admitted that under their "stated studies" there was "no good reason which could be offered [to the women] to explain the necessity for complete examinations."[488] Therefore, he wrote, "[i]t was unfortunately not feasible to attempt mucosal inoculation in the female genitalia to compare the male with the female."[489]

This is the syphilitic chancre of a female psychiatric subject who was exposed to syphilis twice, received some treatment, and later passed away. *From the National Archives and Records Administration*

Injection and Contact Method

In May 1947, the researchers began their artificial inoculation syphilis experiments in the Psychiatric Hospital with two different exposure methods using the injection technique that was employed in the Penitentiary as well, and the "contact" method that Drs. Mahoney and Arnold used previously in rabbit experiments.[490] Dr. Arnold had explained how best to expose the subjects via contact method in a letter to Dr. Cutler in April.[491] Dr. Cutler used this method because both he and Dr. Mahoney felt that it was the procedure most "closely approximating" normal sexual intercourse.[492] During the "contact method":

> "[A] cotton pledget was placed at the frenum and moistened with varying amounts of suspension and at intervals, dependent upon the experiment. The pledget was moistened by dropping the fluid through a 25 gauge needle onto the pledget. The foreskin was replaced to normal position concealing the pledget entirely."[493]

Dr. Cutler later reported a 17.9-percent transmission rate for this method.[494]

Scarification and Abrasion

On September 24, 1947, after six contact and injection experiments in the Psychiatric Hospital, the researchers began abrading the membranes of psychiatric subjects' penises to improve the syphilis transmission rate.[495] But, like the artificial gonorrhea inoculations, this technique raised some serious doubts with Dr. Cutler's supervisors at the VDRL. On September 8, Dr. Mahoney reminded Dr. Cutler "we have delayed setting up a field trial of the prophylactic agent in the hope that the Guatemala work would give precise data which would support, even in a small way, the experimental findings in animals."[496] Dr. Mahoney felt that both scarification and abrasion were "drastic," were "beyond the range of natural transmission and [would] not serve as a basis for the study of a locally applied prophylactic agent."[497] Dr. Mahoney told Dr. Cutler "unless we can transmit the infection readily and without recourse to scarification or direct implantation, the possibilities of studying the subject are not bright."[498]

This male patient in the Psychiatric Hospital was exposed to syphilis twice and was treated with penicillin. He also was involved in the serological testing for syphilis. His age and original diagnosis, and reason for hospital treatment, are unknown.
From the National Archives and Records Administration

In another letter the same day, Dr. Mahoney continued:

> "I wish you would give some thought to the future of the work in Guatemala. In the event of the prophylaxis angle proving to be impossible of resolution, we will have left only the serology study and the work in penicillin therapy. We would surely have difficulty in selling an expensive project of this kind to the Public Health Service."[499]

SUBJECT PROFILE: CELSO

Celso was a male patient in the Psychiatric Hospital. His age and the illness that brought him to the hospital are unknown.

Celso was involved in two syphilis experiments in 1947 where an emulsion containing syphilis was applied to his penis. In one experiment he received a prophylaxis of penicillin and in the other he received no prophylaxis. Celso was enrolled in his third and final experiment in January 1948. As part of this experiment, Celso's penis was abraded and then syphilis was applied. In March and April 1948, Celso exhibited multiple clinical symptoms of syphilis. In May 1948, Celso was treated with penicillin, but subsequent examinations in June 1948 determined his case had developed into secondary stage syphilis. There is no record of additional treatment.

In June 1949, Dr. Cutler's notes state Celso died as a result of a lobotomy and that an autopsy was performed. However, a letter was sent to Dr. Cutler in 1952 that said Celso was alive and he had no clinical symptoms of syphilis. It is unclear which record is accurate.

On September 18, Dr. Cutler wrote Dr. Mahoney that the "vast amount of fundamental work to be done in experimental syphilis in man and in serology" should make it "easy to justify continuation of the study even though we are not able to study simple prophylaxis as originally planned."[500] He emphasized the unusual opportunity presented in Guatemala for "pure science":

> "With the opportunity offered here to study syphilis from the standpoint of pure science just as Chesney studied it in the rabbit it should be possible to justify the project in the event of the impossibility of resolution of the prophylactic program. But we feel that we shall be able to subject prophylaxis to a severe trial. Along the same line of thought of investigation in pure science I shall have a chance later to do a survey on a small group of pure Indians being worked [on] by the Carnegie Institution. If any interesting findings result it may give us new leads for investigation on a purely scientific basis."[501]

Dr. Cutler disregarded his supervisor's objections to scarification and abrasion. He argued instead that "we shall be able to study prophylaxis by other methods to subject it to much more severe tests than those occurring normally."[502] Dr. Cutler wrote in correspondence to Dr. Mahoney that "[t]he low incidence of infection following natural exposure indicates that the test to which the [prophylaxis] method was submitted is much more drastic than that occurring under conditions of normal exposure."[503]

Dr. Cutler justified his "heroic challenge methods"[504] in the Final Syphilis Report as a means to provide more rigorous experimentation:

> "It was realized at the outset that the mechanical abrasion would probably be more severe than that occurring naturally and might permit more ready penetration of the organisms. But it was felt that under such circumstances any agent to be tested for prophylactic value would be subjected to a more severe test condition than that occurring naturally."[505]

He offered a parallel rationale for the artificial exposure techniques in his Experimental Studies in Gonorrhea report:

> "A comparison between the rate of infection of (5/93) 5.4% following normal exposure to an infected female and (47/87) 54% following superficial inoculation indicates that a prophylactic agent tested against superficially inoculated patients is subjected to a very severe test indeed, so that a preparation found to be effective under these circumstances should be expected to show up well when subjected to the less-severe test of routine risk of infection."[506]

In addition, based on observations of "reddened and battered-looking" penises, Dr. Cutler concluded that there was "probably a good deal of penile trauma during intercourse with breaks in the membrane."[507] Dr. Cutler reasoned that the infection with syphilis might be dependent on these "breaks in the continuity of the mucous membrane" and that "any method of inoculation which destroyed the continuity of the skin or mucous membrane might offer a more nearly physiological approach to the problem of bringing about experimental infection."[508] Dr. Cutler made this argument justifying scarification to both Dr. Arnold[509] and Dr. Mahoney[510] in September. Later, in a historical review of STD control (written in 1989), Dr. Cutler concluded, "studies on human inoculation with syphilis demonstrated the value of intact, healthy skin and mucous membrane in preventing infection."[511] The evidence he cited for this assertion was "a conversation with JM Funes, MD (December 1947)."[512]

The researchers continued to employ the contact method after they had begun abrasion because "[a]s yet there was doubt as to the advisability of utilizing a

method of inoculation involving damage to [the] mucous membrane in testing prophylaxis."[513] Dr. Cutler responded to Dr. Mahoney's concerns with assurance that "within the next few days we hope to have the prophylaxis study in syphilis under way as originally planned." He concluded that "[w]e know nothing of infection following scarification, but it is my own feeling that we have underestimated the importance of the breaks in the continuity of the mucous membrane in the invasion of the spirochete."[514]

However, by November, Dr. Cutler concluded that abrasion was "the only practicable method" of prophylaxis testing "approximating normal sexual exposure…"[515] When locally applying syphilitic material to the abraded mucous membrane of the penis:

> "[T]he foreskin was retracted and the glans placed on a stretch over the forefinger of the left hand of the physician. Using the long end of a 20 gauge, long-bevel hypodermic needle held in the right hand, the dorsal surface of the glans just distal to the coronal sulcus was lightly abraded over an area of about 2 x 5 mm. We tried to stop the abrasion short of drawing blood or serum, barely removing the surface layer, but not infrequently small bleeding points could be noted. The abraded area was covered with…[a] cotton pledget [soaked in *Treponema pallidum*]."[516]

Dr. Cutler later reported that the researchers achieved a 91.6-percent transmission rate through this mode of inoculation, which was considerably greater than the rate following sexual intercourse. Dr. Cutler concluded that this method of inoculation should therefore "provide a most severe test of clinical efficacy of any prophylactic agent."[517]

During a related mode of infection, the "multiple pressure technique":

> "The inoculation was performed over the deltoid region…one or two drops of the spirochetal emulsion was allowed to drop on the surface. Through this drop, and using a sterile sewing needle or small-gauge hypodermic needle a series of 2-30 strokes was made by the technic [sic] utilized for smallpox vaccination and the material was allowed to dry. An attempt was made not to penetrate the dermis or to draw blood."[518]

After the subject was abraded and inoculum applied as described above, a small amount of the prophylactic was "placed in the meatus" and the rest of the material was "thoroughly rubbed into the glans, foreskin, shaft of the penis, and onto the pubic hair by the physician."[519]

As "[c]omplete results of any given experimental procedure were not available for at least 4 months following inoculation," Dr. Cutler wrote:

> "With limited time available for completion of the project it was thus not feasible to delay four months between each experimental run so as to plan successive experiments on the basis of knowledge gained from the predecessors. Thus it was necessary to anticipate results upon bases of early observations and to move ahead on the strength of incomplete experimental data with knowledge that final analysis would be made of the completed work so that any errors in the early hypothesis would be shown up."[520]

Oral Contagion and Cisternal Punctures

The researchers also decided to undertake other types of inoculation in the Psychiatric Hospital, including oral ingestion of syphilitic material. For this work, the researchers were curious about the ability of the syphilis spirochete

CISTERNAL PUNCTURE

Seven women in the Psychiatric Hospital were exposed to syphilis via cisternal puncture, the injection of syphilis into the spinal fluid from the back of the skull.

Dr. Cutler wrote in his Final Syphilis Report that the reason they inoculated the women in this fashion was to determine the effectiveness of the "blood-spinal-fluid" barrier, as well as to attempt to "shock" the women out of their epilepsy.

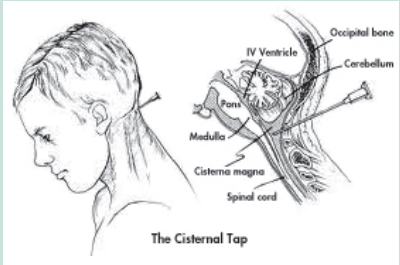


Diagram of a cisternal puncture.
From Alexander G. Reeves, M.D. and Rand S. Swenson, M.D., Ph.D., "Disorders of the Nervous System"

Two of the women subjected to cisternal puncture developed headaches and one lost the use of her legs for a period of time. Five of the seven women were eventually treated, one received penicillin only as a prophylaxis, and one never received any penicillin. One of the women who received penicillin later died.

to penetrate the intact mucous membrane of the gastrointestinal system to clarify "the problem of oral contagion through kissing and oro-genital sexual contacts."[521] To test this question: "[a] mixture of testicular tissue and supernatant fluid was well mixed. One cc. of this mixture was placed in a small beaker to which was added 20 ccs of distilled water. The patient was given the dose to swallow…"[522]

The researchers also sought to determine the effectiveness of the "blood-spinal-fluid barrier" in preventing *Treponema pallidum* "between the systems"[523] and "directly into the central nervous system,"[524] and to do so, they performed "hundreds" of cisternal punctures for diagnostic purposes, and several for intentional exposure.[525] According to Dr. Cutler in 1955, "deteriorated and debilitated epileptics" were given intracisternal inoculation as:

> "it was hoped that by shock of inoculation it might be possible to influence favorably their epilepsy. This experiment was undertaken at the expressed desire of the clinical director [Carlos Salvado] in hopes that he might be able to do something for these women who had been completely resistant to all types of anticonvulsive therapy. All of these were so uncontrollable that they had inflicted serious injuries upon themselves such as burns leading to contractures, blindness, wounds, etc., as a result of the loss of consciousness and motor activity due to epileptic attacks."[526]

To accomplish the intentional exposure experiment:

> "A cisternal puncture was made and about 10 ccs. of spinal fluid was removed. The syringe was withdrawn from the spinal needle, and the syringe containing the emulsion introduced 0.1 cc of emulsion. Some of the patients fluid was used (about 5 ccs.) to wash the spinal needle to ensure a complete dose of the spirochetes."[527]

Cisternal puncture, which involves the withdrawal of cerebral spinal fluid from the back of the skull, is particularly dangerous because of its proximity to the brain stem.[528] It would have been unclear at the time what types of reactions would occur from injection of foreign material, let alone infectious material, into the cerebral spinal fluid. Dr. Cutler was at least aware of some risk; he specifically mentioned in his 1955 report that even with all of the

punctures he performed, "none resulted fatally…"[529] Moreover, Dr. Cutler admitted that some subjects experienced "a simple bacterial meningitis" manifested by headaches and stiffness of the neck.[530] The inoculum made from lesions of other syphilitic subjects "was certain to contain secondary bacterial invaders…," he said.[531] Dr. Cutler reported that the symptoms subsided within a few days.[532] Several cisternal puncture subjects developed secondary syphilis and neurosyphilis, and one subject lost the use of her legs for over two months.[533]

Fellow researcher William Curth, when he was in Guatemala in the 1930s, deemed it "unwise" to attempt any type of spinal puncture "[o]wing to the many superstitions of the Indians."[534] Dr. Cutler reported in 1955, however, that the Psychiatric Hospital subjects "minded the procedure so little" that they lined up "day after day" for the puncture, to receive the reward of two packs of cigarettes.[535] There is no contemporaneous evidence to support this claim.

In February 1948, Surgeon General Thomas Parran, who supported the work in Guatemala, was replaced by Dr. Leonard Scheele. Dr. Mahoney told Dr. Cutler that they had "lost a very good friend and that it appears to be advisable to get our ducks in line."[536] Because of that, Dr. Mahoney said, "we feel that the Guatemala project should be brought to the innocuous stage as rapidly as possible."[537]

The researchers, however, continued with syphilis experiments in the Psychiatric Hospital through October 1948. They moved beyond their original questions and began testing issues such as the validity of accidental needle stick procedures for needles exposed to syphilis in clinics in the United States.[538] One subject underwent scarification followed by injection into the dorsum of the penis in hopes of producing a representative chancre specifically for the purpose of taking photographs.[539] In July, the researchers conducted one of the last Psychiatric Hospital intentional exposure experiments, which involved inoculating, through "a number of different techniques," all of the subjects who had been protected by a prophylaxis or had simply failed to become infected in previous experiments.[540]

Chancroid Experiments

Overview

Chancroid is a bacterial disease caused by *Haemophilus ducreyi*. It is spread through sexual contact. Signs of infection begin with the development of a small bump that transforms into an ulcer. It is diagnosed by examining the ulcers and checking for swollen lymph nodes. There is no blood test available to check for infection. Chancroid is treated with antibiotics and large lymph nodes can be drained with a needle or local surgery.

The researchers conducted experiments involving chancroid (the STD caused by the bacterium *Haemophilus ducreyi*) on 133 subjects in the Psychiatric Hospital and Army in October 1948. These experiments occurred several months after Dr. Mahoney informed Dr. Cutler that he would not renew the Guatemala grant.[541] Cutaneous inoculation of the arms and back was the exposure method used.[542] The primary goal of the chancroid experiments was to test the orvus-mapharsen prophylaxis, as Dr. Cutler felt it had held up well against syphilis and gonorrhea.[543] The researchers treated the soldiers they infected (131) with sulfathiazole (one gram per day for five days). Of the 133 subjects exposed to chancroid, 131 received some form of treatment.[544]

The injection site of a female psychiatric subject who was exposed to syphilis three times and received some treatment. *From the National Archives and Records Administration*

Psychiatric Hospital

The researchers conducted three chancroid experiments in the Psychiatric Hospital from October 10-12, 1948.[545] The researchers used 41 subjects in total, treating 39 of them.[546] They tested the orvus-mapharsen prophylaxis as compared to the U.S. Army pro kit.[547] Methods of inoculation were tested mostly on women's forearms and shoulders by scarification with a needle. Of note, one group of three women was inoculated three times in the arms before an infection occured.[548] Dr. Cutler noted that two of the women inoculated with chancroid in this experiment later died, one just 13 days after inoculation.[549]

PATIENT PROFILE: MARIO

Mario was a soldier in the Guatemalan Army's Honor Guard. His age was not recorded.

In March 1947 Mario was one of the soldiers who had sexual contact with commercial sex workers who had been inoculated with gonorrhea; he was then given a placebo treatment of 0.1cc sterile distilled water.

On October 23, 1948, researchers applied cultured chancroid material to scratches on Mario's arms and shoulder. Mario's right arm was then washed with orvus-mapharsen for 30 seconds; his left was washed with the standard U.S. Army pro kit. The next day, all three sites were swollen and indurated. Mario was treated with sulfathiazole ointment for five days.

Guatemalan Army

In October 1948, the researchers began testing the orvus-mapharsen prophylaxis for prevention of chancroidal infection in the Guatemalan Army.[550] Dr. Cutler had discussed this work with Dr. Tejeda in August and received approval to start work on chancroid as soon as the cultured material was available. For the rest of the soldiers, the researchers compared the orvus-mapharsen prophylaxis to the standard U.S. Army pro kit with 81 soldiers, all of whom were then treated.[551] They inoculated each soldier in three sites simultaneously: on two of the sites they tested a prophylaxis, and on one site they did not apply a prophylaxis so the subject could serve as his own control.[552] To infect the men, half-inch scratches were made by a hypodermic needle, just deep enough to draw blood.[553] Dr. Tejeda made the right arm scratch, Dr. Levitan made the left arm scratch, and Dr. Maza scratched the shoulder[554] (see Appendix II). After the scratches were made, 0.01cc of chancroidal inoculum "was placed on the abraided [sic] area and gently rubbed in by the flat surface of another needle."[555] After one, two, or four hours, the different prophylaxes were applied. Dr. Cutler noted in his Chancroid Experiment report that the researchers also took "moving pictures of patients with chancroid inoculation."[556]

Winding Down the Guatemala Experiments

Extension of the Grant

As the date of the Guatemala grant expiration approached, Dr. Cutler began to address what would happen to both the work and the facilities after his departure. He focused on ensuring that there would be sufficient time and money to complete the ongoing research and follow up. Dr. Mahoney's letters, on the other hand, focused on an orderly winding down of the "terminal phases of the Guatemala study."[557]

Funding to support the Guatemala research ran through June 1948, but the Research Grants Office at NIH, on request from the PASB, authorized continued work in Guatemala until the end of December, without additional funding.[558] Dr. Cutler urged Dr. Mahoney to seek additional financial support for the work, arguing "because of the importance of the study and because of our responsibility to the patients, it should be possible to justify a small grant for the second year to avoid any possible repercussions in the event of the complete expenditure of the present grant."[559] Dr. Mahoney dismissed that suggestion as "a new grant has some drawback in that it will require a progress report dealing with the work which has been accomplished. This we might not care to do at the present time."[560] Alternatively, Dr. Mahoney suggested that Dr. Cutler re-apportion the funds to carry out the essential follow-up services for two years.[561]

Disposition of the Laboratory

Dr. Cutler was also concerned about the fate of the laboratory facilities. He wrote to Dr. Mahoney in June 1948 to argue that they should leave the laboratory intact so that the Ministry of Public Health could continue to use the facility: "[i]n view of the wholehearted cooperation that we have received officially and unofficially from the Guatemala Medical profession and government Agencies and in view of the fact that we may later want to return for other work and will want to continue to enjoy the same cooperative relationship I feel that it would be a mistake not to leave the laboratory fully equipped and functioning upon our departure."[562] Dr. Cutler also requested that Dr. Abel Paredes Luna, a Guatemalan Public Health Service physician who worked with PASB, receive a fellowship at Staten Island and be given the opportunity to study with Dr. Mahoney.[563]

The Ministry of Public Health was also eager to continue the relationship. It expressed an interest in taking over the facility in the event that PASB did not want to continue to occupy it, and Dr. Luis Galich, who was the head of the Ministry of Public Health, discussed the matter with PASB personnel on several occasions, including during a trip to Washington in June 1948.[564] PASB Assistant Director John Murdock, for his part, agreed that long-term support for public health activities in Guatemala was always envisioned. "From the very beginning of the Project," Dr. Murdock wrote to Dr. Cutler in June 1948, "the staff at the [PASB] headquarters has felt that on the completion of

the research in which you are presently engaged, the Bureau in cooperation with health authorities of Guatemala would utilize the Laboratory as a training center for serologists and technicians and for standardization of other laboratories in Central America." Dr. Mahoney was equally enthusiastic, arguing that "this culmination is the most desirable possible and…the laboratory should be capable of extending a helpful service in the future."[565] Dr. Mahoney assisted in this regard, as is explained further in this report below, by identifying and facilitating the move of Ms. Genevieve Stout from the PHS to PASB to manage the laboratory in Guatemala after Dr. Cutler left.

Race and Secrecy during the Guatemala Experiments

Issues of Race

Dr. Cutler did not discuss the race of his experimental subjects as an ethical issue in his correspondence or reports, but race, as understood in that era, was clearly an important component of the Guatemala experiments. At the time, many physicians believed that syphilis affected different races differently. For example, Surgeon General Thomas Parran, described syphilis as being "biologically different" in African Americans, and said that African American women "remain[ed] infectious two and one-half times as long as the white woman."[566] In addition, the belief in some quarters that African Americans were sexually promiscuous was used to bolster arguments that African Americans were more likely to contract syphilis, and against treating the disease in that population.[567] These convictions played a role in the PHS Tuskegee Syphilis Study, in which Dr. Cutler also was involved as a primary researcher in the 1950s.[568] At Tuskegee, PHS doctors told syphilitic African American men from Macon County, Alabama, that they would receive free health care for their "bad blood." While doctors monitored the progress of the disease, the PHS doctors provided no treatment during the span of the experiment (1932-1972). The belief that syphilis was widespread among African Americans provided justification for the experiment to continue long after penicillin was proved to cure syphilis: "[a]s sickness replaced health as the normal condition of the [African American] race, something was lost from the sense of horror and urgency with which physicians had defined disease."[569]

While Dr. Cutler never discusses sexual promiscuity in his final reports, he does partially account for the low gonorrhea transmission rate by the

"duration of coitus" in the "culture group" involved in the Guatemalan Army experiments:

> "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. 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."[570]

In the 1930s, U.S. researchers also speculated that syphilis affected some Latin Americans differently from Caucasian North Americans or Europeans and that "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."[571] Some physicians believed that syphilis originated in Central America, leading the indigenous population to acquire immunity to it.[572] Just as U.S. researchers linked high rates of syphilis in African Americans with sexual promiscuity, W. Curth's *Syphilis in the Highlands of Guatemala* concludes:

> "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 ['Indian-Spanish crosses'], 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."[573]

Dr. Cutler mentioned in his Final Syphilis Report that he did not have access to ethnological information regarding their subjects, although he believed Guatemala City to be "approximately 85% Indian…"[574] 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]."[575] Dr. Spoto, the PHS onchocerciasis researcher, told Dr. Cutler that he need not explain the experiments at all to the "Indians" in the Penitentiary "as they are only confused by explanations and knowing what is happening."[576] Dr. Mahoney observed upon his visit to Guatemala City and his trip to the city of Chichicastenango that he did "not think much of the natives."[577]

Despite the pervasive belief that the effects of syphilis varied among races, and despite the underlying beliefs about the indigenous population that the researchers may have harbored, Dr. Cutler concluded in his Final Syphilis Report that the researchers found no evidence of "'racial immunity' in the Central American Indian."[578] He speculated that the authors of earlier articles claiming that such immunity existed had instead encountered the same serology-testing problems that the researchers experienced and were interpreting their diagnostic false positives incorrectly.[579]

Concerns about Secrecy

The Cutler Documents specifically elucidate contemporaneous efforts to limit knowledge about the experiments. "[a]s a result of experience elsewhere," Dr. Cutler wrote in 1955, "it was deemed advisable, from the point of view of public and personnel relations, to work so that as few people as possible know the experimental procedure."[580] In February 1947, the same month the researchers began sexual intercourse experiments in the Guatemalan Army, G. Robert Coatney, a PHS malariologist, wrote Dr. Cutler about Surgeon General Parran's interest in his work.

> "I saw Doctor Parran on Friday [February 14] and he wanted to know if I had had a chance to visit your project. Since the answer was yes, he asked me to tell him about it and I did so to the best of my ability. He was familiar with all the arrangements and wanted to be brought up to date on what progress had been made. As you well know, he is very much interested in the project and a merry twinkle came into his eye when he said, 'You know, we couldn't do such an experiment in this country.'"[581]

In May 1947, Dr. Cutler pointed Dr. Mahoney to a "Note on Science" that appeared in the April 27 *New York Times* regarding a new scientific advancement by syphilologist Dr. Harry Eagle (member of the Syphilis Study Section that approved the Guatemala project) and others.[582] The *New York Times* note read:

> "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. This 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*" (emphasis added).[583]

Waldemar Kaempffert, the *New York Times* science editor, authored the note.[584] Between the time when the note was published and when Dr. Cutler called Dr. Mahoney's attention to it, the researchers in Guatemala had begun injecting "living syphilis germs into human bodies"[585]—exactly what Kaempffert had asserted was "ethically impossible."

Eight days after the publication of the note in the *New York Times*, Dr. Mahoney wrote Dr. Cutler to say that Dr. Van Slyke had made a "hurried trip from Washington" to tell Dr. Mahoney that the same physician discussed in the note, Dr. Eagle, was, despite the conclusion in the *New York Times*:

> "…about to complain to the Surgeon General [Parran] that I have not been extremely enthusiastic about allowing him to enter the Guatemala study. As you may know, he has done considerable animal work in prophylaxis in syphilis by use of penicillin and can only prove the thesis by a human experiment."[586]

Dr. Mahoney opposed allowing Dr. Eagle to join Dr. Cutler in Guatemala because he "could not see wherein a study of that kind would have other than an academic value if an injection technique was employed…."[587] In addition, Dr. Mahoney "thought it would be of still less importance if an oral preparation of penicillin was to be studied as a prophylactic agent."[588]

When Dr. Cutler highlighted the *New York Times* report on Dr. Eagle's work to Dr. Mahoney, he noted that 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."[589] Knowing that Kaempffert had just written that the Guatemala protocol was "ethically impossible," Dr. Cutler confided to Dr. Mahoney that:

> "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."[590]

John R. Heller
From the National Library of Medicine

Also in May of 1947, Dr. Mahoney told Dr. Cutler that he had "gather[ed] the impression" that Dr. John Heller, who had joined Drs. Mahoney and Van Slyke in touring the Guatemala work the previous month, "would feel considerably more secure if we were to set up an advisory group of leading figures in the world of science to serve as a background for the study."[591] Dr. Mahoney said "I have never been a believer in this type of thing and I do not think that an advisory committee would help us greatly," but he admitted that they "might have to defer to political expediency."[592] Dr. Mahoney went on to say, "[t]here are several men whom I would not mind being associated with the work," but that there were "several other leading figures" that he thought "would be a distinct detriment."[593]

On June 22, 1947 (after artificial inoculation with gonorrhea and syphilis had begun in the Guatemalan Army, Penitentiary, and the Psychiatric Hospital), Dr. Cutler wrote to Dr. Mahoney "personally and unofficially" with several questions. Dr. Cutler first emphasized to Dr. Mahoney the staff's desire to conduct prophylaxis work, and the belief that the treatment work undertaken in the Penitentiary had supplied the necessary groundwork to secure "volunteers":

> "When the program was originally set up it was the plan to get the volunteers at the prison and pay them. You are well acquainted with the reasons why it was not thus carried out. Drs. Funes, Harlow and I have considered the matter carefully and feel that on the basis of our experience to date and [of] our work at the penitentiary which has resulted, we feel, in confidence in us, that we might approach the colo[nel] [Tejeda] and then the prisoners to secure volunteers first for more carefully [con]trolled gonorrhea work and then on syphilis. I feel that I can appri[illegible] colonel and the prisoners now on a more or less personal basis with [dis]cussion of our army experience and say that we still have unanswer[ed] [questions] which could be answered there. Doing it openly instead of [illegible] as we had considered would, we feel, give us much more mate [illegible] time in which to take advantage of it . . . . It is unfortunate that we have to work in such a guarded, even subterranean way, but it seems to be very necessary."[594]

Writing back, Dr. Mahoney endorsed the proposal, saying that the use of volunteers other than the type employed up to that point would be "more than satisfactory," as "our budget would stand for almost any fee for volunteers which you consider to be advisable."[595]

The second concern Dr. Cutler highlighted for Dr. Mahoney in the June 22 letter involved the replacement of Dr. Hugh Cumming by Dr. Fred Soper as the Director of PASB. Dr. Cutler asked Dr. Mahoney about the "extent of Dr. Soper's knowledge of our project"[596] and told Dr. Mahoney that when Dr. Soper arrived on July 7, apparently to visit in Guatemala, Dr. Cutler would inform him "the less he talks the better."[597] Responding to Dr. Cutler, Dr. Mahoney said that he had never met Dr. Soper himself and told Dr. Cutler "[y]ou will have to be guided by your own impressions as to freedom in discussing the

work." Dr. Mahoney did point out, however, that Dr. Soper was the responsible official of the study and as such was "entitled to complete confidence."[598]

In the same letter, Dr. Cutler also cautioned that, as Dr. Mahoney knew, "it is imperative that the least possible be known and said about this project, for a few words to the wrong person here, or even at home, might wreck it or parts of it."[599] Dr. Cutler told Dr. Mahoney that his staff had found that there had been "more talk here than we like" and that knowledge of the work had turned up in "queer places."[600] Dr. Cutler said that he believed the whole staff realized the confidential nature of the project but that husbands and wives also knew about the project, and with the "frequent social gatherings at which especially interesting topics may be discussed," it was "quite a temptation to talk more than is wise."[601]

Dr. Cutler told Dr. Mahoney that the "four of us in our project"[602] had discussed the matter and felt that "we should do all possible to keep knowledge of our project restricted."[603] To that end, Dr. Cutler requested permission from Dr. Mahoney to send the "detailed reports and discussions of our work directly to you and not through any other person here."[604] While the NIH Division of Research Grants under Dr. Van Slyke did not require more than annual reports from its researchers,[605] PASB required monthly progress reports from the Guatemala staff.[606] In order to fulfill this requirement, Dr. Cutler suggested that they could send PASB "the barest summaries of our progress."[607] Dr. Cutler also had sent monthly progress reports to VDRL on Staten Island,[608] but in June he requested that he might send these monthly reports directly to Dr. Mahoney and not through any other person in Guatemala. Dr. Cutler also told Dr. Mahoney that "any letters directly respecting our work" could be sent to him through "APO [Army/Air Force Post Office] if not urgent" or sent to him at the Ministry of Public Health.[609]

"In regard to the amount of gossip which the work in Guatemala had engendered," Dr. Mahoney later assured Dr. Cutler, "we are doing our utmost here to restrict our own conversations and those of others bearing upon the matter."[610] Dr. Mahoney had "been aware of considerable conversation and discussion" that was "being carried out in rather high places, much of which has not helped the work greatly."[611] Dr. Mahoney advised Dr. Cutler that they were forwarding all of Dr. Cutler's reports to Dr. Heller "in a way which we

hope will prevent their being read by unauthorized persons."[612] Dr. Mahoney added, however, that he hoped Dr. Cutler would "not hesitate to stop the experimental work in the event of there being so undue amount of interest in that phase of the study." Dr. Mahoney felt that "[i]t would be preferable to delay the work than to risk the development of an antagonistic atmosphere."[613] The intentional exposure experiments continued for 16 months longer.

THE POST-CUTLER CONTINUATION OF THE GUATEMALA EXPERIMENTS AND FINAL REPORTS 1948-1955

After Dr. Cutler left Guatemala in December 1948, several investigators continued with discrete aspects of the work he had begun. Genevieve Stout conducted a series of serology experiments that, while similar to Dr. Cutler's serology work, functioned as stand-alone experiments that she (and others) published independently.[614] Dr. Juan Funes, Chief of the Venereal Disease Section at the Guatemalan National Department of Health, and Dr. Carlos Salvado, the Director of the Psychiatric Hospital, carried out follow up on subsets of the subjects enrolled in the serology and intentional exposure experiments. Despite the time spent in Guatemala and the continuing observations of subjects that were funded, the Guatemala intentional exposure data were never published directly by any of the researchers.

Serology Experiments

Genevieve Stout at a convention of the Montana Society of Medical Technologists, 1953 *From Leo Carper*

PASB hired Genevieve Stout (on leave from PHS) in 1948 "to continue the laboratory as a training center for serologists and technicians" and to "promote the standardization of serological techniques of other laboratories in Central America and Panama."[615] PASB and the Ministry of Public Health agreed to make the new project a joint endeavor and planned to enter into a two-year contract to establish the new laboratory.[616] "Dr. Galich…agreed to assign the entire personnel of the present serological laboratory of Sanidad Pública [the Ministry of Public Health] to this laboratory and to pay their salaries," and PASB agreed to provide funding for a number of staff members as well.[617] Stout was instrumental in establishing the new venture; she arrived in August 1948 to "activate the Venereal Disease Laboratory and Training Center for Central America" and remained in Guatemala until August 1951.[618]

Stout and her staff conducted a number of serological experiments.[619] They primarily worked in six recently established laboratories across Central America, and in at least one experiment they worked with a total of 11 different laboratories.[620] Many of the experiments directed by Stout sought to standardize the Kahn Standard and VDRL slide test in use at these laboratories.[621]

Continuing Observations

PHS hired two Guatemalan physicians, Drs. Funes and Salvado, to continue "the observation of certain of the patient groups" after Dr. Cutler left Guatemala in 1948.[622] These appointments offered the opportunity to advance the scientists' careers. As Dr. Mahoney observed, "[w]e have always felt that it would be expedient to do everything possible to push Funes to the fore as the leading Central American syphilologist. I am sure that this will be worthwhile in the event of the broad program of venereal disease control work being developed in Central America."[623] Dr. Salvado also received a fellowship in the United States at that time.[624]

Dr. Funes's staff continued to collect data on residents of the Orphanage, inmates of the Penitentiary, individuals from the Psychiatric Hospital, schoolchildren, and the members of "various Indian tribes in the vicinity of Guatemala" who had participated in the experiments.[625] Dr. Funes's U.S. government personnel files indicate that he was hired to "advise concerning the clinical examinations of treated patients, their re-treatment as may be required, the collection of blood specimens for serologic examinations at periodic intervals, the preparation and shipment of all blood specimens collected for serologic examination" to the United States, and "the submission of such reports as may be necessary for the completion of the study of this patient group."[626]

Dr. Funes's staff collected samples from subjects and, as agreed, shipped them to the United States for analysis.[627] Based on the one report available in the Cutler Documents, they followed approximately 248 people from the mental institution, completing 243 blood draws and 170 lumbar punctures.[628] Several of those subjects tested positive for syphilis during the follow-up experiments.[629] The subjects from the Psychiatric Hospital were followed until at least 1953.[630] The published work resulting from the Guatemala experiments also indicates that Dr. Funes continued to do serological testing on the children at the Orphanage until at least 1949.[631]

PUBLICATION OF THE GUATEMALA DATA

After leaving Guatemala, Dr. Cutler joined a World Health Organization (WHO) Disease Demonstration Team and moved to India. From April 1949 to July 1950, the team worked to establish a "venereal-disease control demonstration" in various parts of the country and teach advanced methods of control for STDs.[632] Over the next several years, while continuing to serve as a PHS officer and earning a master's degree in public health from Johns Hopkins University at the same time, Dr. Cutler prepared his final reports on the STD studies in Guatemala.[633] The Chancroid Experiment report is undated, but Dr. Cutler sent this document to the Director of the VDRL in Chamblee, Georgia, in September 1952. Dr. Cutler asked the Director to keep the report confidential.[634] Dr. Cutler's Experimental Studies in Gonorrhea report is dated October 1952. He marked it as "SECRET-CONFIDENTIAL" and edited out identifying details.[635] The Final Syphilis Report is dated November 1955. No evidence shows that the syphilis or ghonorrhea reports were provided to anyone.[636]

While the results of the serological experiments were published in several different articles,[637] and the intentional exposure experiments were referred to indirectly in later publications,[638] the Commission found no evidence that Dr. Cutler's final reports or the results of the exposure and prophylaxis experiments were submitted for peer review or published. There are several published examples in which Dr. Cutler discusses data from these experiments but misleadingly cites another published study. In these cases, the published study cited does not actually support the data presented.[639] In addition, the Guatemala experiments are notably absent from historical reviews of STD research authored by the researchers.[640]

An enormous amount of money, time, and effort went into the Guatemala experiments, and the exact motivations for hiding the results is unclear, particularly because the VDRL researchers published widely on their research activities, including other STD intentional inoculation experiments during the time and the serology results from Guatemala.[641]

AFTERWORD

Many of the key investigators involved in this case continued to work in medical research and clinical care after the experiments ended. Dr. Cutler continued his career with PHS through the 1950s and much of the 1960s, during which time he held several positions of note. During his time working in the PHS Venereal Disease Division from 1951 to 1954, Dr. Cutler, along with Dr. Sidney Olansky, became a lead researcher for the ongoing PHS study of syphilis among rural African Americans in Tuskegee, Alabama.[642] In 1955, as Acting Chief of the PHS Venereal Disease Division, Dr. Cutler supervised a syphilis study that used prisoner subjects at Sing Sing State Prison in New York.[643] In 1961, Dr. Cutler became Assistant Director and later Deputy Director of PASB.[644]

In 1967, Dr. Cutler retired from PHS and joined the faculty at the University of Pittsburgh, where in 1968 and 1969, he served as the Acting Dean of the Graduate School of Public Health.[645] While at Pittsburgh, he remained engaged in research concerning the prophylaxis of STDs. Dr. Cutler received a contract from the U.S. Agency for International Development in 1970 to study the use of a vaginal contraceptive, Conceptrol Cream, as a prophylaxis against gonorrhea.[646] Although early versions of the proposal called for clinical studies outside the United States in countries such as Jamaica, Taiwan, and Guatemala, the award was granted only for a local field trial in Allegheny County, Pennsylvania.[647] Dr. Cutler died on February 8, 2003.[648]

Dr. Richard Arnold remained with VRDL until 1951, when he became Chief of Technical Services at the National Heart Institute within NIH.[649] In 1959, Dr. Arnold rose to the position of PHS Assistant Surgeon General for Personnel and Training.[650] He retired from PHS in 1963 and joined the Missouri State Health Department, where he later became the Medical Director for the Missouri Crippled Children's Service.[651] Dr. Arnold died on October 17, 1992.[652]

Dr. Juan Funes remained Chief of the Venereal Disease Section of the Guatemalan Department of Health.[653] He also remained a special consultant of the Venereal Disease Division of the U.S. PHS from 1948 to 1956.[654] By 1950 Dr. Funes had become Vice-Chairman of the WHO Syphilis Study Commission.[655] In 1954, he became Chief of the National Anti-Venereal Campaign of Guatemala.[656]

Dr. John Mahoney remained the director of the VDRL until 1950, when he retired from the PHS and became New York City Health Commissioner. He continued to serve the PHS as an uncompensated special consultant until his death in February 1957.[657]

Surgeon General Thomas Parran retired from the PHS in 1948 and became the first head of the Graduate School of Public Health at the University of Pittsburgh. After his retirement, Dr. Parran continued to serve in both paid and unpaid consulting positions to the U.S. government. He also remained a leader in the international and public health fields, serving on many national boards and commissions. Dr. Parran died on February 16, 1968.[658]

Dr. Van Slyke left the Division of Research Grants in August 1948 to become director of the newly-established National Heart Institute. He served there until December 1952, when he became Associate Director (for extramural programs) of the National Institutes of Health. He retired from the PHS in 1959. He continued to serve the PHS as a paid consultant through 1963. In 1957, he received the Albert Lasker Award of the American Public Health Association "for distinguished contributions to the nation's health in advancing the foundations of public health progress—medical research and staff training."[659]

REVIEWING ETHICAL STANDARDS IN CONTEXT

In the Commission's view, the Guatemala experiments involved unconscionable violations of ethics, even as judged against the researchers' own understanding of the practices and requirements of medical ethics of the day. Many of their actions disregarded principles widely accepted as applicable across time, as well as the standards of our own time that are embodied in the ethics and regulation of biomedical research today. The Guatemala experiments could not be approved under the current system for protecting human subjects in U.S.-funded research. Widely discussed cases in the post-World War II era with some similar features have led to a greater appreciation and articulation of the moral principles underlying medical research. A clear consensus has emerged that medical research must not undermine the very human flourishing it seeks to advance in future patients. The Guatemala experiments and other troubling violations of this norm that have come to light in the last 60 years truly shock the conscience, precisely because of their medical context.[660]

Current Human Research Protections and Ethical Requirements of Our Own Time

The standards of ethical human subjects research today are expressed in the medical ethics literature and through government regulations and international covenants and declarations. All of these documents share certain principles. Informed consent, called for by the principles of autonomy and dignity, is a cornerstone, as are requirements for minimization of risks, a reasonable balance of risks and benefits, sound scientific justification, protection of privacy and confidentiality, and special protections for those who are especially vulnerable, including minors, prisoners, and those with impaired decision making.[661] Crucially, a careful and accountable independent review is required prior to the initiation of clinical research.

None of these elements were satisfied in Guatemala. As the Commission's investigation shows, there is no evidence that consent was sought or obtained from the individual subjects who were the subjects of the research.[662] On the contrary, there were examples of active deceit.[663] Individual experiments appeared to have been haphazardly designed and initiated with little apparent appreciation for the relative risks and benefits to research subjects or the articulation of a sound scientific justification for particular research designs.[664]

Many of the experiments, particularly those involving intentional exposure to syphilis, gonorrhea, or chancroid, would fail to satisfy any serious assessment of risks to individual subjects in medical research.

The research specifically included populations that are currently recognized as vulnerable and thereby deserving of additional safeguards to ensure adequate protection for human subjects. Prison inmates, institutionalized and mentally disabled individuals, and children were among the groups most frequently included in the Guatemala experiments. Federal regulations, international codes, and the ethics literature today all acknowledge that research involving these groups raises unique issues requiring additional attention.[665] These requirements recognize the challenges in ensuring adequate informed consent in vulnerable populations as well as the risk that members of these groups could be unjustly included primarily as convenient sources of research subjects.

The researchers in Guatemala and their immediate supervisors at the VDRL appear to have had considerable latitude in the design and conduct of individual experiments, with little evidence of substantive independent review for the conduct of the research. On the contrary, substantial evidence reflects efforts by the researchers to limit knowledge of the Guatemala activities as much as possible to colleagues predisposed to support it.[666] The experimenters in Guatemala, both those from the United States and their local colleagues, consistently failed to act in accordance with our contemporary understanding of human rights and morality in the context of research.

Longstanding Ethical Principles

In the Commission's view, the Guatemala experiments involved gross violations of ethics as judged not only in light of modern human research ethics, but also against the researchers' own understanding of medical ethics practices and requirements of the day. The Commission believes not only that there were moral wrongs carried out in Guatemala, but also that some of the participants were morally culpable and blameworthy for these wrongs. Admittedly, making moral judgments about past actions and agents is not a straightforward process and is not without its hazards. In this case, however, the usual challenges associated with making moral judgments about the past are not substantial obstacles for the Commission in reaching its conclusions because many of the actions undertaken in Guatemala were especially

egregious moral wrongs and because many of the individuals involved held positions of public institutional responsibility.

Careful consideration of the ways these actions violated ethical principles both honors the memory of these victims and helps ensure that society learns from these offenses. To that end, the Commission turns to a set of fundamental moral commitments that find expression in moral philosophy, theological traditions, and more highly specified codes, rules, and regulations. An ethical assessment of the Guatemala experiments does not, strictly speaking, require a comprehensive set of ethical principles, which would be more usefully invoked to evaluate experiments that do not so blatantly violate widely recognized fundamentals. Instead, for the purpose of creating a structure upon which to evaluate past violations and in order to help inform future practices, the Commission elucidates three longstanding and widely accepted moral principles of particular relevance to the Guatemala experiments. These moral principles are also fitting to guide current conduct, with exceptions allowed only with stringent justification. Each of these three principles is necessary, but no single principle is alone sufficient for the justification of an experiment involving human subjects.

1) One ought to treat people fairly and with respect.

Treating persons fairly and with respect prohibits choosing more vulnerable people upon whom to experiment when research could be done with less vulnerable populations. This principle also requires special steps and precautions to protect those who cannot protect themselves or give informed consent under any circumstances. Vulnerable groups should not disproportionately bear the burdens of research. The violation of this principle of respect becomes all the more serious an offense when the risks of research are imposed on vulnerable populations without their consent, or on those who are both vulnerable and incapable of providing consent. As stated in the first sentence of the Nuremberg Code, "the voluntary consent of the human subject is absolutely essential."[667]

The Guatemala research targeted some of the most vulnerable groups in any society (prisoners, conscripted soldiers, institutionalized psychiatric patients, and children), and also was conducted in an underdeveloped country with pervasive social inequalities that exacerbated their vulnerabilities. Such

populations are given special protections in modern society because of their limited abilities to protect their own interests. The ethical requirement of consent is intended specifically to enable persons to be treated respectfully and in accord with their understanding of their interests, and in more limited cases according to the judgment of those who are in the best position to speak for them. In the Guatemala experiments the most vulnerable populations appear to have been targeted specifically because of their inability to protect themselves or to have others represent their interests. As explained below, even at that time there was a basic conception of voluntary consent and an understanding of differential vulnerability in various populations. Not only is there no record of consent to participation in the experiments, there are also several examples of active deceit on the part of the researchers.

2) One ought not to subject people to harm or the risk of harm, even with their consent, unless the risk is reasonable and there is a proportionate humanitarian benefit to be obtained.

Morally sound scientific research involving human subjects includes this humanitarian principle: the degree of risk should be minimized and never be disproportionate to the humanitarian importance of the problem to be solved by the experiment. This principle was recognized in the Nuremberg Code: experiments on human subjects that risk harm "should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature."[668] Careful and scientifically sound research design is a *sine qua non* of medical ethics, without which it is unethical to ask persons to submit themselves as experimental subjects.

The Guatemala experiments were not carefully designed by either current or contemporaneous understandings of appropriate scientific methods: modes of transmission were used that supervisors warned would not withstand scrutiny, and data were altered or excised before inclusion in summary reports. Aggravating the failure to ensure valid methodology is the fact that not all of the patients given STDs were treated, making the risks clearly unreasonable. Therefore, not only did the researchers put their subjects at gratuitous risk, including risk of death in some cases, through this faulty scientific design, a violation of the prohibition against unjustifiable harm, but the unreliability of the data produced in this fashion further degrades the subjects' sacrifices.

3) One ought not to treat people as mere means to the ends of others.

Subjects involved in experiments must not be treated as mere means to the ends of researchers or supervisors.[669] It follows that researchers must obtain the informed consent of individuals before experimenting on them as a necessary, but not sufficient, condition. Informed consent also rules out deception, unless individuals are informed and agree to be part of a practice that may entail deception. In that case they are not treated as mere means, as they have been informed and have agreed to be part of a practice that includes potentially justifiable deception. Without this condition another critical element of the Nuremberg Code cannot be satisfied, that the experimental subject must be free to withdraw from the study at any time.

The individuals involved in the Guatemala experiments were used as mere means to further the ends of researchers and those responsible for their caretaking in a way that seems to ignore even the rudimentary consideration they should have been granted as human beings. Even a praiseworthy goal (in this case, finding effective prevention of STDs) does not justify the use of persons as mere means to that goal. Sophisticated expressions of moral philosophy and governmental or professional codes of research ethics are built upon the recognition of violations of human dignity, violations that characterize many of the practices involved in these experiments. The researchers and government officials who were involved in these experiments, both in the United States and in Guatemala, acted in ways that violated basic moral norms.

Morally serious persons may disagree about the specific articulation of the elements of a list of principles such as those described above, and about their ultimate moral justification. As guides to conduct, they admit to exceptions and are subject to interpretation and application. Nonetheless, the Commission finds that, to a shocking degree, actions undertaken as part of the Guatemala experiments unjustifiably and often grossly violated the widely shared, basic sense of human decency encoded in such principled elements of the moral life.[670] Although much of the discussion that follows draws upon a fine-grained historical examination of formalized research practices and norms at that time, the Commission does not want to lose sight of a more basic point: many of the actions performed as part of the Guatemala project were unconscionable and those responsible for those actions were morally blameworthy.

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

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.

Evaluating General Mitigating Arguments

Mitigating factors can moderate or reduce the blame deserved by individual actors, as well as confound the determination of individual blameworthiness, independent of judgments regarding the rightness or wrongness of the actions themselves. Mitigating conditions of a general nature include:

- Non-negligent factual ignorance;
- Culturally induced ignorance about relevant moral considerations;
- Evolution in the interpretation and specification of moral principles; and
- Indeterminacy in an organization's division of labor, with the result that it is unclear who has responsibility for implementing the commitments of the organization.[694]

Examining these four potentially mitigating conditions in the context of the Guatemala research, the Commission finds, first, that the researchers were well aware of the factual circumstances. While much may have been unknown about the prevention and treatment of the STDs being studied in Guatemala, the devastating impact of the diseases themselves on individuals and communities was well understood. It was exactly this knowledge of the consequences of STD infection that motivated the researchers to pursue this research program despite the ethical objections they knew would be voiced if others learned of their work.[695]

It is true that during the period 1946 to 1948 the interpretation and specification of research ethics principles were evolving. However, these researchers constituted a small and coherent professional network that had previously engaged in analogous studies in the United States. The *de facto* standards that they applied in the Terre Haute prison, particularly with respect to written consent, stand in stark contrast to those in the Guatemala experiments. The extensive attention given in the former case to questions regarding research involving intentional infection with STDs, consent procedures, and unique issues related to research in prisons provides clear evidence that the Guatemala investigators were familiar with such concerns. Although the interpretation and specification of moral principles may have been gradually evolving during this period, the Terre Haute work indicates that these concepts were not unfamiliar to the researchers. In this sense, the defense of culturally induced moral ignorance is inadequate.

There is another sense of culturally induced moral ignorance, one that may have stemmed from the small circle of researchers themselves. Perhaps they believed that culturally available moral concerns were not binding on them because they took their research to be more important than respecting the readily available human subjects, obtaining their consent, and avoiding needless harm. They might have known that these were moral concerns to which the public expected them to adhere, hence their efforts at secrecy so as not to be subject to criticism from their own medical colleagues and from the public. But even if they took these moral concerns as purely practical side constraints, to be evaded if at all possible, this does not lessen their culpability. Indeed, it makes them more arrogant, for they then would not have the excuse of ignorance or compulsion. We may find this conclusion especially disconcerting

when those who cannot be excused are physicians and public officials who are dedicated to finding cures for serious diseases. Nonetheless, they bear moral responsibility when they put their actions and their science above moral rules on the ground that their science is more important than the rules. Neither a bioethics commission nor the American people should accept such an excuse.

Again, the documentary evidence indicates that the investigative team in Guatemala recognized the relevant moral considerations—even if these moral considerations were devalued by some as mere defensive measures against bad publicity. And, given their positions of scientific and medical responsibility, they could and should be held culpable for a failure to recognize the moral considerations of their work. Yet these concerns were routinely ignored or dismissed in favor of the continued pursuit of new scientific knowledge with minimal external interference.[696] An appreciation of possible objections to their work on moral grounds (whether they agreed with these objections or not), and the practical consequences of those objections for the future of the activities in Guatemala, is reflected clearly in the extensive interest in minimizing knowledge of the research program beyond a small circle of insiders associated with the VDRL.[697]

Why was Guatemala found to be such an opportune environment for these excesses? Among the relevant factors was surely the eager cooperation of Guatemalan authorities. As well, it is difficult to ignore the possibility that class, ethnic, and racial differences were among the factors that numbed the researchers to the larger moral context of their work. It is plausible that once they initiated the research program, the researchers became increasingly inured to the ethical violations of which they were a part. Not only was the VDRL itself a limited circle of insiders, the researchers in Guatemala operated as a still smaller, mutually reinforcing group culture far from home, distant from peers, and in a very different societal environment from that of the United States. These factors may have contributed to a collective numbing to ethical norms, a hypothesis that may help to explain the conduct of the researchers but by no means excuses it.

It cannot be said, however, that the chain of command was faulty with respect to professional responsibility in the context of the Guatemala research. Despite the physical distance between the research sites and the

relevant U.S. administrative entities responsible for oversight, correspondence between Dr. Cutler and his superiors at the VDRL demonstrates a clearly defined, well-understood hierarchy regarding the design and conduct of the research. Complementing this correspondence are references to site visits conducted by more senior officials in PHS and evidence of the Surgeon General's own knowledge of the work being conducted under his administrative purview. Rather than a faulty chain of command, there was a failure of both professional and institutional leadership in disregarding the excesses of the Guatemala experiments.

Evaluating Historically Specific Mitigating Arguments

There are other, more historically specific arguments that might also be offered to explain the actions of and potentially mitigate the culpability of the physicians and government officials who participated in the Guatemala experiments:

- That the experiments were conducted for national security purposes and therefore the conventional standards of medical ethics could be waived;
- That there was a powerful public health need for such experiments due to the prevalence of STDs such that the balance of risk and benefit justified the effort, however much it might compromise individual rights; and
- That although the conditions set out by Dr. Ivy of the AMA were cited as conventional, in fact, at the time, understanding of the moral norms for research by scientists and others was evolving and rules and principles were just beginning to be codified.

The Radiation Experiments Commission addressed the national security defense when it found that "for the period 1944 to 1974 there is no evidence that any government statement or policy on research involving human subjects contained a provision permitting a waiver of consent requirements for national security reasons."[698] However, there is evidence that government agencies in this period decided not to disclose certain experiments to the public for fear of government embarrassment and potential legal liability.

It could be argued that the case of ionizing radiation experiments differed from that of STDs because the latter were of immediate and pressing concern

for military readiness, as had been shown during World War II.[699] Experiments involving ionizing radiation were highly speculative and the benefits remote, whereas the need for improvements in the treatment and prevention of STDs was intense[700] and, especially with the advent of penicillin, seemingly within reach. But the Guatemala experiments were initiated after the war had ended and while the country was at peace, so there was no immediate military necessity in the form of an existential threat to the United States. A more plausible argument is that there was a pressing public health need to address these human scourges that had caused, and continued to cause, vast suffering throughout the world.

There is no question that campaigns for the eradication of dire threats to the public health have often been justifiably aggressive, in accordance with a strongly utilitarian moral philosophy. However, not all threats to the public health are so grave that any and all interventions may be justified by a crude utilitarianism. Whether the threat to public health posed by a particular disease outbreak is severe enough to justify aggressive tactics that temporarily suspend our usual ethical norms is itself an important question of ethics and policy.[701] Only after such an assessment is decided in favor of suspending our usual ethical norms should the question be considered whether there is sufficient justification for selecting one location or population to be subjected to overriding typical rights.

Moreover, when the public health activity in question is experimental (as was the case in Guatemala), the justificatory bar must be set still higher in order to comply with the principles and requirements of research involving human subjects. The corresponding ethical burden to justify the selection of locations and populations is considerably greater in the context of human subjects research. In research, one justification for selecting a certain site or population could be that the disease does not occur with adequate frequency in other places to make experimental work feasible elsewhere. This was one of the justifications for the location of the Tuskegee syphilis study. Again, however, the rationale for place or population selection does not excuse experimenters from other ethical requirements, such as informed consent, and limiting foreseeable harm, requirements that were grievously and notoriously violated in the Tuskegee experiment and elsewhere.

No such justification was available in the Guatemala experiments. Rather, it is likely that the Guatemalan sites were chosen precisely because they would be out of public view in the United States and beyond the reach of our laws and research norms. The subjects may have been viewed as powerless and easily available; and local authorities were not merely cooperative but enthusiastic partners. In Guatemala, the diseases were not especially endemic to the local community, as was the case in Tuskegee.[702] Given the focus of the Guatemala research on prophylaxis and diagnosis, the majority of the subjects were not already infected, again unlike Tuskegee. A "methodological" justification was the opportunity to use commercial sex workers—whose work was legal in Guatemala but not in the United States—as vectors to study STDs "as acquired in the usual manner."[703] A possible remaining but clearly unacceptable explanation for choosing Guatemala would reflect the notion that the Guatemalans were a suitable, if not preferable, experimental population by virtue of poverty, ethnicity, race, remoteness, national status, or some combination of these factors. Stated differently, the commercial sex workers, prisoners, psychiatric patients, and soldiers may have been seen as convenient and, on the whole, captive. But convenience, however expedient, is by itself no moral justification, as the *Belmont Report* cogently concluded decades later.[704]

The fact that local authorities in Guatemala made their institutions available to the U.S. researchers similarly fails to provide any moral justification. Perhaps the U.S. officials and physicians convinced themselves that the Guatemala authorities somehow represented the interests of the potential subjects, an argument that is hardly plausible under the circumstances, and in any case not one that was forthrightly stated or likely to be persuasive upon scrutiny. The materials available to the Commission provide only limited insight into the decision-making processes of the Guatemalan health authorities and government officials, but the U.S. researchers had ample authority, experience, and opportunity to have prevented moral wrongs from occurring, independent of the decisions and actions of their Guatemalan partners. The cooperation by the Guatemalan health authorities and government officials fails to provide moral justification for the actions of Dr. Cutler and others. Rather, cooperation by Guatemalan health authorities and government officials also reveals their culpability in allowing these wrongs to be perpetrated.

One final view that some suggest might mitigate the moral culpability of the participants, though it will not excuse it, is that the ethical conventions of that era were evolving and were frequently violated in practice. On this view, it would be unfair to hold certain researchers to standards to which many researchers did not abide. Depending on the stakes involved, we might not require professionals to place themselves at substantial personal risk, including compromising their career prospects, in order to change the status quo by insisting on certain ethical norms. Here it is important to distinguish between moral heroism, which is not morally required of an individual, although it is praiseworthy, and simply the act of standing up against a bad practice. The failure to stand up to a bad practice cannot be excused. In this case the stakes for failing to stand up to practices as bad as those in the Guatemala experiments were high indeed. They extended not only to the dignity but also to the health and well-being of highly vulnerable persons. The discussions about using different techniques of exposure to pathogens of one group or another suggest that the vulnerability of their subjects was apparent to these investigators.[705] Additionally, the doctors involved were not all subordinate or junior in their status; some were in positions of high responsibility in government. Their failure to exercise moral leadership cannot be excused, and their failure led to practices that were so wrong as to be fairly characterized as heinous. Those who committed these actions were not under any unusual pressure to do so. They thought that they were above the rules, and went to some lengths to shield themselves from normal institutionally imposed scrutiny.

The Guatemala Experiments—Looking Back, Looking Ahead, and Apportioning Blame

The Guatemala case differs from some potentially analogous cases in the post-World War II period in ways that facilitate the process of reaching moral judgments. This comprehensive discovery and review of historical documents reveal a great deal of discussion among the protagonists that demonstrates their awareness of relevant ethical considerations and the corresponding reactions that would follow if their activities became widely known. This is true even during a time of evolution of interpretation and specification of moral principles in human research. In other words, the contemporaneous actions and words of the principal actors constitute their own moral indictment.

As a direct result of the decisions and actions of the PHS researchers and their superiors, profoundly vulnerable persons, some in the saddest and most despairing states, had their bodies systematically and repeatedly violated. An intense and uncritical commitment to advancing knowledge under convenient conditions does not account for the suspension of moral sensitivity that should have been stimulated by the suffering of their fellow persons, suffering that the researchers themselves in some cases grievously aggravated.

It is clear that many of the actions undertaken within the Guatemala experiments were morally wrong. The Commission further concludes that the individuals who approved, conducted, facilitated, and funded these experiments are morally culpable to various degrees for these wrongs. The Commission reaches these conclusions on the basis of basic moral principles, the moral norms that were articulated at the time, the strikingly contrasting practices in Terre Haute, and the statements of the protagonists themselves during the period of work in Guatemala. Our moral norms today also endorse this judgment for reasons fully compatible with the norms—and the reasoning supporting them—that were available to the researchers and public officials involved in the Guatemalan experiments. This is not a judgment that the Commission reaches lightly, but one that it feels compelled to reach by the facts of the case and by the logic of the moral argument.

Although some individuals are more blameworthy than others, the blame for this episode cannot be said to fall solely on the shoulders of one or two individuals. The unconscionable events that unfolded in Guatemala in the years 1946 to 1948 also represented an institutional failure of the sort that modern requirements of transparency and accountability are designed to prevent. In the final analysis, institutions are comprised of individuals who, however flawed, are expected to exercise sound judgment in the pursuit of their institutional mission. This is all the more true and important when those individuals hold privileged and powerful roles as professionals and public officials. One lesson of the Guatemala experiments, never to take ethics for granted, let alone confuse ethical principles with burdensome obstacles to be overcome or evaded, is a sobering one for our own and all subsequent generations. We should be ever vigilant to ensure that such reprehensible exploitation of our fellow human beings is never repeated.

TABLES AND FIGURES

Table 1: The Cutler Documents

DOCUMENT NAME	DATE	DESCRIPTION	DISTRIBUTION	CONCLUSIONS
Correspondence	Aug. 1946–Nov. 1948	Hundreds of written exchanges regarding a variety of topics, including letters on formal letterhead as well as informal discussions among colleagues	Includes correspondence between Drs. Cutler, Arnold, Mahoney, Tejeda, and many other affiliates of the study	N/A
Experimental Logbooks	Various	The two "Daily Laboratory" notebooks contain handwritten lists of subjects and potential subjects alongside the results of various tests The two "Studies in the Military" notebooks vary in their contents	Unknown	N/A
Subject Note Cards	Various	Individual records of subjects in the Penitentiary and Psychiatric Hospital	Unknown	N/A
Photographs	Various	A total of 594 photos were taken, including 372 photos of infected subjects from the Psychiatric Hospital and Penitentiary, 215 portraits taken of subjects in the Psychiatric Hospital, and seven photos of prophylactic procedures	Dr. Heller was "interested in having photographic records …" Photographs were also taken so Dr. Mahoney could "have all information necessary to do any talking that you desire" Dr. Ingalls H. Simmons asked the PHS team for photographs "of the common venereal lesions for the Army teaching program," and Dr. Cutler sent "photographs of typical venereal lesions" to Dr. Simmons to be used for "teaching filmstrips"	N/A

DOCUMENT NAME	DATE	DESCRIPTION	DISTRIBUTION	CONCLUSIONS
Chancroid Experiment	Undated, but Dr. Cutler sent the document to the Director of the Venereal Disease Research Laboratory at Chamblee, Georgia, in Sept. 1952	Describes the effectiveness of the orvus-mapharsen prophylaxis	Sent to the Director of the VDRL at Chamblee, Georgia, but with some information from an original draft censored; the Director was asked to "handle and treat this document as confidential" (emphasis in original)	Orvus-mapharsen prophylaxis was not effective
Experimental Studies in Gonorrhea	Oct. 29, 1952	Describes the effectiveness, side effects, and drawbacks of prophylactic methods (10% argyrol solution, the U.S. Army pro kit, penicillin, and orvus-mapharsen)	Marked as "SECRET-CONFIDENTIAL" with some identifying details masked (e.g., identities of physicians involved) No evidence that Dr. Cutler shared this report with anyone	All tested prophylactic methods were effective, but the orvus-mapharsen solution was found to be the best option
Final Syphilis Report	Feb. 24, 1955	Describes different methods of prophylaxis against syphilis Describes effects of penicillin in treatment of syphilis Describes use of serology testing Describes understanding of syphilis in man	Not marked "confidential," and no indication from the documents that Dr. Cutler did not intend it to circulate, but also no record that Dr. Cutler ever provided this report to any outside party	The highest degree of prophylactic effectiveness was obtained with either orvus-mapharsen, calomel ointment, oral penicillin, or intravenous mapharsen Penicillin almost invariably cured primary and secondary syphilis No specific serology conclusions were made Various observations of syphilis in man were recorded

Table 2: Individuals Involved in the STD Experiments in Guatemala

NAME	AFFILIATION	TITLE	KNOWN ROLE IN GUATEMALA EXPERIMENTS
Aguilar, Casta Luis	Guatemala Ministry of Public Health	Director of Research Laboratory	Guatemalan government participant in the syphilis experiments Co-author of orvus-mapharsen study in sex workers with Dr. Funes
Aragon, Dr. Hector	National Orphanage of Guatemala	Director	Approved the serological experiments Published on serological data with the researchers and spoke on the topic at the Second Congress of Venereal Diseases in Central America in 1948
Arnold, Dr. Richard C.	U.S. Public Health Service (USPHS), Venereal Disease Research Laboratory (VDRL), Staten Island, New York	Senior Surgeon, USPHS Director of Syphilis Research, VDRL (1939-1951)	Secondary supervisor of the experiments Received Dr. Cutler's reports on the experiments Visited the Guatemala site at least two times, 1947 and 1948
Chinchilla, Dr. Roberto Robles	Central Penitentiary, Guatemala City	Director of Medical Services	Guatemalan government participant Wrote Dr. Cutler thank you letter that was included in Dr. Cutler's Final Syphilis Report
Cutler, Dr. John C.	USPHS / PASB, Guatemala	Senior Surgeon, USPHS Director, STD Research in Guatemala	Principal on-site investigator, Guatemala Leader of the intentional exposure experiments
Eagle, Dr. Harry	USPHS / National Institute of Health (NIH), Syphilis Study Section	Member, Syphilis Study Section Commissioned Officer, USPHS (1936-1961) Director, Laboratory of Experimental Therapeutics and Venereal Disease Research Laboratory, Johns Hopkins School of Hygiene and Public Health and the Public Health Service Hospital in Baltimore (1936-1948)	Member of the Syphilis Study Section that approved the Guatemala research grant Requested to do own prophylaxis research on subjects in Guatemala

NAME	AFFILIATION	TITLE	KNOWN ROLE IN GUATEMALA EXPERIMENTS
Funes, Dr. Juan M.	Guatemala Ministry of Public Health	Chief, Venereal Disease Section, National Department of Health Special Consultant with the Venereal Disease Division, Bureau of State Services, USPHS (1948-1956)	Proposed that the researchers go to Guatemala while a Fellow at the VDRL Involved in the referral of sex workers with STDs from the Venereal Disease and Sexual Prophylaxis Hospital (VDSPH) to Dr. Cutler Active participant in exposure experiments Continued to collect data on individuals involved in the VDRL experiments until 1953
Funes, Rolando	Guatemala Ministry of Public Health	Serologist	Guatemalan government participant in the syphilis experiments
Galich, Dr. Luis	Guatemala Ministry of Public Health	Director	Involved in the referral of sex workers with STDs from the VDSPH to Dr. Cutler Oversaw transfer of laboratory from the researchers to the Guatemalan government Sought and received permission for VDRL to use serology data in 1948
Harding, Virginia Lee	USPHS / PASB, Guatemala	Bacteriologist, USPHS	Worked in laboratory
Harlow, Dr. Elliot	USPHS / PASB, Guatemala	Assistant Surgeon, USPHS	Assisted with the intentional exposure experiments
Heller, Dr. John R.	USPHS	Chief, Venereal Disease Division (1943-1948)	Member of the Syphilis Study Section that approved the Guatemala research grant Requested photographs be taken during the experiments Received Dr. Cutler's reports on the experiments Visited the Guatemala site at least once in April 1947
Levitan, Dr. Sacha	USPHS / PASB, Guatemala	Senior Surgeon, USPHS Assistant Director, STD Research in Guatemala	Active participant in the intentional exposure experiments
Luna, Dr. Abel Paredes	Guatemala Ministry of Public Health	Physician for the Guatemalan Public Health Service and PASB	After Guatemala experiment given fellowship on Staten Island and studied with Dr. Mahoney

continued

Table 2: Individuals Involved in the STD Experiments in Guatemala

NAME	AFFILIATION	TITLE	KNOWN ROLE IN GUATEMALA EXPERIMENTS
Mahoney, Dr. John F.	USPHS, VDRL, NIH, Syphilis Study Section	Director, VDRL (1929-1949)	Member of the Syphilis Study Section that approved the Guatemala research grant Primary supervisor of the experiments Received Cutler's reports on the experiments Visited the Guatemala site at least once in April 1947
Maza, Dr. Raul	Guatemala National Army of the Revolution Military Hospital		Active in intentional exposure experiments
Moore, Dr. Joseph E.	NIH, Syphilis Study Section Chairman of the National Research Council, Subcommittee on Venereal Diseases	Chairman, Syphilis Study Section Associate Professor, Johns Hopkins University	Chairman of the Syphilis Study Section that approved the Guatemala research grant Advised Committee on Medical Research on the importance of prophylactic research
Oliva, Dr. Joseph	Guatemala National Army of the Revolution	Colonel	Participant in the syphilis experiments
Parran, Dr. Thomas	USPHS	U.S. Surgeon General (1936-1948)	Granted final approval for the Guatemala research grant
Portnoy, Joseph	USPHS / PASB, Guatemala	Serologist, USPHS Chief, Laboratory Guatemala City, USPHS (Sept. 1946-Apr. 1948)	Participant in the syphilis experiments
Salvado, Dr. Carlos	Guatemala National Psychiatric Hospital	Hospital Director Special Consultant with the Venereal Disease Division, Bureau of State Services, USPHS with supervision by PASB (Dec. 1948-May 1950)	Invited the researchers to do experiments in the Psychiatric Hospital Active participant in the intentional exposure experiments Involved in the continuation of data collection from subjects until 1953
Spoto, Dr. Joseph	USPHS / PASB, Guatemala and USPHS, Washington DC	Assistant Chief, Venereal Disease Division, USPHS (1947-1948) Chief, PASB Guatemala Office (1945-1946)	Facilitated PASB construction and other activities at start of research Introduced researchers to Guatemalan officials who assisted in the experiments

NAME	AFFILIATION	TITLE	KNOWN ROLE IN GUATEMALA EXPERIMENTS
Stout, Genevieve	USPHS / PASB, Guatemala	Serologist, USPHS Director, Venereal Disease Laboratory and Training Center, Guatemala City, Guatemala (Aug. 1948-Aug. 1951)	Led PASB laboratory after Dr. Cutler's departure Did further work in serology in the Guatemalan population
Tejeda, Dr. Carlos E.	Guatemala National Army of the Revolution	Colonel, Chief of the Army Medical Department	Active participant in intentional exposure experiments Involved in the continuation of data collection from subjects until 1953
Van Slyke, Dr. Cassius J.	USPHS, NIH	Medical Director, USPHS Chief, Research Grants Office, NIH (1946-1948)	Approved the Guatemala research grant Visited the Guatemala site at least once in April 1947
Walker, Alice	USPHS / PASB, Guatemala	Bacteriologist, USPHS	Worked in laboratory

Table 3: Timeline of all Guatemala Experiments

1946			
MONTH	**LOCATION**	**TEST**	
Feb.			NIH Syphilis Study Section recommends STD research in Guatemala
Mar.			National Advisory Health Council meeting that approved the proposal that became "Research Grant No.65 (RG-65)"
Apr.			PASB starts project
Aug.			Dr. Cutler arrives in Guatemala
			PASB officials sign agreements with the Guatemalan government
	Army Penitentiary		Treatment programs begin
Nov.	Penitentiary	Serology	Studies begin
Dec.			"The Surgeon General [Parran] has become keenly interested in the Guatemala project."
1947			
Feb.	Army	Gonorrhea	First intentional exposure experiment
			Dr. Arnold visits Guatemala
Apr.			Drs. Mahoney, Heller and Van Slyke visit Guatemala
			New York Times says human intentional infection syphilis experiments "ethically impossible"
	Army	Gonorrhea	First artificial inoculation (deep inoculation) experiment
May	Penitentiary	Syphilis	First normal exposure experiment involving sex workers
	Hospital	Syphilis	First artificial inoculation experiment
	Penitentiary	Syphilis	First artificial inoculation experiment
	School children	Serology	Studies begin
	Orphanage	Serology	Studies begin
June			Dr. Cutler concerned that the wrong person finding out about the experiments "might wreck it or parts of it" and proposes to start sending "barest summaries of our progress" to PASB
Aug.	Hospital	Syphilis	First abrasion experiment
Sept.			Dr. Mahoney tells Dr. Cutler that the abrasion methods are "drastic"

1948			
MONTH	**LOCATION**	**TEST**	
Apr.			Second Congress of Venereal Diseases in Central America; Dr. Arnold visits and presents
June			Original end date of RG-65(c); extension granted
July	Army	Gonorrhea	Last experiment
Aug.			Stout arrives to manage the Venereal Disease Laboratory and Training Center
Sept.			Dr. Mahoney refuses to consider an extension of the grant
	Penitentiary	Syphilis	Last experiment
Oct.	Hospital	Chancroid	Artificial inoculation experiment
	Army	Chancroid	Artificial inoculation experiment
Dec.			End of RG-65(c) extension; Dr. Cutler leaves Guatemala
1949			
Aug.	Orphanage	Serology	Study ends
1951			
Aug.			Stout leaves Guatemala
1952			
Sept.			Chancroid Experiment report distributed
Oct.			Experimental Studies in Gonorrhea report prepared
1953			
Apr.	Hospital	Serology	Dr. Cutler receives specimens from Dr. Funes taken from ongoing observations
1955			
Feb.			Final Syphilis Report prepared

Table 4: Subject and Population Specific Data[1]

	COMMERCIAL SEX WORKERS	SOLDIERS	PRISONERS[2]	ORPHANS, SCHOOL-CHILDREN, "INDIAN," AND "LADINO" CHILDREN	LEPROSARIUM PATIENTS	PSYCHIATRIC PATIENTS	U.S. SERVICEMEN IN GUATEMALA	NOT SPECIFIED[3]	TOTAL
Subjects Identified Either by Aggregate or by Name in the Cutler Documents and Corresponding Articles[4]									
Number of Subjects	14	1017	976	1384	51	716	23	1359	5540
Age Range, Mean (Mode)[5]	16-18 17 (16, 18)	10-72 22 (20)	15-62 29 (22)	1-18 Not available	Not available	14-58 29 (17)	Not available	19-45 27 (19)	Range: 1-72 Not available
Subjects Involved in Diagnostic Testing									
Number of Subjects	14	897	842	1384	51	642	23	1275	5128
Subjects Receiving Some Form of Treatment for an STD									
Number of Subjects	0[6]	309	139	3	Not available	334	Not available	35	820
Subjects Exposed to Any STDs[7]/Number of Subjects Exposed Who Received Some Form of Treatment for an STD[8]									
Gonorrhea	4/0	518/202	0	N/A	N/A	50/32	N/A	10/3	582/237
Syphilis	5/0	0	219/92	N/A	N/A	446/294	N/A	18/2	688/388
Chancroid	0	81/81	0	N/A	N/A	41/39	N/A	11/11	133/131
Total Subjects	6/0	558/242	219/92	N/A	N/A	486/328	N/A	39/16	1308/678

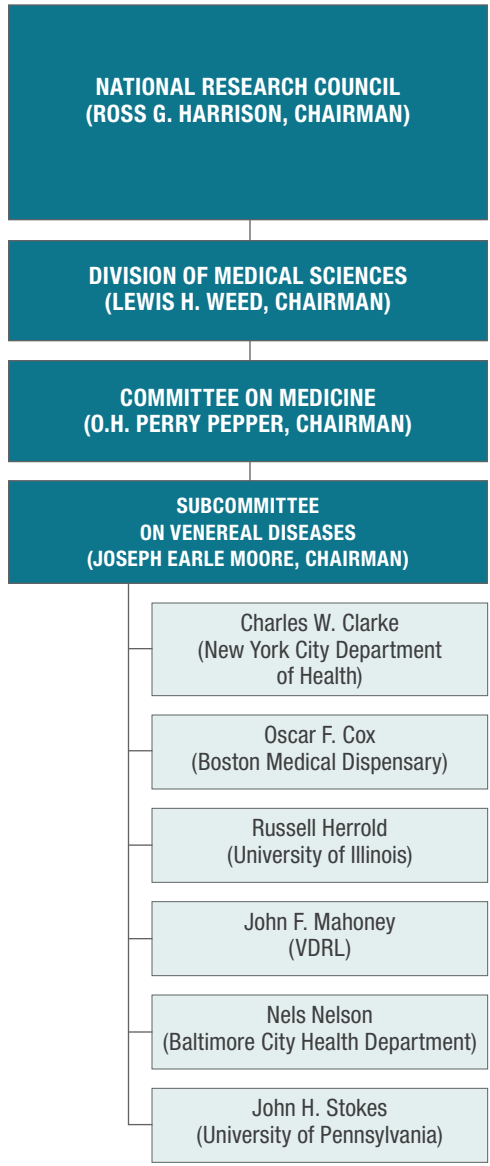
1 For methods and limitations, please see "Appendix IV: Subject Database Methods."
2 These numbers include several prison guards.
3 Includes women referred by Dr. Funes, Dr. Galich, or the Venereal Disease and Sexual Prophylaxis Hospital, where commercial sex workers were required to report twice a week for STD testing and treatment.
4 Including persons who may have been listed in the Cutler Documents for non-research purposes (e.g., general medical care, referred for enrollment, etc.).
5 Age range, mean, and mode based on age numbers that were available. Not all ages of subjects were recorded and available in the Cutler Documents.
6 There were no clear treatment data available for any of the commercial sex workers.
7 Includes all subjects exposed to an STD, whether or not additional data indicate the subject was in fact infected with the STD.
8 Includes all subjects who were exposed to an STD and received some form of treatment, whether or not additional data indicate the subject was in fact infected with the STD. While some subjects were exposed to an STD multiple times, they were included in the "treatment" column if they received treatment for any exposure even once. In the case of syphilis, the Commission considered penicillin given within 21 days of exposure to be a prophylaxis, and penicillin given 21 days after exposure to be a treatment. For more information please see "Appendix IX: Subject Database Methods."

	COMMERCIAL SEX WORKERS	GUATEMALAN ARMY	PENITENTIARY	ORPHANS AND SCHOOLCHILDREN	PSYCHIATRIC HOSPITAL
Methods of Inoculation					
Gonorrhea	Swabbing of cervix	Sexual contact with infected commercial sex workers Inoculation inside the penis Inoculation inside the penis after sexual exposure	None	None	Inoculation inside the urethra Inoculation of the rectum Inoculation of the eyes
Syphilis	Injection of cervix	None	Sexual contact with infected commercial sex workers Injection	None	Injection Inoculation by contact with the penis Abrasion of skin and penis Oral ingestion Cisternal puncture
Chancroid	None	Abrasion and rubbing in of inoculum on arms and back	None	None	Abrasion and rubbing in of inoculum on arms and back

Figure 1: Organizational Chart of the Office of Scientific Research and Development

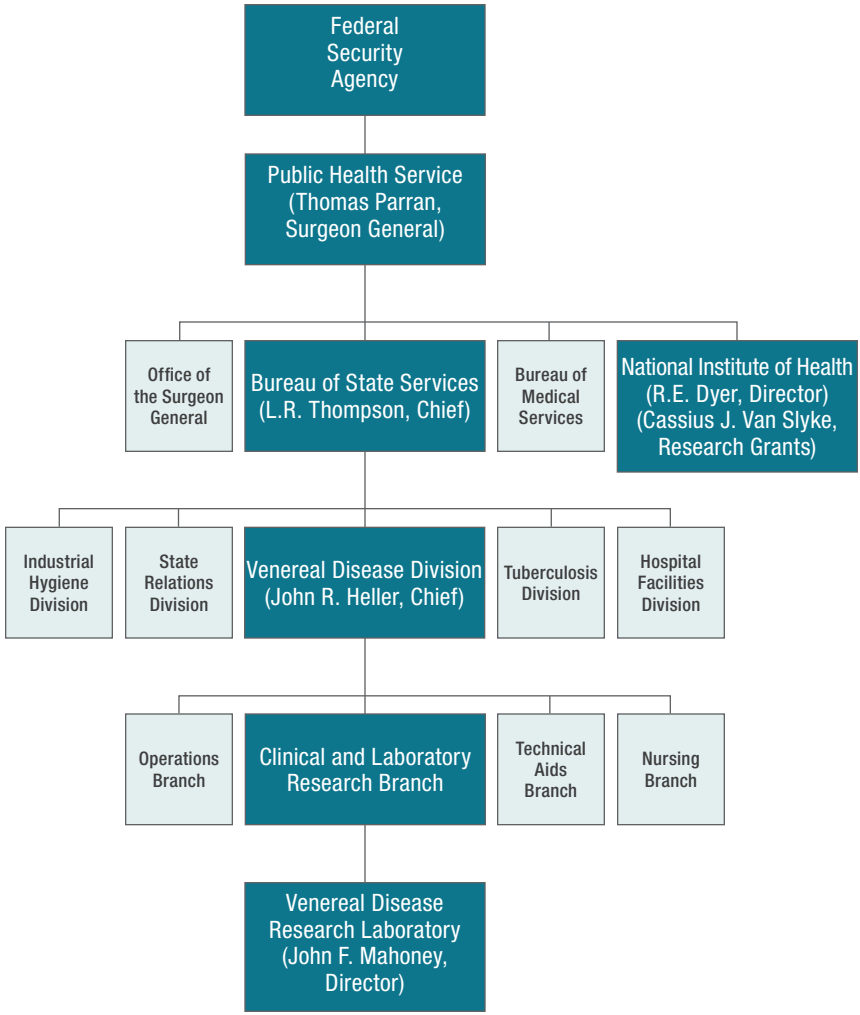
Sources: First Draft of Proposed C.M.R. Chapter for Irvin Stewart's Administrative History of OSRD. (1945, January 12). PCSBI HSPI Archives, NARA-II_0000354; Lockwood, J.S. (1946, August). War-time activities of the National Research Council and the Committee on Medical Research; with particular reference to team-work on studies of wounds and burns. *Annals of Surgery* 124(2):314-315.

Figure 2: Organizational Chart of the National Research Council



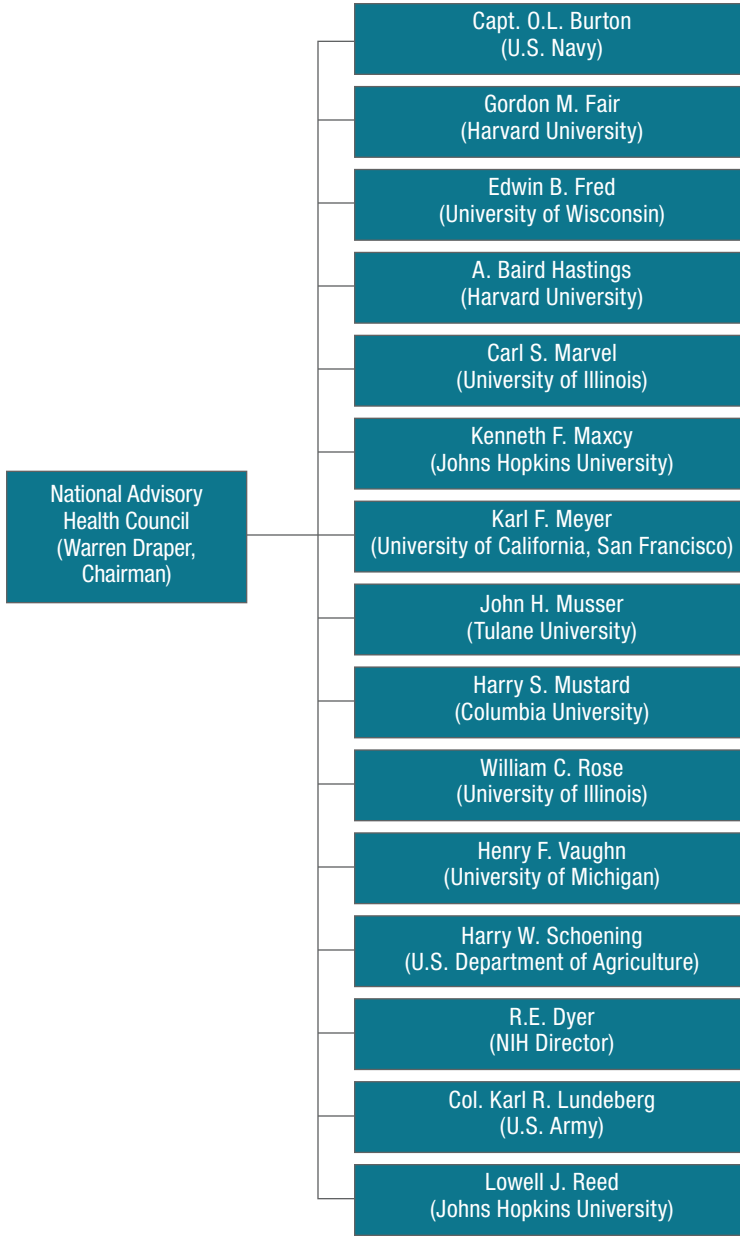
Sources: Lewis H. Weed to Charles Taft. (1943, November 6). Correspondence. PCSBI HSPI Archives, NAS_0000458; O.H. Perry Pepper to E.H. Cushing. (1942, May 29). Correspondence. PCSBI HSPI Archives, NAS_0000540; E.H. Cushing to Robert L. Dickinson. (1942, December 9). Correspondence. PCSBI HSPI Archives, NAS_0000446.

Figure 3: Organizational Chart for the U.S. Public Health Service, 1946



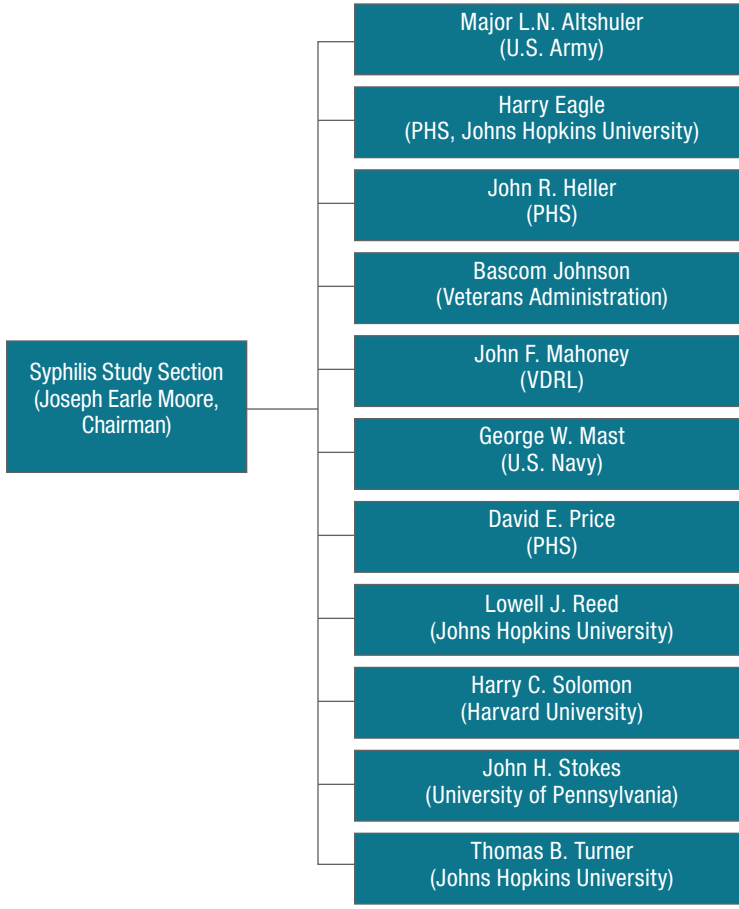
Sources: Public Health Service Act of 1944, Public Law No. 78-410, 58 Stat. 682.; Training Division, Communicable Disease Center, U.S. Public Health Service. (1947, January 15). Organization and Functions of the U.S. Public Health Service. PCSBI HSPI Archives, NARA-SE_0000148.; PCSBI HSPI Archives, MISC_0000909.; Federal Security Agency Notice of Personnel Action (1946). PCSBI HSPI Archives, NPRC_0001673.

Figure 4: Organizational Chart for the National Advisory Health Council, December 1946



Sources: National Advisory Health Council Meeting, U.S. Public Health Service. (1946, March 8 and 9). PCSBI HSPI Archives, NARA-II_0000544; Van Slyke, C.J. (1946, December 13). New horizons in medical research. *Science* 104(2711): 567.

Figure 5: Organizational Chart for the Syphilis Study Section



Source: Van Slyke, C.J. (1946, December 13). New horizons in medical research. *Science* 104(2711):567.

Figure 6: Intentional Exposure Experiments Goals over Time

Figure 7: Intentional Exposure Experiments over Time

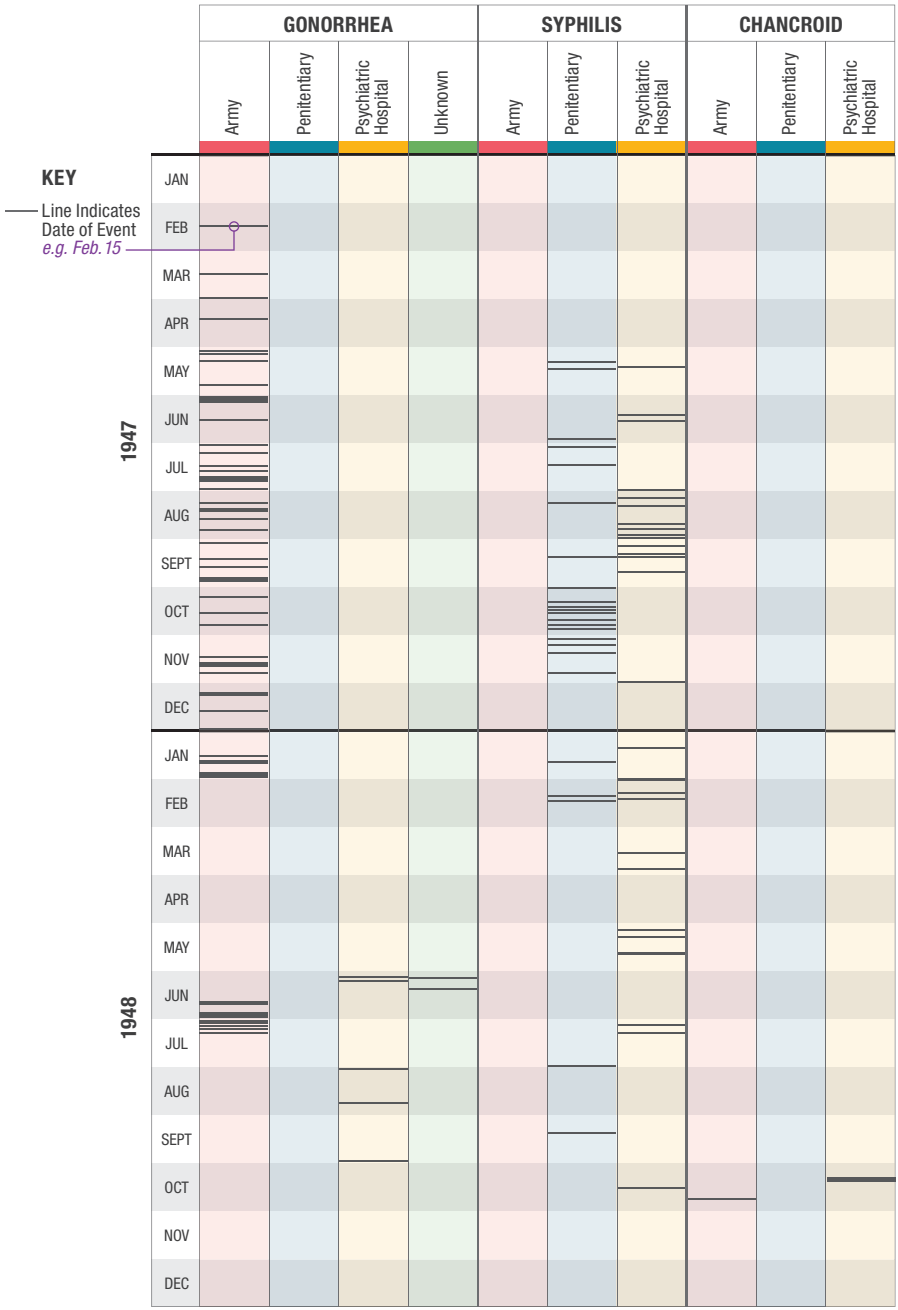


Figure 8: Methods of Exposure over Time

GLOSSARY OF KEY TERMS

abscess – a collection of pus that typically causes swelling and inflammation around it.

abrasion – scraping the surface of the skin in order to facilitate disease transmission.

alkyl aryl sulfate – a sulfur-based component of orvus-mapharsen.

antibody – a protein that is generated by the body's immune system when foreign substances, called antigens, are recognized.

anticonvulsant – a medication used to treat or prevent seizures.

argyrol solution – an antiseptic containing a compound of protein and silver.

bismuth – a metallic element similar to arsenic that is often used in pharmaceutical compounds.

brain stem – the part of the brain that connects the spinal cord to the forebrain and cerebrum.

calomel ointment – a substance used by the U.S. Army and Navy as a post-exposure prophylaxis for syphilis.

cerebrospinal fluid – a clear liquid that is secreted from the blood into the ventricles of the brain and serves to maintain uniform pressure within the brain and the spinal cord.

cervix – the opening of the uterus.

chancre – an ulcer that forms at the site of infection in the primary stages of syphilis.

chancroid – a bacterial disease caused by *Haemophilus ducreyi* that is spread through sexual contact. The disease is characterized by bumps that transform into ulcers.

chemical prophylaxis – a chemical agent used as a protective or preventative treatment against disease.

chemotherapy – the use of chemical agents in the treatment of a disease.

cisternal puncture (a kind of spinal tap) – the withdrawal of cerebral spinal fluid from the back of the skull.

congenital syphilis – a bacterial disease caused by *Treponema pallidum* that is transferred from mother to child through pregnancy or at birth.

conjunctiva – a clear membrane that lines the inside of the eyelid and covers the eyeball.

cutaneous – relating to the skin.

distal – far from the center of the body.

dorsum of the penis – the upper surface of the penis.

Duracillin – the procaine salt of penicillin in a peanut oil base.

foreskin – skin that covers the head of the penis.

fossa navicularum – the dilated portion of the urethra in the head of the penis.

frenum (plural of frenulum) of the penis – elastic band of tissue that connects the glans of the penis to the foreskin and helps retract the foreskin from the glans.

Frew strain – one of the strains of infectious material used by Dr. Cutler and his colleagues for the syphilis experiments.

glans of the penis – head of the penis.

gonorrhea – a contagious disease caused by the bacterium *Neisseria gonorrhoeae*. It is transmitted largely through sexual contact with an infected individual.

histologic – relating to microscopic anatomy, such as body tissues and cells.

hunterian chancre – another term for a "typical" chancre caused by syphilis—i.e., one that is solitary, round or oval, and has a firm base, a convex surface, and a hemorrhagic border.

immunity – resistance to a particular disease.

inoculate – to introduce an organism into the body such as bacteria.

inoculum – a substance used for inoculation.

intracutaneous – administered by entering the skin.

intraurethral – introduced into the urethra.

intravenous – administered by introducing into a vein.

Kahn test – one of the serological tests for syphilis used by Dr. Cutler and his colleagues.

leprosarium – a hospital for leprosy patients.

leprosy (Hansen's disease) – a chronic bacterial infection caused by *Mycobacterium leprae* characterized by skin lesions.

lesion – an abnormal change to a part of the body, particularly one that is circumscribed and well-defined, caused by infection or injury, .

lumbar puncture (a kind of spinal tap) – a puncture of the space between the vertebrae in the lower back to extract cerebrospinal fluid.

malaria – a parasitic disease spread by mosquitoes and characterized by periodic bouts of fever and chills.

Mazzini test – one of the serological tests for syphilis used by Dr. Cutler and his colleagues.

meatus – the opening of the urethra.

meningitis – a disease caused by the inflammation of the membranes covering the brain and spinal cord known as the meninges. This disease can be caused by either viruses or bacteria. The bacterial variety is typically more severe. Meningitis is characterized by fever, headache, and a stiff neck, and is sometimes fatal.

microbiologist – a scientist who specializes in the branch of biology dealing with microscopic organisms.

mucosa – mucous membrane.

Neisseria gonorrhoeae – the bacterium that causes gonorrhea.

Nichols strain – one of the strains of infectious material used by Dr. Cutler and his colleagues for the syphilis experiments.

onchocerciasis (River Blindness) – a parasitic disease spread by the black fly that is characterized by blindness.

orvus-mapharsen – made up of 1% orvus (alkyl aryl sulfate0 and 0.15% mapharsen in aqueous solution and was supposed to be applied after sexual intercourse to prevent infection.

pelvic inflammatory disease – an infection of the uterus, fallopian tubes, and other reproductive organs that can cause abdominal pain, ectopic pregnancy, and infertility.

penicillin – an antibiotic either obtained through *Penicillium* molds or produced synthetically that is used to treat various diseases and infections.

penile – relating to or affecting the penis.

pinto – a bacterial infection caused by *Treponema pallidum carateum*.

placebo – an inactive substance given instead of treatment, often used as a control in a pharmaceutical experiment.

pledget – small, absorbent piece of material used to cover a wound or sore on the body.

POB – a preparation of penicillin in a medium of peanut oil and beeswax to ensure a slow steady release.

post-exposure prophylaxis – a prophylaxis designed for use after exposure to an infection.

preventive medical measures – the word used to describe these measures was "prophylaxis." This term included the steps taken after sexual exposure, such as washing and applying medicinal ointment containing mercury and/or arsenical compounds that would forestall "seroconversion," the systemic infection evidenced by appearance of antibodies to the bacteria in the bloodstream.

prophylaxis – a measure taken as a preventative for a disease or condition.

rectum – the portion of the intestine between the colon and the anus.

salvarsan – an arsenic-based compound used in the treatment of syphilis.

serological – having to do with blood serum, particularly with regards to its reactions and properties.

serologists – scientists who specialize in the reactions and properties of blood serum.

seronegative – having a negative serum reaction, particularly with regard to a test for a particular antibody.

seropositive – having a positive result from a serological test for a disease, in this case syphilis.

serum – a clear fluid that is left over from blood plasma after clotting factors (such as fibrinogen) have been removed through the process of clot formation.

sexually transmitted diseases (STDs) – diseases that are spread through sexual contact (vaginal, oral, or anal).

silver proteinate – the active ingredient in one of the post-exposure prophylaxis regimens used for gonorrhea.

spirochetal – caused by or consisting of spirochetes.

spirochete – a spiral-shaped bacterium. Syphilis is among the diseases caused by spirochetes.

submucosal – introduced beneath a mucous membrane.

sulfonamide compounds (including sulfanilamide and sulfathiazole) – an early antimicrobial drug used to treat gonorrhea before the advent of penicillin.

sulcus (or coronal) of the penis – a groove in the surface of the penis.

super-infect – to infect with an additional strain of a disease already present.

symptomatic – having symptoms associated with a disease.

syphilis – a contagious disease caused by the bacterium *Treponema pallidum*. It is mainly spread through sexual contact and is characterized by both recognizable and unrecognizable sores.

syphilomata (plural of syphiloma) – a tumor caused by infection with syphilis.

syphilologist – a physician who specializes in the study of syphilis.

Treponema pallidum – the bacterium that causes syphilis.

tuberculosis – a bacterial infection caused by *Mycobacterium tuberculosis*; characterized by coughing up blood, weakness and fatigue, fever, chills, and night sweats.

typhus – a potentially lethal disease transmitted through fleas and lice, caused by a type of bacteria.

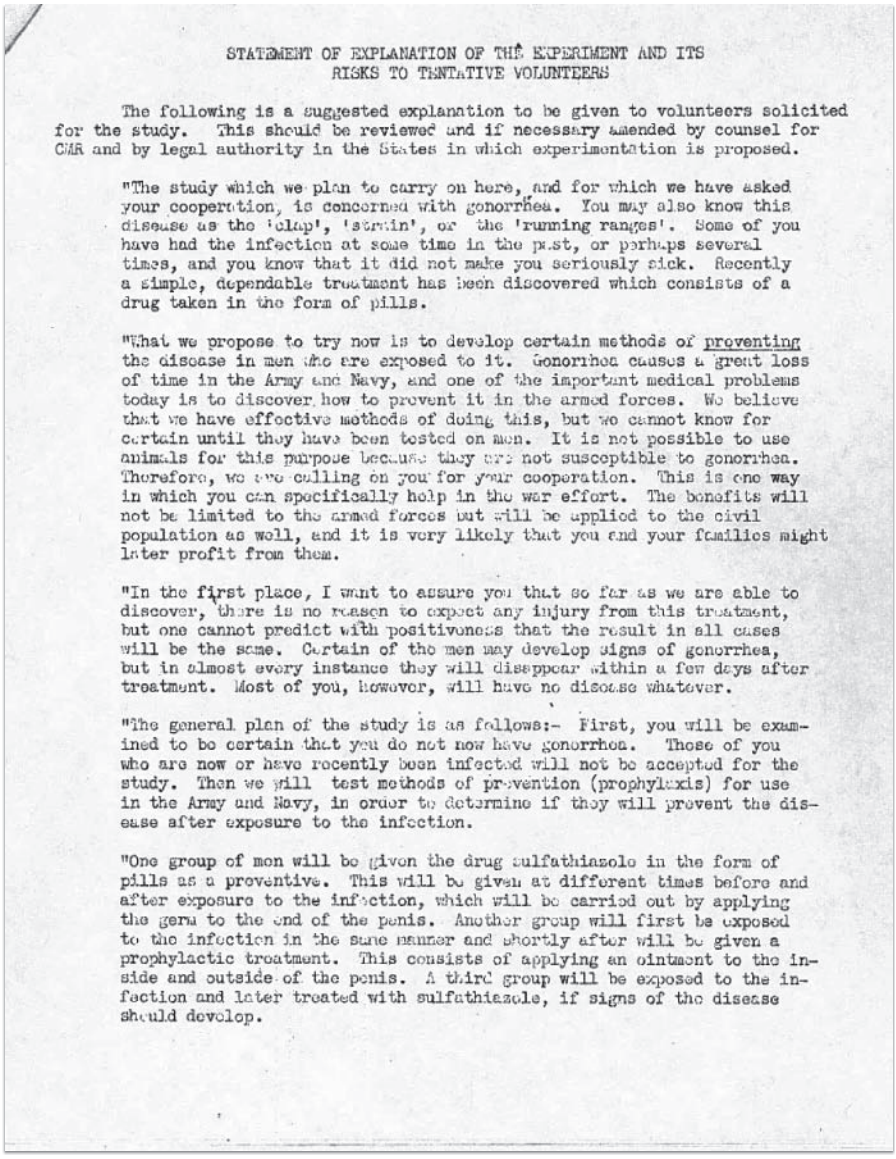
urethra – canal that removes urine from the bladder and, in men, also allows for the passage of semen out of the body.

vector – an organism, such as a mosquito, that transmits a disease-causing pathogen.

zoonotic pathogen – an infection of a human from an animal source.

APPENDICES

Appendix I: Waiver Form Proposed in Preparation for the Terre Haute 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 preventing 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.

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.

"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

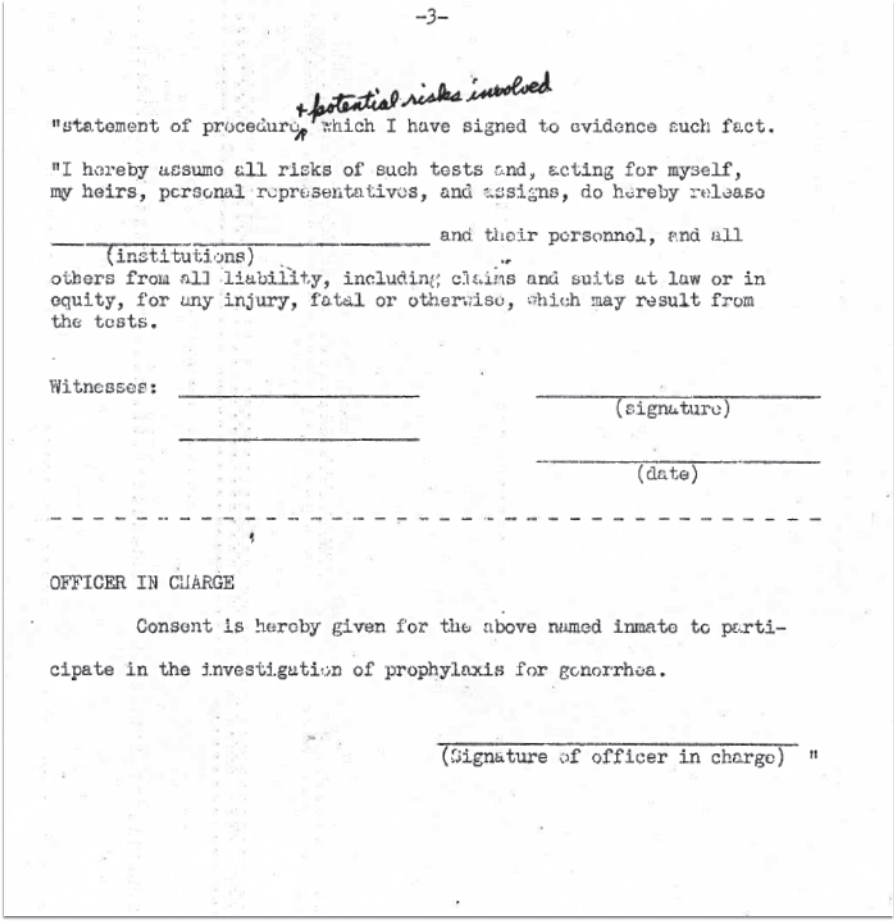
APPLICATION FOR INCLUSION IN STUDY ON
CHEMICAL PROPHYLAXIS FOR GONORRHEA

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

for inclusion in the investigation on prophylaxis for gonorrhea.

I have read, or have had read to me, and I understand the attached

Appendix I: Waiver Form Proposed in Preparation for the Terre Haute Experiments



-3-

"statement of procedure, + potential risks involved 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)

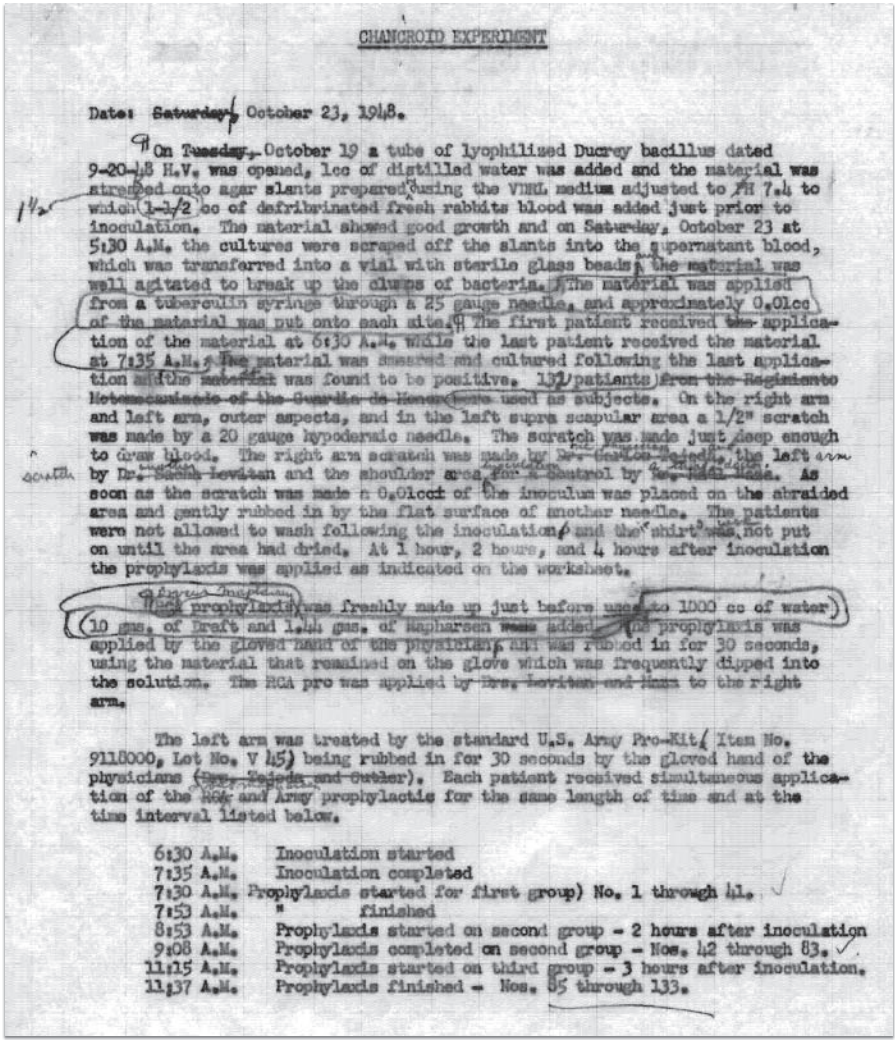
- -

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) "

Appendix II: Chancroid Experiment Report Excerpt



CHANCROID EXPERIMENT

Date: ~~Saturday~~, October 23, 1948.

On ~~Tuesday~~, October 19 a tube of lyophilized Ducrey bacillus dated 9-20-48 H.V. was opened, 1cc of distilled water was added and the material was streaked onto agar slants prepared using the VDRL medium adjusted to PH 7.4 to which ~~1-1/2~~ 2 cc of defibrinated fresh rabbits blood was added just prior to inoculation. The material showed good growth and on Saturday, October 23 at 5:30 A.M. the cultures were scraped off the slants into the supernatant blood, which was transferred into a vial with sterile glass beads, the material was well agitated to break up the clumps of bacteria. The material was applied from a tuberculin syringe through a 25 gauge needle, and approximately 0.01cc of the material was put onto each site. The first patient received the application of the material at 6:30 A.M. while the last patient received the material at 7:35 A.M. The material was smeared and cultured following the last application and the material was found to be positive. 133 patients ~~from the Regimiento Motomecanizado of the Guardia de Honor~~ were used as subjects. On the right arm and left arm, outer aspects, and in the left supra scapular area a 1/2" scratch was made by a 20 gauge hypodermic needle. The scratch was made just deep enough to draw blood. The right arm scratch was made by ~~Dr. Garcia-Tejeda~~, the left arm by Dr. ~~Sarah~~ Levitan and the shoulder area for a control by ~~Dra. Abad~~. As soon as the scratch was made a 0.01cc of the inoculum was placed on the abraided area and gently rubbed in by the flat surface of another needle. The patients were not allowed to wash following the inoculation and the shirt was not put on until the area had dried. At 1 hour, 2 hours, and 4 hours after inoculation the prophylaxis was applied as indicated on the worksheet.

~~Each~~ prophylaxis was freshly made up just before use ~~to~~ 1000 cc of water) 10 gms. of Ivory Soap and 1.44 gms. of Napharsen were added. The prophylaxis was applied by the gloved hand of the physician. All was rubbed in for 30 seconds, using the material that remained on the glove which was frequently dipped into the solution. The RCA pro was applied by ~~Drs. Levitan and Hunt~~ to the right arm.

The left arm was treated by the standard U.S. Army Pro-Kit (Item No. 9118000, Lot No. V 45) being rubbed in for 30 seconds by the gloved hand of the physicians (~~Drs. Tejeda and Cutler~~). Each patient received simultaneous application of the RCA and Army prophylactic for the same length of time and at the time interval listed below.

6:30 A.M.	Inoculation started
7:35 A.M.	Inoculation completed
7:30 A.M.	Prophylaxis started for first group) No. 1 through 41.
7:53 A.M.	" finished
8:53 A.M.	Prophylaxis started on second group - 2 hours after inoculation
9:08 A.M.	Prophylaxis completed on second group - Nos. 42 through 83.
11:15 A.M.	Prophylaxis started on third group - 3 hours after inoculation.
11:37 A.M.	Prophylaxis finished - Nos. 85 through 133.

Chancroid Experiment. Report. PCSBI HSPI Archives, CTLR-0000978.

Appendix III: Investigation Methods

Commission staff broadly searched for relevant documents from 1935, 10 years preceding the initial planning for the work in Guatemala, through 1956, one year after Dr. Cutler finished preparing the final report on the studies. Secondary literature and additional records from after this time specifically related to Dr. Cutler, intentional exposure, and STD research were also examined. The Commission staff worked with archivists, historians, government officials, and scholars from across the country.

Searches were undertaken in:

- Johns Hopkins Medical Institutions, Baltimore, MD
- National Archives and Records Administration, various locations:
  - College Park, MD
  - Morrow, GA
  - St. Louis, MO
- National Academy of Sciences, Washington, DC
- National Library of Medicine, Bethesda, MD
- New York City Municipal Archives, New York, NY
- Pan American Health Organization Headquarters Library, Washington, DC
- University of Minnesota, Minneapolis, MN
- University of Pennsylvania, University Archives and Records Center, Philadelphia, PA
- University of Pittsburgh Archives, Pittsburgh, PA
- University of Virginia Library, Charlottesville, VA

Additionally, Commission staff specifically requested documents from selected government agencies and non-governmental organizations as follows:

The Center for Mesoamerican Research (CIRMA): historical materials or photographs related to U.S. Public Health Service activities or personnel in Guatemala in the 1940s.

Missouri State Archives: records related to Dr. Richard C. Arnold.

National Archives and Records Administration: records related to the experiments conducted in Guatemala by U.S. PHS officers between 1946-1948; any documents relating to the Federal Security Administration, Bureau of State Services, U.S. PHS, Venereal Disease Division between 1935-1955, and personnel records

for: L.N. Altshuler, Casta Luis Aguilar, Richard C. Arnold, Theodore J. Bauer, Frederick J. Brady, Opal Christopherson, G. Robert Coatney, Hugh Cumming Sr., John C. Cutler, Harry Eagle, Juan M. Funes, Virginia Lee Harding, Elliot L. Harlow, Ad Harris, John R. Heller, Bascom Johnson Jr., Henry C. Miller, Sacha Levitan, John F. Mahoney, George W. Mast, William J. McNally Jr., Joseph Earle Moore, John R. Murdoch, Thomas Parran, David E. Price, Joseph Portnoy, Lowell J. Reed, Carlos A. Salvado, Harry C. Solomon, Fred L. Soper, Joseph S. Spoto, John H. Stokes, Genevieve W. Stout, James D. Thayer, Thomas B. Turner, Cassius J. Van Slyke, Alice Walker, and Margaret R. Zwalley.

Office of Research Information Systems, National Institutes of Health (NIH): all records related to the experiments conducted in Guatemala by U.S. PHS officers between 1946-1948, including any records relating to the funding of Research Grant 65, 65 (c) by the NIH Division of Research Grants.

Pan American Health Organization (PAHO): all records related to the experiments conducted in Guatemala by U.S. PHS officers between 1946-1948, under the auspices of the Pan-American Sanitary Bureau (a predecessor organization to PAHO).

United States Agency for International Development: any and all records related to grants issued to, and grant applications received from, Dr. John Cutler.

U.S. Departments of Defense, Energy, State, and Veterans Affairs: all records during the time period of issue related to:

1. STD experiments conducted by U.S. PHS officers in Guatemala between 1946-1948;
2. Clinical studies funded, approved, facilitated, or coordinated by the U.S. government that:
   a. related to STD research;
   b. involved the use of vulnerable subject populations;
   c. were conducted or partially conducted outside of the United States; or
   d. involved the use of intentional infection protocols;
3. Ethical standards and conventions of human subject experimentation, particularly those that fall between the time frame of 1935-1955; or

4. Collaboration between the agency and the U.S. PHS, particularly with regard to activities that:
   a. related to STD research;
   b. involved the use of vulnerable subject populations;
   c. were conducted or partially conducted outside of the United States; or
   d. involved the use of intentional infection protocols.

U.S. Department of Justice: all records that relate to the use of prisoners as subjects in clinical trials, particularly those trials that were conducted at the Federal Penitentiary at Terre Haute (1942-1943) and at Sing Sing Correctional Facility (1954-56).

U.S. Public Health Service Commissioned Officers Association: records related to any living U.S. PHS officers who may have had a firsthand knowledge of the U.S. PHS Venereal Disease Research Laboratory during the time period that the STD experiments were underway in Guatemala.

In total, Commission staff reviewed over 125,000 pages of original records, 550 secondary sources and publications, and collected thousands of relevant documents. The collected documents of the Commission investigation are organized as follows:

PCSBI-HSPI record group 1 – National Archives and Records Administration (NARA): NARA Southeast Region (Morrow, GA)

- NARA record group 442 – Records of Dr. John C. Cutler
- NARA record group 442 – Records of the U.S. PHS

PCSBI-HSPI record group 2 – NARA-II facility (College Park, MD)

- NARA record group 59 – General Records of the Department of State
- NARA record group 84 – Records of the Foreign Service of the Department of State
- NARA record group 220 – Records of the Advisory Commission on Human Radiation Experiments
- NARA record group 227 – Records of the Office of Scientific Research and Development
- NARA record group 229 – Office of Inter American Affairs
- NARA record group 443 – Records of the NIH Division of Research Grants

PCSBI-HSPI record group 3 – NARA Personnel Record Center (St. Louis, MO)

- U.S. government personnel records for: Richard C. Arnold, Theodore J. Bauer, Frederick J. Brady, G. Robert Coatney, Hugh Cumming, Sr., John C. Cutler, Harry Eagle, Juan M. Funes, Elliot L. Harlow, John R. Heller, Bascom Johnson, Jr., Sacha Levitan, John F. Mahoney, George W. Mast, William J. McNally, Jr., Joseph Earle Moore, Thomas Parran, Joseph Portnoy, Lowell J. Reed, Carlos A. Salvado, Harry C. Solomon, Fred L. Soper, Joseph S. Spoto, John H. Stokes, Genevieve W. Stout, Thomas B. Turner, and Cassius J. Van Slyke

PCSBI-HSPI record group 4 - Pan American Health Organization Headquarters Library (Washington, DC)

- World Health Organization publications
- Pan American Sanitary Bureau publications

PCSBI-HSPI record group 5 – National Academy of Sciences (Washington, DC)

- Records of the Advisory Committees to the Surgeons General of the War and Navy Departments and U.S. Public Health Service Records Group (also known as the Military Medicine Committees)
- Records of the National Research Council Division of Medical Sciences
- National Academy of Sciences – National Research Council Central Policy Files Records Group

PCSBI-HSPI record group 6 – National Library of Medicine, National Institutes of Health (Washington, DC)

- Files of Dr. Fred Soper
- Files of Dr. John C. Cutler
- Files of Dr. Thomas Parran
- Files of PHS Office of the Historian

PCSBI-HSPI record group 7 – Alan Mason Chesney Archives of The Johns Hopkins Medical Institutions (Baltimore, MD)

- Thomas B. Turner Collection
- Biographical File – Dr. John C. Cutler
- Biographical File – Dr. Harry Eagle
- Biographical File – Dr. Joseph Earle Moore

PCSBI-HSPI record group 8 – University of Pennsylvania, University Archives and Records Center (Philadelphia, PA)

- Papers of Dr. A.N. Richards

PCSBI-HSPI record group 9 – University of Pittsburgh (Pittsburgh, PA)

- Dr. Thomas Parran Collection

PCSBI-HSPI record group 10 – University of Minnesota, Social Welfare History Archives (Minneapolis, MN)

- Archives of the American Social Health Association

PCSBI-HSPI record group 11 – Various Records Compiled by U.S. government agencies in Response to PCSBI Document Requests

- Documents from the U.S. Agency for International Development
- Documents from the U.S. Department of Defense
- Documents from the U.S. Department of Justice
- Documents from the U.S. Department of Veterans Affairs

PCSBI-HSPI record group 12 – Miscellaneous Documents

- Documents collected from various sources not otherwise listed above, including: NIH, Office of Research Information Systems; the Center for Mesoamerican Research; and historical press clippings from Guatemala

Research in Guatemala

Martin Rangel, an archaeologist and freelance social science researcher in Guatemala, assisted the Commission in the collection of historical press articles and published materials relevant to the intentional exposure experiments. Those materials are kept within the PCSBI HSPI archives.

Advisors to the Investigation

Over the course of the investigation, the Commission was invaluably served by its three Senior Advisors: Dr. Paul Lombardo, Bobby Lee Cook Professor of Law, Georgia State University; Dr. Jonathan D. Moreno, David and Lyn Silfen University Professor of Ethics, Professor of Medical Ethics and Health Policy, of History and Sociology of Science, and of Philosophy at the University of Pennsylvania; and Dr. Jeremy Sugarman, Harvey M. Meyerhoff Professor of Bioethics and Medicine at Johns Hopkins University. Their leadership and expertise helped guide the investigation and proved a great asset in writing the report.

The Commission also received significant input and valuable advice from Dr. Jonathan Zenilman, Professor, Division of Infectious Diseases, Johns Hopkins School of Medicine, and Johns Hopkins School of Public Health, who served as a technical consultant to the investigation.

Commission staff also benefited from the assistance and advice of many outside experts and informal advisors. In many cases, these experts in the fields of history, bioethics, archival research, medicine, medical research, and law volunteered many hours of their time to meet with Commission staff members to share their insights and often the results of their own independent research. These individuals include:

- Linnea Anderson – Interim Archivist, Social Welfare History Archives, University of Minnesota
- Dan Guttman, Ph.D. – former Executive Director, Advisory Committee on the Human Radiation Experiments.
- Stephen J. Greenberg, Ph.D. – Coordinator of Public Services, History of Medicine Division, National Library of Medicine
- James H. Jones, Ph.D. – author, *Bad Blood: The Tuskegee Syphilis Experiments* (1976)
- Suzanne Junod, Ph.D. – Historian, FDA History Office
- Susan Lederer, Ph.D. – Robert Turell Professor of Medical History and Bioethics, University of Wisconsin
- Richard Mandel, Ph.D. – Lead Technical Information Specialist, NIH Executive Secretariat
- Robert Martensen, M.D., Ph.D. – Director, NIH Office of History
- Nancy McCall – Director, Alan Mason Chesney Medical Archives of The Johns Hopkins Medical Institutions
- Robert F. Moore – Historian/Consultant, Office of Research Information Systems, National Institutes of Health
- John Parascandola, Ph.D. – U.S. Public Health Service Historian (retired)
- Katrina Pearson – Office of Research Information Systems, NIH
- Richard Peuser – Assistant Chief, National Archives and Records Administration
- John Rees – Curator, National Library of Medicine
- Susan Reverby, Ph.D. – Marion Butler McLean Professor in the History of Ideas and Professor of Women's and Gender Studies, Wellesley College
- Paul Theerman, Ph.D. – Head of Archives, National Library of Medicine

Targeted Interviews

Commission staff conducted a series of informal interviews for background information on the STD experiments in Guatemala with individuals who knew Dr. Cutler. The interviews were conducted by phone. A full listing of those interviewed follows:

Dr. Donald S. Burke
Dr. Michael E. Dalmat
Ms. Lois G. Michaels
Dr. Jerry Michael
Dr. David Sencer
Dr. Michael Utidjian

Staff Delegation to Guatemala

At Guatemalan Vice President Dr. Rafael Espada's invitation, a small delegation of Commission staff members visited Guatemala from April 30 to May 3, 2011. They met with Vice President Espada and the government of Guatemala's investigation commission, toured the Central American Archives, and visited relevant historical sites. The visit served to introduce the Commission's work to the members of the Guatemalan commission and gather information about their activities. It also enabled staff to gain a better understanding of the context in which the research proceeded. The Commission staff delegation included Valerie Bonham, Brian Eiler, Dr. Paul Lombardo, and Kayte Spector-Bagdady.

Translation

Among the records collected and reviewed over the course of the investigation were many Spanish language documents. These documents included correspondence between U.S. PHS officers and Guatemalan officials, published works of scientific scholarship, press articles, and selected pages from laboratory notebooks. Relevant documents were translated by an independent translator, Cetra Language Solutions of Elkins Park, Pennsylvania. The translated documents are kept within the PCSBI HSPI archives.

Appendix IV: Subject Database Methods

In order to specifically identify the number of individuals involved in the research, and better understand what happened to them, the nearly 10,000 pages from the Cutler Documents were read and analyzed with a particular focus on information about individual research subjects. Commission staff created a comprehensive database of individual subject information from these records.

Creation of Subject Database

A great deal of historical research was done to help interpret the Cutler Documents. The Commission relied heavily on *Modern Clinical Syphilology* (1944) by John H. Stokes, Herman Beerman, and Norman R. Ingraham, which was considered the definitive text on syphilis at the time. In addition, the Commission consulted regularly with Dr. Jonathan Zenilman, Chief of the Infectious Diseases Division of the Johns Hopkins Bayview Medical Center.

For data extraction and analysis purposes, the data sources were divided into two categories: research notebooks and additional archive documents.

Research Notebooks

The Cutler Documents include four research notebooks, two laboratory notebooks (Notebooks 1 and 2), and two clinical notebooks (Notebooks 3 and 4). The laboratory notebooks primarily contain laboratory test results. The clinical notebooks primarily contain research subject histories and clinical notes. All notebooks contain entries written in both English and Spanish.

The primary data of interest included patient profile information (e.g., name, age, subject number, study population), inoculation data, treatment data, and information that independently raised ethical concerns (e.g., evidence of deceit on the part of the researchers or resistance on the part of the subjects).

Based on a detailed reading of Notebook 1 and a review of Notebooks 2, 3, and 4, an initial coding scheme was developed to capture relevant information from the notebooks in an Excel database. Four coders then used the preliminary coding scheme to code a sample of about 10 pages from each of the four notebooks. Following each preliminary coding trial, the data were

discussed and the codes refined with input from Dr. Zenilman. Once the preliminary coding and revisions were complete, double coding began, with two coders working on the laboratory notebooks and two on the clinical notebooks (the coders working on the clinical notebooks had moderate to high Spanish fluency). Each pair of coders worked through a number of pages of their notebook independently, then met to reconcile their coding. One member of each team maintained the master database with reconciled data. The coding scheme was revised iteratively, as new information was encountered that was not being adequately captured. When the coding scheme was revised, previously coded data were recoded to reflect the revised scheme.

The rules employed during coding included:

- Use one line for each entry about each person per date. Simple direct Spanish translation permitted (e.g., "orinas" in the data source became "urines" in the database)
- Long or complex Spanish translations should be preceded in the database by '[Translation]'
- Where handwriting cannot be interpreted, denote as '[illegible]'
- Where handwriting is difficult to interpret, use brackets [] to denote coder's interpretation of entry
- Coding test results
  - N (any variation) = negative
  - P (any variation) = positive
  - D (any variation) = doubtful
  - WP = weakly positive
  - QNS = quantity not sufficient
  - If there is a N, D, or WP and a P on the same line, code as "conflicting"
  - If there is a N and a D on the same line code as "negative"

A detailed data interpretation and coding key is available upon request.

Additional Cutler Documents

Additional Cutler Documents included Dr. Cutler's final research reports, photographs, correspondence, individual experiment files, and about a dozen miscellaneous documents.[706] There were also approximately 7,000 research subject note cards. Overall, the content of these data sources was much less

rich than that of the Research Notebooks, with the possible exception of the subject note cards. There was a tremendous amount of variation in the contents of the note cards, with some cards containing nothing but a name or subject number and some cards containing detailed clinical notes about a named individual.

All of these documents were single-coded, meaning that only one person coded any given document. Each coder's work was regularly audited for faithful recording of data from the source documents, appropriate application of the coding scheme, and consistency.

Subject Database Quality Control

Once all sources were coded, separate databases were combined into one master Subject Database, with over 30,000 lines of data on over 5,000 individual subjects. The database was checked for obvious coding errors (e.g., a name where a date should be, mode of inoculation where a test result should be) and corrected where necessary. The Subject Database was saved and archived.

In order to identify the total number of subjects involved in the studies, as well as information about inoculation and treatment, further quality control of the database began. The first step was to review the names, where possible, in an effort to ensure that any given individual was only counted once. A new column was created ("Full Name Clean") to hold the best assessment of an individual's name in cases where ambiguity existed. A paradigmatic case is one where one (or many) line includes information on A. Gomes and another line (or many) includes data on A. Gomez. In this instance, if it was found that a second piece of information (subject number, date, population, age, or experiment number) on each individual matched, those two lines of data were assumed to be on the same individual. All lines with information on that individual were then assigned either the majority name or the most logical name—in our example, all lines would be assigned the name of "A. Gomez" in the Full Name Clean column. The First Name and Last Name columns were always left untouched, changing the name only in the Full Name Clean column.

If a line of data could not be assigned to a unique individual, the data were not included in our subsequent calculations.

In order to enable calculation of the number of subjects exposed to syphilis, gonorrhea, and chancroid, an additional column was added to the database: "STD Exposure." Based on data available about each unique individual, the STD Exposure column was populated with the disease used in exposure, for those individuals who were exposed. Frequently the disease involved in the exposure was explicit, but in instances where it was not, the disease was determined based on knowledge about the exposure methods used for each disease and the populations in which various experiments were conducted, based on the retrospective reports that Dr. Cutler authored on the experiments.

In a second round of data review, an attempt was made to fill in missing but known data (e.g., if there are 12 lines about A. Gomez—per the Full Name Clean column—and one of them lists age, age was filled in for all corresponding lines about him). In cases where an individual's population (Commercial Sex Worker, Prisoner, Psychiatric Patient, Soldier) was missing, an effort was made to determine the population by comparing the date and nature of the experiment in which the individual was involved with the timeline of all of the experiments (assembled from Dr. Cutler's final reports.) In cases where there was an obvious conflict between the database and Dr. Cutler's reports (e.g., chancroid inoculation in a population not reported by Dr. Cutler to have been involved in chancroid experiments), the original archive documents were checked and the data verified or corrected. There were a number of commercial sex workers who were mentioned in the documents and were referred to Dr. Cutler for potential involvement in the inoculation studies, but who never participated. These individuals were identified as a discrete population ("Referred by VDSPH") and included in the database, but in all cases, the only data available for these individuals were gonorrhea test results. The database was also double checked for individuals who have the exact same name in the Full Name Clean column, but were clearly not the same person (e.g., A. Gomez who was in the prison and A. Gomez who was in the mental health hospital), to ensure that both individuals were counted.

Challenges in distinguishing between penicillin used as a prophylaxis for syphilis following exposure and penicillin used as a treatment for diagnosed syphilis infection arose. After consulting with Dr. Zenilman, the following standard was applied: as the incubation period of syphilis for lesion development is mean 21 days, all dosages of penicillin before 21 days were

considered prophylactic in nature, and all dosages after 21 days were considered treatment.

In all cases, where no data were available or reasonably interpretable, the cell was left with "nd," denoting no data.

Limitations

Limitations inevitably attach to trying to interpret and analyze incomplete and decades-old data sources. The documents contained a mix of English and Spanish written by multiple individuals with varying levels of fluency, proficiency with spelling, and penmanship. They reflect inconsistency in the spelling of individuals' names and assigning the subject numbers, further complicating this investigation; for example, on one page, an individual's name would be recorded as "Gomez," but the next entry referencing the same person might be noted as "Gomes," likewise for "J.O. Hernandez" and "Jorge Oscar Hernandez."

In addition, though Dr. Cutler's final reports provide some information on timing and some experimental details, they are not comprehensive, as, for example, there are experimental results in the Research Notebooks that were not mentioned in the final reports. Conversely, Dr. Cutler includes over 10 experiments in his Final Syphilis Report for which the Commission did not find corroborating evidence in the contemporaneous laboratory or clinical notes. For example, Dr. Cutler describes a superficial inoculation gonorrhea experiment in the Guatemalan Army on May 9, 1947, but there are no additional subject data available in the Cutler Documents to evidence this experiment.[707] The reason for this discrepancy is unclear; however, there is reason to believe that the Commission is not in possession of all of the clinical notes from the Guatemala experiments. For example, one of the clinical notebooks includes an instruction to please "[s]ee Miss [Alice] Walker's record book."[708] This referenced notebook is not among those included in the Cutler Documents.

Additionally, the experiments described in these documents were conducted in the 1940s, at a time when diagnosis and treatment methods for STDs were not as settled as they are today, and the syphilis organism was poorly understood. Sixty-five years later, it is difficult to know what the researchers thought and understood about the diseases they were working with and the

tests they were conducting. Given this, the Commission did not attempt to identify how many people were clinically infected or how many people received adequate treatment. In the case of syphilis, for example, the serological testing conducted was unreliable and highly dependent on the skill, precise method, and consistency of an individual laboratory and the quality of the clinical assessment. As a result, the database focuses on the number of individuals exposed to, rather than infected with, STD.

Lastly, due to time and resource constraints, research records deemed of greatest significance, specifically the majority of the clinical and laboratory notebooks, were double-coded (meaning by two or more people), but the majority of records were single-coded. Periodic audits were conducted of all work.

Figures 6, 7, and 8

Figures 6, 7, and 8 were created using amalgamated data from the Subject Database derived from the Cutler Documents. As Dr. Cutler's retrospective counts of his experiments are inconsistent, these figures are based on an independent count of days on which intentional exposure to STD occurred for an individual or population. This exposure day count excludes days on which commercial sex workers alone were exposed, as Dr. Cutler did not consider these instances "experiments" or the sex workers as "subjects."

Appendix V: Suggestions for Further Reading

Advisory Committee on Human Radiation Experiments. (1996). *Final Report of the Advisory Committee on Human Radiation Experiments*. New York: Oxford University Press.

Annas, G.J., Glantz, L.H., and B.F. Katz. (1977). *Informed Consent to Human Experimentation: The Subject's Dilemma*. Cambridge: Ballinger.

Annas, G.J., and M.A. Grodin. (1992). *The Nazi Doctors and the Nuremberg Code*. New York: Oxford University Press.

Altman, L.K. (1986). *Who Goes First? The Story of Self-Experimentation in Medicine*. New York: Random House.

Beecher, H.K. (1966). Ethics and clinical research. *The New England Journal of Medicine* 274(24):1354-1360.

Beecher, H.K. (1959). Report to the Council: Experimentation in man. *Journal of the American Medical Association* 69(5):461-478.

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

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

Emanuel, E.J., Grady, C., Crouch, R.A., Lie, R.K., Miller, F.G., and D. Wendler. (2008). *The Oxford Textbook of Clinical Research Ethics*. New York: Oxford University Press.

Faden, R.R. and T.L. Beauchamp. (1986). *A History and Theory of Informed Consent*. New York: Oxford University Press.

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

Harkness, J.M., Lederer, S.E., and D. Wikler. (2001). Laying ethical foundations for clinical research. *Bulletin of the World Health Organization* 79(4): 365-366.

Hornblum, A.M. (1998). *Acres of Skin: Human Experiments at Holmesburg Prison*. New York: Routledge.

Jones, J.H. (1993). *Bad Blood: The Tuskegee Syphilis Experiment*. New York: The Free Press.

Kahn, J.P., Mastroianni, A.C., and J. Sugarman. (1998). *Beyond Consent: Seeking Justice in Research*. 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.

Kraut, A.M. (2003). *Goldberger's War: The Life and Work of a Public Health Crusader*. New York: Hill and Wang.

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

Levine, C.R., Grady, C., Hammerschmidt, D., Eckenwiler, L., and J. Sugarman. (2004). The limitations of 'vulnerability' as a protection for human research participants. *American Journal of Bioethics* 4(3):44-49.

Levine, R.J. (1988). *Ethics and Regulation of Clinical Research*. New Haven, Connecticut: Yale University Press.

Lombardo, P.A. (2009). Tracking chromosomes, castrating dwarves: Uninformed consent and eugenic research. *Ethics and Medicine* 25(3):149-164.

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.

Marks, H.M. (1997). *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990*. New York: Cambridge University Press.

Mastroianni, A.C., and J.P. Kahn. Special Issue: Advisory Committee on Human Radiation Experiments." *Kennedy Institute of Ethics Journal* 6(3): ix-322.

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

Moreno, J.D. (1998). Regulation of research on the decisionally impaired: History and gaps in the current regulatory system. *Journal of Health Care Law and Policy* (1):1-21.

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.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1976). *Report and Recommendations: Research Involving Prisoners*. Washington, D.C.: Department of Health, Education, and Welfare.

The 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, D.C.: Department of Health, Education, and Welfare.

Reverby, S.M. (2000). *Tuskegee's Truths: Rethinking the Tuskegee Syphilis Study*. Chapel Hill: University of North Carolina Press.

Ross, L.F. (2006). *Children in Medical Research: Access versus Protection*. New York: Oxford University Press.

Rothman, D.J. (2008). *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making*. New Brunswick: Aldine Transaction.

Tucker, T. (2006). *The Great Starvation Experiment: The Heroic Men who Starved so that Millions Could Live*. New York: The Free Press.

ENDNOTES

[1] Throughout this report, the Commission uses contemporary language (e.g., "STDs" instead of "venereal diseases") as opposed to the terminology used in the recovered historical documents, except when directly quoting from those materials. Dr. Susan M. Reverby, of Wellesley College, notified the U.S. government about the events involving the intentional exposure to STDs in the summer of 2010.

[2] Read-out of the President's Call with Guatemalan President Colom. (2010, October 1). Available at http://www.whitehouse.gov/the-press-office/2010/10/01/read-out-presidents-call-with-guatemalan-president-colom (accessed July 22, 2011).

[3] Joint Statement by Secretaries Clinton and Sebelius on a 1946-1948 Study. (2010, October 1). Available at http://www.hhs.gov/news/press/2010pres/10/20101001a.html (accessed July 22, 2011).

[4] Ibid.

[5] Caplan, A. (2010, October 1). "Horrific medical tests of past raise concerns for today," *MSNBC*. Available at http://www.msnbc.msn.com/id/39463624/ns/health-health_care/t/horrific-medical-tests-past-raise-concerns-today/ (accessed August 10, 2011). ("The impact of Tuskegee experiment has had a lasting effect on the lack of trust and suspicion minorities have about medical research… Many African-Americans believe that the government let doctors give people syphilis. While that did not happen in Tuskegee, the revelation of the Guatemalan research is a stark reminder that racism and indifference to the weak and the vulnerable did permit incredible abuses.") Landau, E. (2010, October 1). "Studies show 'dark chapter' of medical research," *CNN*. Available at http://www.cnn.com/ 2010/HEALTH/10/01/guatemala.syphilis.tuskegee/index.html?iref=allsearch (accessed August 30, 2011).

[6] Previously, the historical review was to be performed by the Institute of Medicine of the U.S. National Academies. The assignment moved to the Commission as more facts came to light. On November 24, 2010, the Academies explained: "Since receiving the request from [D]HHS, we have learned that at the time of the 1940s Guatemala study at least five individuals served simultaneously on the National Institutes of Health Study Section on Syphilis and the National Research Council's Subcommittee on Venereal Diseases. The same individual served as chair of both groups. Because of these overlapping appointments between our institution and a body involved in the federal government's syphilis research program, the National Academies should not conduct this historical review." National Academies Statement on the 1940s Guatemalan Syphilis Studies. (2010, November 24). Available at http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=20101124.

[7] Memorandum from President Barack Obama to Dr. Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues. (2010, November 24). Available at http://www.bioethics.gov/documents/Human-Subjects-Protection-Letter-from-President-Obama-11.24.10.pdf (accessed July 22, 2011).

[8] Ibid.

[9] Testimony of Executive Director Valerie H. Bonham to Commission, March 1, 2011.

[10] Personal communication, Susan Reverby, Wellesley College, to Brian Eiler, Commission staff, August 3, 2011. Speaking to the Boston Globe in October 2010, Dr. Reverby described her discovery: "I expected to find something on Tuskegee…There was nothing. What he left behind were these records from the Guatemala study." When Dr. Reverby "happened upon the documents" she "was just completely blown away." As she described in the interview: "I was floored." Smith, S. (2010). Wellesley Professor unearths a horror: Syphilis experiments in Guatemala. *The Boston Globe*. October 2, 2010. Available at http://articles.boston.com/2010-10-02/news/29290885_1 _reprehensible-research-susan-m-reverby-syphilis-experiments (accessed September 8, 2011).

[11] Reverby, S.M. (2010, May 2). *'Normal Exposure' and Inoculation Syphilis: PHS 'Tuskegee' Doctors in Guatemala, 1946-48 and at Sing Sing Prison, Ossining, New York, 1953-54*. Paper presented at the annual meeting of the American Association for the History of Medicine, Mayo Clinic, Rochester, MN.

[12] National Archives Press Release. (2011, March 28). Available at http://www.archives.gov/press/press-releases/2011/nr11-94.html (accessed September 7, 2011).

[13] For a history of the VDRL, see Parascandola, J. (2001). John Mahoney and the introduction of penicillin to treat syphilis. *Pharmacy in History* 43:3-13. In 1948 VDRL moved from its home in Staten Island, New York, to Chamblee, Georgia. *See* VDRL cooperates with state laboratories. (1954). *Public Health Reports* 69 (2): 202. In 1957, VDRL, along with the rest of the PHS Venereal Disease Division, was absorbed by

the Communicable Disease Center, and the functions of the VDRL were transferred to Atlanta, Georgia. Etheridge, E.W. (1992). *Sentinel for Health: A History of the Centers for Disease Control*. Berkeley, California: University of California Press, pp. 88-89. The Communicable Disease Center was renamed the Center for Disease Control in 1970 and was renamed again in 1992 as the Centers for Disease Control and Prevention, while maintaining the acronym CDC. CDC Office of the Associate Director for Communication. (2011, July 7). Available at http://www.cdc.gov/about/history/timeline.htm (accessed August 30, 2011). The U.S. Public Health Service's venereal disease control and laboratory activities now operate as part of CDC's Division of STD Prevention within the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention.

14 The Commission requested information when it visited Guatemala April 30 to May 3, 2011, and again after Guatemalan media reported that the government of Guatemala had identified living victims of the research. A regulation passed in Guatemala on May 1, 2011 precluded release of all records relating to the Guatemalan government's investigation prior to release of its final investigation report. Guatemala government Resolution Number 131-2011. Presidential Commission for the Study of Bioethical Issues Human Subjects Protections I (PCSBI HSPI) Archives, MISC_0000638. While unable to obtain specific records, Commission staff met with the Directors of the three Guatemalan Archives, Ana Carla Ericastilla (Central American Archives), Marco Tulio Alvarez (Peace Archives), and Gustavo Meono Brenner (Police Archives). They confirmed to the Commission staff that numerous records had been found in Guatemala substantiating the information from the Cutler Documents and also providing additional evidence surrounding the conduct of the experiments. The Guatemalan media has also reported that the government of Guatemala possesses records from the national hospital, the former Department of Public Health, and the psychiatric hospital. Villasenor, C.M. (2010, November 25). Archivo General de CA resguardará expediente de experimentos de EE. UU. *Prensa Libre*. (2010, November 11). Archivos de hospital mental no se destruyeron en 1960. *Prensa Libre*.

15 The Commission identified only one living person with first-hand knowledge of the events, though her recollection is limited and she was able to offer no specifics. The documents indicate that Mrs. John C. (Eliese S.) Cutler lived and worked with Dr. Cutler in Guatemala from 1946 into 1948. Commission staff contacted Mrs. Cutler, but she declined to speak with the staff. She did, however, send a letter to the Commission, writing: "I have no recollection of any such medical testing other than that conducted in the mental institution." Personal communication, Eliese S. Cutler to Valerie Bonham. (2011, June 25). PCSBI HSPI Archives, MISC_0000523.

16 Meeting, February 11, 2011. Vice President Espada was invited to speak at two Commission meetings held during the investigation, but regrettably for both parties, unanticipated events prevented him from traveling.

17 While unable to obtain specific records during its trip, the Commission was later aided by the work of an independent researcher in Guatemala, Mr. Martin Rangel, who provided relevant contemporaneous reports from Guatemalan media.

18 Beginning in 1924, PASB was the principal coordinating entity of international health activities in the Americas. During the time period of the STD studies in Guatemala, the PASB was closely linked with the U.S. PHS. In 1946, the PHS assigned "practically all of the professional staff of the Bureau." In 1947 and 1948, the PHS paid for the salaries of the PASB Assistant Director, the Chiefs of the Lima and Guatemala Zone Offices as well as officers and personnel assigned to special projects of the PHS. The two organizations shared the same leader, the U.S. Surgeon General, until 1936. (Hugh S. Cumming Sr., assumed the position of PASB Director when he took office as U.S. Surgeon General in 1920. In 1936, he retired as Surgeon General but remained PASB Director until 1947.) Fred L. Soper. (n.d.). Report of the Director of the Pan-American Sanitary Bureau to the Member Governments of the Pan American Sanitary Organization: January 1947-April 1950, p. 30. PCSBI HSPI Archives, PAHO_0000486. In 1949, the PASB became the Regional Office of the Americas of the World Health Organization, an arm of the Pan American Sanitary Organization, which is today known as the Pan American Health Organization. Cueto, M. (2007). *The Value of Health: A History of the Pan American Health Organization*. Washington, DC: Pan American Health Organization, pp. 63-108.

19 RG-65, awarded July 1946; RG-65(C), awarded July 1947, and extended to December 1948. Funding through 1953 was provided by PHS to several Guatemalan researchers. See, e.g., Juan M. Funes Personnel Files. (1948, December 10). PCSBI HSPI Archives, NPRC_0000807.

[20] It is important to recognize that "exposure" to an STD is not the same as "infection" with an STD. Subjects who were exposed to an STD by the researchers ran the risk of becoming infected with that STD, but many of the subjects that were exposed to an STD were not infected.

[21] PCSBI. (2011). Subject Database. This number represents the number of separate individuals exposed at least one time. Some individuals were exposed more than once.

[22] Ibid.

[23] All of the sex workers employed for the research were women.

[24] PCSBI. (2011). Subject Database.

[25] The available records show that the researchers did not inoculate the children in the orphanage or school with STDs.

[26] Stout, G.W., Cutler, J.C. (1951, September). Serology problems (syphilis) in Central America. *Journal of Venereal Disease Information*, 32(7): 238-239; Portnoy, J., Galvez, R., Cutler, J.C. (1952). Clinical and serologic studies with reference to syphilis in Guatemala, Central America. III. Studies of comparative performance of the Kahn, Kolmer, Mazzini, and VDRL slide tests among leprosy patients. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* 36(3):566-570.

[27] Falcone, V.H., Harris, A., Olansky, S., Salvado, C., Cutler, J.C. (1953). A study of the Neurath Inhibition Phenomenon in the serodiagnosis of syphilis. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* 37(3):264-272.

[28] A lumbar or cisternal puncture is the removal of cerebrospinal fluid through a needle inserted between two vertebrae in the lower back (lumbar) or into the base of the skull (cisternal).

[29] Report on Serologic Follow-up on Patients Done at CDC in 1953, Samples sent from Guatemala. (1953.) PCSBI HSPI Archives, CTLR_0001436.

[30] John Cutler to John Mahoney. (1947, September 18). Correspondence. PCSBI HSPI Archives, CTLR_0001231.

[31] Advisory Committee on Human Radiation Experiments. (1996). *Final Report of the Advisory Committee on Human Radiation Experiments.* New York: Oxford University Press; Moreno, J.D. (1999). *Undue Risk: Secret State Experiments on Humans.* New York: W.H. Freeman & Co.; Faden, R.R., Beauchamp, T.L. (1986). *A History and Theory of Informed Consent.* New York: Oxford University Press; Rothman, D.J. (1991). *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making.* New Brunswick: Aldine Transaction.

[32] See, e.g., World Medical Association. (1964). *Code of Ethics of the World Medical Association: Declaration of Helsinki.* Helsinki, Finland: World Medical Association; Drug Amendments of 1962, Public Law No. 87-781 (1962), *codified at* 21 U.S.C. 355 (requiring informed consent in certain FDA-regulated research); 21 C.F.R. 50 (same); National Research Act of 1974, Public Law No. 93-348 (1974), *codified at* 42 U.S.C. 218 (requiring informed consent and independent review in HHS-sponsored research); 45 C.F.R. 46 (same); Emanuel, E.J., Wendler, D., Grady, C. (2000). What makes clinical research ethical? *JAMA* 283(20):2701-2711.

[33] See 45 CFR 46, Subparts B-D (allowing for research on vulnerable populations, including prisoners and children, provided additional protections are in place); 45 C.F.R. § 46.116(d) (allowing for waiver of informed consent when: the research involves no more than minimal risk, the waiver will not adversely affect subjects' rights and welfare, the research could not practicably be conducted without the waiver, and, where appropriate, subjects are provided with additional information after participation). Today, intentional infection research is used for a variety of purposes, including proof of microbial pathogenicity, definition of protective antigens, identification of factors that influence disease acquisition and severity, assessment of vaccine efficacy, demonstration of infection-derived immunity, identification of protective immune responses, and refinement of vaccine formulation, schedule, and delivery. Kotloff, K.L. (2003). Human challenge studies with infectious agents. *Journal of Investigative Medicine* 51(Supp.): S6-S7. See also Cohen, M.S., Cannon, J.G. (1994). Human experimentation with *Neisseria gonorrhoeae*: Rationale, methods, and implications for the biology of infection and vaccine development. *Journal of Infectious Diseases.* 169:532-537 (providing an example of recent intentional infection research in gonorrhea).

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

[35] Ibid.

[36] Ibid.

[37] Ibid.

[38] Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000620.

[39] La Follette-Bulwinkle Act (Venereal Diseases), Public Law No. 75-540; 75 Cong. Ch. 267; 52 Stat. 439 (May 24, 1938). The Act made provisions for "establishing and maintaining adequate measures for prevention, treatment and control of VD [and] for the purpose of making studies, investigations and demonstrations to develop more effective measures for prevention, treatment, and control."

[40] 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 143.

[41] Ibid, at 144.

[42] Ibid.

[43] Draft of Committee on Medical Research History, Section on Venereal Disease attached to February 25, 1946, Memorandum from E. Cowles Andrus to Chester S. Keefer. (n.d.). PCSBI HSPI Archives, NARA-II_0000414. Indeed, only a year later, in 1944, the Army decided it could no longer use arsenical and bismuth treatment for the treatment of syphilis, given combat conditions, and sought advice from the Subcommittee on Venereal Diseases on how best to administer penicillin as an alternative treatment. Penicillin Conference Under the Auspices of the U.S. Public Health Service, Food and Drug Administration, and National Research Council. March 27, 1946, at 158.

[44] Ibid.

[45] Ibid, PCSBI HSPI Archives, NARA-II_0000415.

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

[47] The National Research Council (NRC) was organized in 1916 as an arm of the National Academy of Sciences by the National Academy of Sciences, under its congressional charter. In 1918, President Woodrow Wilson established the Council as a standing organization by Executive Order. Executive Order No. 2859, May 11, 1918.

[48] Joseph Moore to A.N. Richards. (1943, February 1). Correspondence. PCSBI HSPI Archives, NARA-II_0000176.

[49] Ibid.

[50] The membership of the CMR included Dr. A.N. Richards, Chairman; Rear Admiral Harold W. Smith (Navy); Brig. Gen. James S. Simmons (Army); Dr. R.E. Dyer (PHS); Dr. A.B. Hastings (Harvard University), and Dr. A.R. Dochez (Cloumbia University). First Draft of Proposed C.M.R. Chapter for Irvin Stewart's Administrative History of OSRD. (1945, January 12). PCSBI HSPI Archives, NARA-II_0000354; Lockwood, J.S. (1946, August). War-time activities of the National Research Council and the Committee on Medical Research; With particular reference to team-work on studies of wounds and burns. *Annals of Surgery* 124(2):314-315.

[51] First Draft of Proposed C.M.R. Chapter for Irvin Stewart's Administrative History of OSRD, 12 Jan. 1945, PCSBI HSPI Archives, NARA-II_0000354; Executive Order. (June 28, 1941).

[52] Ibid

[53] Ibid

[54] Rothman, D.J., op cit., pp. 30-31.

[55] Joseph Earle Moore Obituary. (1958). *British Journal of Venereal Disease* 34:58-59. When he died, Moore's memorial emphasized that he had devoted his "whole professional career…to the study and treatment of syphilis"; Thomas, H.M. (1960). Memorial: Joseph Earle Moore, MD. *Transactions of the American Clinical and Climatological Association* 71: xlix-l; Curriculum Vitae – Joseph Earle Moore, M.D. (n.d.). PCSBI HSPI Archives, JHU_0000035.

[56] Fox, D.M. (1987). The politics of the NIH Extramural Program, 1937-1950. *Journal of the History of Medicine and Allied Sciences* 42(4):452.

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

[58] Ibid.

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

[60] Ibid.

[61] Minutes of a Conference on Chemical Prophylaxis. (1942, November 18). PCSBI HSPI Archives, NARA-II_0000332. The Subcommittee on Venereal Diseases was formed within NRC on June 7, 1940, to make "general recommendations to The Surgeons General of the Army and the Navy concerning the prevention and treatment of the venereal diseases." See Padget, P. Diagnosis and treatment of the venereal diseases. In Coates, J.B. (Ed.). (1963). *Internal Medicine in World War II, Volume II: Infectious Diseases.* Washington, D.C.: Office of the Surgeon General, Department of the Army, p. 410.

[62] The Subcommittee consisted of Drs. Joseph E. Moore, Charles W. Clarke, Oscar F. Cox, Russell Herrold, John F. Mahoney, Nels Nelson, and John H. Stokes; E.H. Cushing to Robert L. Dickinson. (1942, December 9). Correspondence. PCSBI HSPI Archives, NAS_0000446.

[63] Minutes of a Conference on Chemical Prophylaxis (1942, November 18). PCSBI HSPI Archives, NARA-II_0000334.

[64] Thomas Parran to Lewis H. Weed. (1942, November 19). Correspondence. PCSBI HSPI Archives, NARA-II_0000284. Of note, Dr. Parran, former President of the American Neisserian Medical Society, may well have been familiar with the case of Albert Neisser, famous for his discovery of the bacterium that causes gonorrhea, who was fined by the government of Prussia for infecting prostitutes with syphilis without their knowledge or consent in 1898. Vollman, J., Winau, R. (1996). The Prussian regulation of 1900: Early ethical standards for human experimentation in Germany. *IRB: Ethics and Human Research* 18: 9-10. Kampmeier, R.H. (1984). Section I: The years of the American Neisserian Medical Society, 1934-1942. *Sexually Transmitted Diseases* 11(3):193.

[65] John A. Rogers to Lewis H. Weed. (1942, December 4). Correspondence. PCSBI HSPI Archives, NARA-II_0000283.

[66] Ross T. McIntire to Lewis H. Weed. (1942, December 5). Correspondence. PCSBI HSPI Archives, NARA-II_0000282.

[67] Ibid.

[68] The CMR consisted of, aside from Dr. Richards, Dr. Lewis H. Weed (Vice-Chairman), Rear Admiral Harold W. Smith (Navy), Brig. Gen. James S. Simmons (Army), Dr. R.E. Dyer (PHS), Dr. A.B. Hastings (Harvard University), and Dr. A.R. Dochez (Columbia University). First Draft of Proposed C.M.R. Chapter for Irvin Stewart's Administrative History of OSRD. (1945, January 12). PCSBI HSPI Archives, NARA-II_0000354.

[69] Minutes of the Seventeenth Meeting of the Subcommittee on Venereal Diseases – National Research Council. (1942, December 1). PCSBI HSPI Archives, NARA-II_0000342.

[70] Ibid; O.H. Perry Pepper to Lewis H. Weed. (1942, December 14). Correspondence. PCSBI HSPI Archives NAS_0000707.

[71] A.N. Richards to Joseph E. Moore. (1942, December 12). Correspondence. PCSBI HSPI Archives, NARA-II_0000136.

[72] The conference group consisted of: 1) Drs. Joseph Earle Moore, Oscar Cox, and Russell Herrold (from the Subcommittee on Venereal Diseases), 2) Drs. Alfred Cohn and Theodore Rosenthal (from the New York City Health Department), 3) Drs. James H. Lade and M. deMello (from the New York State Health Department), 4) Dr. Charles M. Carpenter (University of Rochester), 5) Dr. C. Phillip Miller (University of Chicago), 6) Drs. O.H. Perry Pepper, T.R. Forbes, G.A. Carden, and Wilbur Davison (NRC), 7) Dr. Lowell J. Reed (Johns Hopkins University), 8) Dr. Hugo Muench (International Health Division, Rockefeller Foundation), 9) Lt. Col. T.B. Turner, Maj. Gaylord W. Anderson, Maj. Thomas H. Sternberg, Maj. Robert Dyar, and Capt. Robert H. Reidel (U.S. Army), 10) Lt. J.F. Shronts and Cmdr. R.W. Mussen, R.N., British Liaison Officer (U.S. Navy), and 11) Dr. R.A. Vonderlehr (U.S. PHS).

[73] Minutes of a Conference on Human Experimentation in Gonorrhea Held Under the Auspices of the Subcommittee on Venereal Diseases and Exhibit B to Same. (1942, December 29). PCSBI HSPI Archives, NARA-II_0000157-175.

[74] Dr. Carpenter's statement on The Evaluation of Prophylactic Agents and Procedures in the Prevention of Gonorrhea. (n.d.). PCSBI HSPI Archives, NARA-II_0000162.

[75] Proposed Plan of Procedure in the Study of Chemical Prophylaxis in Human Volunteers among Prison Inmates, 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_0000168. The extensive consent form (called a "waiver") described the procedures and risks of the study in considerable detail, which suggests that the Subcommittee did want the "volunteers" to understand the study in which they were participating.

[76] 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. More specific evidence that this or a similar form was used in Terre Haute has not been located, but an oral history of the career of Dr. Henrik Blum, one of the PHS medical officers who ran the experiments, affirms that the prisoners were informed about the nature of the study. Dr. Blum had other criticisms of the Terre Haute experiments, but he stated that there was "[n]o question about" whether the prisoners were "aware of what was being done." Crawford, C. (1999). Henrik Blum, M.D., M.P.H., "Equity for the Public's Health: Contra Costa Health Officer; Professor, UC School of Public Health; WHO Fieldworker." An oral history conducted in 1997 by Caroline Crawford, Regional Oral History Office, The Bancroft Library, University of California, Berkeley. Available at http://www.archive.org/stream/equity pubhealth00blumrich/equitypubhealth00blumrich_djvu.txt (accessed May 16, 2011).

[77] 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.

[78] Ibid, PCSBI HSPI Archives, NARA-II_0000174.

[79] Ibid.

[80] The Committee on Medicine was one of eight major committees that made up the NRC's Division of Medical Sciences in 1941. First Draft of Proposed C.M.R. Chapter for Irvin Stewart's Administrative History of OSRD. (1945, January 12). PCSBI HSPI Archives, NARA-II_0000354-56.

[81] American Medical Association. Our History: Full List of Annual Meetings and Presidents. Available at http://www.ama-assn.org/ama/pub/about-ama/our-history/full-list-annual-meetings-presidents.page (accessed August 26, 2011).

[82] James E. Paullin to O.H. Perry Pepper. (1942, January 13). Correspondence. PCSBI HSPI Archives, NARA-II_0000264.

[83] Arthur L. Bloomfield to O.H. Perry Pepper. (1943, January 11). Correspondence. PCSBI HSPI Archives, NARA-II_0000266. Arthur L. Bloomfield was Professor of Medicine and Executive of the Department of Medicine at Stanford University. Cox, A.J., Hilgard, E.R., Rytand, D.A. (1962, September). Arthur L. Bloomfield 1888-1962. *California Medicine* 97(3): 91-192.

[84] Inter-Office Memorandum by J. B. Donovan regarding January 22, 1943 Conference. (n.d.). PCSBI HSPI Archives, NARA-II_0000150.

[85] Memorandum of a Conference of the Prophylaxis of Gonorrhea in Human Volunteers. (1943, January 23). PCSBI HSPI Archives, NARA-II_0000227-228.

[86] New York State law read: "no person shall do 'any act detrimental to the health of any human being.'" See Inter-Office Memorandum by J. B. Donovan regarding January 22, 1943 Conference. (n.d.) PCSBI HSPI Archives, NARA-II_0000151.

[87] Moreno, J.D., op cit., p. 26, describing the widespread use of conscientious objectors in human subject experiments.

[88] Memorandum of a Conference of the Prophylaxis of Gonorrhea in Human Volunteers. (1943, January 23). PCSBI HSPI Archives, NARA-II_0000227-228.

[89] Joseph E. Moore to A.N. Richards. (1943, February 1). Correspondence. PCSBI HSPI Archives NARA-II_0000178.

[90] Neither birth control nor STD prophylaxis was provided to women in the Armed Forces in 1942. See Considerations for Utilizing Women on a Station. (n.d.). PCSBI HSPI Archives, NAS_0000511.

[91] Joseph E. Moore to A.N. Richards. (1943, February 1). Correspondence. PCSBI HSPI Archives, NARA-II_0000177.

[92] Ibid. PCSBI HSPI Archives, NARA-II_0000184-85.

[93] Ibid. PCSBI HSPI Archives, NARA-II_0000183. While there is some discussion of homosexual sex among prisoners, the assumption was that most of the men were not sexually active while in prison. Proposed Plan of Procedure in the Study of Chemical Prophylaxis in Human Volunteers among Prison Inmates, 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_0000169. The various benefits of conducting research among prisoners had not gone unnoticed by other investigators; by the middle of the 20th century, a substantial number of medical experiments had been conducted in the United States using prisoners as subjects. Widespread prison research in the United States continued into the 1970s. See Bonham, V.H., Moreno, J.D. (2008). Research with captive populations: Prisoners, students, and soldiers. In Emanuel, E.E., et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics*. New York: Oxford University Press, pp. 461-474; Moreno, J.D., op cit.; Harkness, J.M. (1996). *Research Behind Bars: A History of Nontherapeutic Research on American Prisoners*, Ph.D. dissertation, University of Wisconsin-Madison.

[94] Joseph E. Moore to A.N. Richards. (1943, February 1). Correspondence. PCSBI HSPI Archives, NARA-II_0000183.

[95] Ibid, PCSBI HSPI Archives, NARA-II_0000184-85.

[96] Ibid.

[97] Ibid.

[98] Ibid, PCSBI HSPI Archives, NARA-II_0000184.

[99] Ibid. Subsequent discussion between NRC and the Surgeon General of the Navy yielded the same result for different reasons. Military personnel were rejected, in part, because of the "impossibility of deliberately exposing military personnel to infection even when volunteering…." Lewis H. Weed to Ross G. Harrison. (1943, March 2). Correspondence. PCSBI HSPI Archives, NARA-II_0000249.

[100] Joseph E. Moore to A.N. Richards. (1943, February 1). Correspondence. PCSBI HSPI Archives, NARA-II_0000184. This statement establishes an important consideration, later disregarded, for not including psychiatric institution patients in STD research. It is unclear if Dr. Moore knew, or approved, the later use in Guatemala of individuals in the psychiatric hospital. Evidence shows that the initial plan for Guatemala, as presented to Moore and others in the Syphilis Study Section in March 1946, included use of prisoners only. John Cutler, Final Syphilis Report. (1955, February 24). PCSBI HSPI Archives, CTLR_0000643; John Cutler to John Mahoney (1947, January 7). Correspondence. PCSBI HSPI Archives, CTLR_0001039.

[101] Joseph E. Moore to A.N. Richards. (1943, February 1). Correspondence. PCSBI HSPI Archives, NARA-II_0000185-86.

[102] Ibid, PCSBI HSPI Archives, NARA-II_0000185.

[103] Ibid, PCSBI HSPI Archives, NARA-II_0000186.

[104] Porter, H.H., et al. (1939). Social diseases at the crossroads. *Journal of the Oklahoma State Medical Association* 32: 54-61.

[105] Joseph E. Moore to A.N. Richards. (1943, February 1). Correspondence. PCSBI HSPI Archives, NARA-II_0000185-86. Some have suggested that few people actually saw either of those articles. See Harkness, J.M., op cit., pp.124-25.

[106] Porter, H.H., op cit., pp. 54-61.

[107] Joseph E. Moore to A.N. Richards. (1942, February 1). Correspondence. PCSBI HSPI Archives, NARA-II_0000186.

[108] James B. Donovan to Irvin Stewart. (1943, February 17). Correspondence. PCSBI HSPI Archives, NARA-II_0000221.

[109] Ibid.

[110] Ibid.

[111] Joseph E. Moore to James V. Bennett. (1943, February 18). Correspondence. PCSBI HSPI Archives, NARA-II_0000156.

[112] Ibid, PCSBI HSPI Archives, NARA-II_0000155.

[113] James V. Bennett to Joseph E. Moore. (1943, February 26). Correspondence. PCSBI HSPI Archives, NARA-II_0000188.

[114] Ibid. It was not uncommon to offer pardons or reduced sentences to prisoners participating in human experiments in prisons in the United States during the first half of the 20th century. Harkness, J.M., op cit., pp. 14-72.

[115] James V. Bennett to Joseph E. Moore. (1943, February 26). Correspondence. PCSBI HSPI Archives, NARA-II_0000188.

[116] Ibid.

[117] Ibid.

[118] Frank B. Jewett and Ross G. Harrison to Vannevar Bush. (1943, March 5). Correspondence. PCSBI HSPI Archives, NARA-II_0000190.

[119] Ibid. The designation of "personal opinion" in an "official capacity" is ambiguous, and no further explanation is contained in the available records.

[120] Ibid.

[121] Ibid, PCSBI HSPI Archives, NARA-II_0000190-192.

[122] On March 6, 1943, a note on a memorandum of a conversation with Joseph E. Moore states "Dr. Bush read this and approves. The V. D. prophylaxis studies can go ahead…" Unsigned conversation of March 5, 1943, with Joseph E. Moore. (1943, March 6). Correspondence. PCSBI HSPI Archives, NARA-II_0000146.

[123] Ibid.

[124] Ibid.

[125] R.A. Vonderlehr to F.M. King. (1943, February 24). Correspondence. PCSBI HSPI Archives, NLM_0000716.

[126] Dr. Bush may have felt also that research conducted directly by the U.S. government would face less public scrutiny. Unsigned conversation of March 5, 1943, with Joseph E. Moore. (1943, March 6). Correspondence. PCSBI HSPI Archives, NARA-II_0000146-47. See also letter from Joseph E. Moore to Thomas Parran, *reproduced in* Minutes of a Conference on Human Experimentation in Gonorrhea Held under the Auspices of the Subcommittee on Venereal Diseases. (1943, March 12). PCSBI HSPI Archives, NAS_0002328-36. These minutes show some internal conflict as Dr. Parran, the PHS Surgeon General, disfavored the proposal initially. He noted that PHS was not technically responsible for the care of federal prisoners. PHS provided personnel to the Bureau of Prisons so it could staff its medical facilities, and PHS was "responsible only for the professional competence of the personnel and the standards of professional care in the prisons." Memorandum from Thomas Parran to R.A. Vonderlehr. (1943, March 11). Correspondence. PCSBI HSPI Archives, NAS_0002342. Dr. Parran's concern appears to have resolved, however, since these materials show that Dr. Vonderlehr subsequently offered substantial support for the project.

[127] R.A. Vonderlehr to J.F. Mahoney. (1943, April 15). Correspondence. PCSBI HSPI Archives, NLM_0000712.

[128] Ibid.

[129] Parascandola, J. (2001). Op cit., p. 7.

[130] Ibid. U.S. Marine Hospitals were operated throughout the country by the PHS. The Marine Hospital Service, which traces its roots back to a 1798 law, was organized as a national organization in 1870.

Originally established to provide medical treatment to merchant seamen in American ports, it grew to become the U.S. Public Health Service, a uniformed service of the U.S. government charged with duties that involved the research, prevention, control, diagnosis, and treatment of human illness throughout the United States. Parascandola, J. (1998). Public Health Service. In Kurian, G.T. (Ed.) *A Historical Guide to the U.S. Government*. New York: Oxford University Press, pp. 487-493.

[131] Parascandola, J. (2001). Op cit., p. 7.

[132] Biographical Sketch, Dr. Cassius J. Van Slyke. (n.d.). PCSBI HSPI Archives, NPRC_0002846.

[133] Parascandola, J. (2001). Op cit, p. 7.

[134] Ibid.

[135] Ibid.

[136] Proposal for Contract in Medical Research Pertaining to National Defense. (1943, June 25). PCSBI HSPI Archives, NARA-II_0000583; Cassius J. Van Slyke Personnel Files. (Various dates). PCSBI HSPI Archives, NPRC_0002844-57.

[137] Ibid, PCSBI HSPI Archives, NARA-II_0000585.

[138] Approximately $590,000 today, when adjusted for inflation.

[139] Proposal for Contract in Medical Research Pertaining to National Defense. (1943, June 25). PCSBI HSPI Archives, NARA-II_0000584.

[140] Report to Subcommittee on Venereal Diseases. (1943, November 11). PCSBI HSPI Archives, NAS_0003530; Draft of CMR History, Section on Venereal Disease attached to February 25, 1946 Memorandum from E. Cowles Andrus to Chester S. Keefer. (n.d.). PCSBI HSPI Archives, NARA-II_0000419; Cutler Award Citation. (n.d.). PCSBI HSPI Archives, MISC_0000341.

[141] Dr. John C. Cutler, CV. (n.d.). PCSBI HSPI Archives, MISC_0000409.

[142] Ibid.

[143] Henrik Blum, M.D., M.P.H., op cit.

[144] Mahoney, J.F., Van Slyke, C.J., Cutler, J.C., Blum, H.L. (1946, January). Experimental gonococcic urethritis in human volunteers. *American Journal of Syphilis, Gonorrhea, and Venereal Disease* 30:3.

[145] Reports to a Conference Held Under the Auspices of the Subcommittee on Venereal Diseases 9 February 1944, on the Chemical Prophylaxis of Venereal Disease. (1944, February 9). PCSBI HSPI Archives, NAS_0003112.

[146] The Department of Justice was unable to locate any records pertaining to this research. E-mail from Mala Adiga, Counsel to the Associate Attorney General, U.S. Department of Justice, to Brian Eiler, Senior Policy and Research Analyst, Presidential Commission for the Study of Bioethical Issues. (2011, June 6). PCSBI HSPI Archives, DOJ_0000098.

[147] Report to Subcommittee on Venereal Diseases. (1943, November 11). PCSBI HSPI Archives, NAS_0003531; Mahoney, J.F., Van Slyke, C.J., Cutler, J.C., Blum, H.L. (1946). Op cit.

[148] Report to Subcommittee on Venereal Diseases. (1943, November 11). PCSBI HSPI Archives, NAS_0003531.

[149] Minutes of the Twenty-First Meeting of the Subcommittee on Venereal Diseases. (1943, November 11). PCSBI HSPI Archives, NAS_0002782; Reports to a Conference Held Under the Auspices of the Subcommittee on Venereal Diseases 9 February 1944, on the Chemical Prophylaxis of Venereal Disease. (1944, February 9). PCSBI HSPI Archives, NAS_0003114-17.

[150] Reports to a Conference Held Under the Auspices of the Subcommittee on Venereal Diseases, op cit.

[151] In an oral history conducted with Dr. Henrik Blum in 1997, he stated that it was his job to "examine[] prostitutes to find gonorrhea bugs to bring fresh bugs in because it was part of our experiment." According to Dr. Blum, the prostitutes had been "picked up by the police. Terre Haute was a town famous for its prostitution because it was the soft coal mining center. The miners came to Terre Haute for recreation--R & R, rest and recreation." Henrik Blum, M.D., M.P.H., op cit.

[152] Minutes of a Conference on Chemical Prophylaxis of Venereal Diseases. (1944, February 9). PCSBI HSPI Archives, NAS_0002070.

[153] Reports to a Conference Held Under the Auspices of the Subcommittee on Venereal Diseases 9 February 1944, on the Chemical Prophylaxis of Venereal Disease. (1944, February 9). PCSBI HSPI Archives, NAS_0003113.

[154] Ibid.

[155] Minutes of a Conference on Chemical Prophylaxis of Venereal Diseases. (1944, February 9). PCSBI HSPI Archives, NAS_0002072.

[156] Minutes of a Conference on the Prevention of Gonococcal Infection in Experimentally Infected Human Male Volunteers. (1944, April 4). PCSBI HSPI Archives, NAS_0002089.

[157] The conference was attended by: 1) Dr. Oscar F. Cox, Dr. Phillip Miller, and Dr. Russell Herrold (from the NRC), 2) Dr. Marion R. King, Dr. R.O. Settle, and Warden E.B. Swope (from the Bureau of Prisons), and 3) Drs. Mahoney, Van Slyke, Cutler, and Blum, and Mr. Harold Hirschhorn and Miss Millicent R. Chapman (from the PHS). Minutes of a Conference on the Prevention of Gonococcal Infection in Experimentally Infected Human Male Volunteers, (1944, April 4). PCSBI HSPI Archives, NAS_0002089.

[158] Ibid, PCSBI HSPI Archives, NAS_0002090.

[159] Minutes of the Twenty Third Meeting, Subcommittee on Venereal Diseases of the Committee on Medicine. (1944, June 29). PCSBI HSPI Archives, NAS_0002108.

[160] John Cutler to John F. Mahoney. (1947, September 20). Correspondence. PCSBI HSPI Archives, CTLR_0001225.

[161] Final Report, Prevention of Gonococcal Infection in Experimentally Infected Human Volunteers. (1944, July 1). PCSBI HSPI Archives, NAS_0003656.

[162] 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. The Venereal Disease section of the draft was written by a team directed by Dr. Joseph E. Moore.

[163] Ibid, PCSBI HSPI Archives, NARA-II_0000420.

[164] Mahoney, J.F., Van Slyke, C.J., Cutler, J.C., Blum, H.L. (1946). Op cit. The journal was the official publication of the American Neisserian Medical Society and later the American Venereal Disease Association. Kampmeier, R.H. (1974, September). Historical note. *Journal of the American Venereal Disease Association* 1(1): 8-9.

[165] Mahoney, J.F., Van Slyke, C.J., Cutler, J.C., Blum, H.L. (1946). Op cit., p. 32.

[166] Ibid.

[167] Ibid, p. 33.

[168] Since the 18th century, researchers have reported inoculating human subjects, often including themselves, with syphilis, gonorrhea, and chancroid to evaluate questions regarding the nature of these diseases, contagion, immunity, and the like. Weyers, W. (2003). *The Abuse of Man: An Illustrated History of Dubious Medical Experimentation*. New York: Ardor Scribendi, pp. 19-40; Magnuson, H.J., et al. (1956). Inoculation syphilis in human volunteers. *Medicine* 35(1):35-41; Hill, J. (1943). Experimental infection with *Neisseria gonorrhoeae*. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* 27:733-762. The first reported STD inoculation study supported by the U.S. government identified in the course of the Commission's review was published in 1943, "done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Georgia School of Medicine." Human subjects were inoculated in the thigh with chancroid bacterium in order to evaluate the efficacy of various prophylactics. Greenblatt, R.B., et al. (1943). Experimental prophylaxis of Chancroid Disease. *American Journal of Syphilis, Gonorrhea, and Venereal Disease* 27: 30-43; Greenblatt, R.B., et al. (1944). The experimental prophylaxis of Chancroid Disease – II. *American Journal of Syphilis, Gonorrhea, and Venereal Disease* 28:165-178.

[169] These concerns followed the researchers to Guatemala, however, as evidenced by some of their efforts to limit and restrict access to information about the work.

[170] This work also proceeded under the auspices of NRC and OSRD. Mahoney, J.F., Arnold, R.C., Harris, A. (1943). Penicillin treatment of early syphilis: A preliminary report. *American Journal of Public Health and the Nation's Health* 33(12):1390; Parascandola, J. (2008). *Sex, Sin, and Science: A History of Syphilis in America.* Westport, CT: Praeger, 129.

[171] Mahoney, J.F., Arnold, R.C., Harris, A. (1943). Op cit., p. 1390; New Magic Bullet. (1943). *TIME Magazine*, October.

[172] Before the development of penicillin, options for treating syphilis included mercury, arsenic, bismuth, iodides, and sodium thiosulphate. There were several types of arsenical drugs, with varying efficacies and toxicities. Salvarsan proved the most toxic and thus was generally replaced by neoarsphenamine, sulpharsphenamine, and silverarsphenamine. Callis, H.A. (1929). Comparative therapy in syphilis. *Journal of the National Medication Association* 21(2):61-63. However, none of these drugs were completely effective, particularly in the late stages of disease. The larger issue was associated adverse events, including dermatitis, argyria, kidney irritation, and injury to blood, blood-forming organs, and cerebral vessels.

[173] New Magic Bullet. (1943). *TIME Magazine*, October. In 1943, state health departments in the United States reported cases of primary and secondary syphilis at a rate 63.8 per 100,000. Ten years later, once penicillin had been made available and widely adopted throughout the United States, cases of primary and secondary syphilis dropped over 90 percent to a rate of 5.6 per 100,000. CDC. (1998). *Sexually Transmitted Disease Surveillance 1997.* CDC: Prevention, Division STD Prevention, 65.

[174] Moore, J.E., Mahoney, J.F., et al. (1944). The treatment of early syphilis with penicillin: A preliminary report of 1,418 cases. *Journal of the American Medical Association* 126(2):67-73. The experiment began in September 1943.

[175] Parascandola, J. (2008). Op cit., p. 129-130. There was debate about how much penicillin to use in the treatment of syphilis in 1944, as evidenced by discussion at a Penicillin Conference chaired by Dr. Moore and held under the auspices of PHS, the Food and Drug Administration (FDA), and NRC a couple of years later. Dr. Mahoney et al. used 1.2 million units of penicillin over seven and a half days in their first four cases. Mahoney, J.F., Arnold, R.C., Harris, A. (1943). Op cit., p. 1390. According to the discussion at the Penicillin Conference, the Armed Forces, with the advice of the Subcommittee on Venereal Diseases, doubled that when it implemented penicillin treatment for syphilis in 1944, using 2.4 million units in seven and a half days. Penicillin Conference Under the Auspices of the U.S. Public Health Service, Food and Drug Administration, and National Research Council. March 27, 1946, at 158-159.

[176] Moore, J.E., Mahoney, J.F., et al. (1944). Op cit. In response to Mahoney and Arnold's preliminary results, a Penicillin Panel was formed under the auspices of OSRD and the Subcommittee on Venereal Diseases. The Panel initially consisted of Drs. Moore and Mahoney; Commander Walter Schwartz, U.S. Navy; Lieutenant Colonel Thomas Sternberg, U.S. Army Medical Corps; and Dr. Barry Wood. Dr. John Heller, Medical Director in charge of the Venereal Disease Division, was later added to the Panel. As discussed below, the Penicillin Panel was renamed the Syphilis Study Section in 1946. Fox, D.M. (1987). The politics of the NIH Extramural Program, 1937-1950. *Journal of the History of Medicine and Allied Sciences* 42(4):458-459.

[177] In addition, while syphilis is typically only contagious in its first stage, rapid treatment with penicillin may make people susceptible to new infections and put them once again in a transmissible stage.

[178] National Research Council – U.S. Public Health Service. (1946). Transcript: Meeting of Penicillin Investigators, National Academy of Science, Washington, D.C; John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000892.

[179] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000639.

[180] Ibid.

[181] Ibid. The results do not appear to have been published.

[182] Ibid.

[183] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001279.

[184] Ibid, PCSBI HSPI Archives, CTLR_0001278.

[185] Ibid, PCSBI HSPI Archives, CTLR_0001279. This was briefly mentioned in a paper presented by Dr. Paul D. Rosahn of Yale University at a meeting of Penicillin Investigators, sponsored by PHS and NRC February 7-8, 1946. Drs. J.E. Moore and J.H. Stokes, who presided over the meeting, also addressed the question during the general discussion portion of the meeting on the morning of February 7. National Research Council – U.S. Public Health Service. (1946). Transcript: Meeting of Penicillin Investigators, National Academy of Science, Washington, D.C.

[186] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001279.

[187] Mahoney, J.F. (1947, July). Some significant aspects of venereal disease research: Work of the Venereal Disease Research Laboratory, Staten Island, N.Y. *Journal of Venereal Disease Information* 28(7):129.

[188] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000640.

[189] Ibid, PCSBI HSPI Archives, CTLR_0000639-40. Dr. Funes visited the VDRL under the auspices of the Office of Inter-American Affairs (OIAA). The United States created OIAA in 1941 to develop commercial and cultural relations between North and South America. The OIAA's name was changed in 1945 to "Coordinator of Inter American Affairs." Official Personnel Folder: Juan M. Funes, "Special Consultant Appointment Recommendation." (1948, December 10). PCSBI HSPI Archives, NPRC_0000807; John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000639-40; National Archives. (1945). Executive Orders Disposition Tables: Franklin D. Roosevelt-1945. Available at http://www.archives.gov/federal-register/executive-orders/1945-roosevelt.html (accessed May 16, 2011); National Archives. (n.d.). Records of the Office of Inter-American Affairs. Available at http://www.archives.gov/research/holocaust/finding-aid/civilian/rg-229.html (accessed May 16, 2011).

[190] John Cutler (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000639-40.

[191] There are many scientific terms required to describe the experiments in Guatemala. Please see the Glossary of Key Terms at the end of the report for further detail.

[192] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000643.

[193] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001279; John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000640. The researchers categorized sexual intercourse as "normal exposure" to STDs. Dr. Mahoney had long advocated that best practice in syphilis research, at least in rabbits, would "require[]" the intact maintenance of the exposed penile membrane to preserve "whatever mechanical or biological defense mechanisms may be inherent thereto." See Mahoney, J. F. (1936). An experimental resurvey of the basic factors concerned in prophylaxis in syphilis. *The Military Surgeon* 352-53. This approach stood in contrast to the use of "scarification" of the membrane to cause infection (that Dr. Cutler later employed) as such method "permits an unnatural freedom of ingress for the organism." Ibid. Discussing animal inoculation in preparation for the Terre Haute study, Dr. Mahoney again argued that the most favorable method of inoculation was that which most closely "simulated the method of inoculation in human beings exposed by sexual intercourse, i.e., the simple contact of an emulsion of *T. pallidum* with an unbroken mucous surface." Moore, J.E. (1942, March 23). Memorandum: Conference on Chemical Prophylaxis of Venereal Diseases. PCSBI HSPI Archives, NAS_0003411. Dr. Mahoney also reiterated the sentiment that scarification and artificial implementation were "drastic…[and] beyond the range of natural transmission" in a letter to Dr. Cutler in 1947. John Mahoney to John Cutler. (1947, September 8). Correspondence. PCSBI HSPI Archives, CTLR_0001234. Despite his supervisor Mahoney's stated preferences, Dr. Cutler would defend his scarification and other techniques beyond sexual intercourse when inducing infection through sexual intercourse in Guatemala proved difficult. John Cutler to John Mahoney. (1947, September 18). PCSBI HSPI Archives, CTLR_0001231.

[194] The Office was established by Executive Order in July 1941 to promote "the spirit of cooperation between the Americas in the interest of Hemisphere defense." Executive Order 8840, July 30, 1941.

[195] Vought, R.L. (1946). The administration of an Inter-American Cooperative Health Program. *Public Administration Review* 6(1):49; Silva-Lizama, E. (2000). History of dermatology in Guatemala. *International Journal of Dermatology* 39(4):305-311. That hospital, called Roosevelt Hospital (after President Franklin D. Roosevelt) continues to serve as one of two major public hospitals providing free care in the country. Additionally, the presence of the U.S. military base in Guatemala provided Dr. Cutler and the researchers with supplies and equipment through their Army Transport Service and Army Post Office. John Cutler to

John Mahoney. (1946, November 22). Correspondence. PCSBI HSPI Archives, CTLR_0001254; John Cutler to John Mahoney. (1947, January 7). Correspondence. PCSBI HSPI Archives, CTLR_0001037; Richard Arnold to John Cutler. (1947, February 27). Correspondence. PCSBI HSPI Archives, CTLR_0001056; Richard Arnold to John Cutler. (1947, April 18). Correspondence. PCSBI HSPI Archives, CTLR_0001113; Ad Harris to John Cutler. (1947, April 21). Correspondence. PCSBI HSPI Archives, CTLR_0001114; John Cutler to John Mahoney. (1947, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001241.

196 Rothman, D.J., op cit., pp. 30-31.

197 Fox, D.M., op cit., pp. 454-455 discussing the legislation that allowed the PHS to make grants-in-aid.

198 Public Health Service Act of 1944, Public Law No. 78-410, 58 Stat. 682; see also Fox, D.M., op cit., p. 454. Before passage of the Public Health Service Act of 1944, the Public Health Service had more limited authority to provide aid to states and issue grants-in-aid to combat specific medical illnesses under several different statutes. See e.g., Venereal Disease Control Act of 1938, 40 Stat. 886. May 24, 1938; National Cancer Institute Act of 1937, Public Law No. 75-244. August 5, 1937. See also Statement, National Advisory Health Council. (1945). *Science* 102(2640):113, describing new authority of NAHC under the Public Health Service Act of 1944 and Surgeon General Parran's statement regarding that new authority.

199 Public Health and Marine-Hospital Service Act, Public Law No. 57-236, 32 Stat. 712. July 1, 1902.

200 Ransdell Act, Public Law No. 71-251, 46 Stat. 379. May 26, 1930, reorganizing and designating the Hygienic Laboratory as the National Institute of Health. The Advisory Board was renamed the National Advisory Health Council in 1930. Public-Health Activities Act, Public Law No. 71-106, 46 Stat. 150. April 9, 1930. See also Statement, The National Institute of Health. (1930). *Science* 72(1861): 214-215, describing how the Hygienic Laboratory became the National Institute of Health.

201 Meeting of the National Advisory Health Council. (1931). *Science* 73(1894): 412-413.

202 National Institutes of Health, Division of Research Grants. (1996). *Division of Research Grants: A Half Century of Peer Review* Alexandria, Virginia: National Institutes of Health, p. 12.

203 Fox, D.M., op cit., p. 456.

204 Ibid, p. 457; Division of Research Grants, op cit., pp. 16-22, describing the transfer of OSRD contracts to the Research Grants Office. See also Public Health Service Act of 1944, Public Law No. 78-410, 58 Stat. 682; Strickland, S.P. (1989). *The Story of the NIH Grants Program.* Lanham, Maryland: University Press of America, p. 18, describing how the Division of Research Grants arose as a peacetime replacement for OSRD and CMR.

205 Fox, D.M., op cit., p. 457. Dr. Van Slyke, with Drs. Parran and Heller, favored a process to maximize investigator independence. The award process should be accompanied, Dr. Van Slyke stated, by "complete acceptance of a basic tenet of the philosophy upon which the scientific method rests: The integrity and independence of the research worker and his freedom from control, direction, regimentation and outside interference." See Van Slyke, C.J. (1946, December 13). New horizons in medical research. *Science* 104(2711):559-562. See also Strickland, S.P., op cit., p. 22, describing the "grant-contracts" that Drs. Parran and Van Slyke favored as OSRD contracts were transferred to the NIH grant system. In the January 1948 introduction to a *Public Health Reports* supplement, which indexed research awards, Dr. Van Slyke further explained: "wide latitude is allowed the responsible scientific investigator in the use of research grants funds. Recipients of awards are given complete freedom to conduct projects in whatever ways they choose. They are requested to make only such reports as will assure the government that the money being spent for their research is wisely and carefully used." U.S. Public Health Service. (1948). *Research Grants Awarded by Public Health Service, supplement No. 205.* Washington, DC: U.S. Government Printing Office. PCSBI HSPI Archives, MISC_0000037.

206 Van Slyke, C.J., op cit., p. 559; Fox, D.M., op cit., p. 457; Strickland, S.P., op cit., p. 19.

207 Van Slyke, C.J., op cit., p. 559. See also Allen, E.M. (1980). Historical view: Early years of NIH research grants. *NIH Alumni Association Newsletter* 2(2): 6-8.

208 Public Health Service Act of 1944, Public Law No. 78-410, 58 Stat. 692, §301(d); Van Slyke, C.J., op cit., p. 562.

209 Fox, D.M., op cit., pp. 458-459, citing a December 1945 letter from Dr. Parran to the Federal Security Agency administrator. See also Committee on Medical Research and Public Health Service. (1946). The treatment of early syphilis with penicillin: A joint statement. *JAMA* 131(4): 265-266, describing the role of

the NRC Penicillin Panel and the transfer of its responsibilities to the NIH Syphilis Study Section "with the same membership" plus two clinicians and a biostatician.

[210] The Syphilis Study Section convened to "hear papers and progress reports of the syphilis and penicillin investigations." See Ernest Allen to R.E. Dyer. (1946, March 8). Correspondence. PCSBI HSPI Archives, NARA-II_0000129. No specific protocols or applications considered by the group, including those for the Guatemala research, could be located.

[211] There is no evidence that Dr. Mahoney, an architect and supervisor of the Guatemala work, recused himself from reviewing the project.

[212] The membership list comes from a December 1946 publication of then NIH Research Grants Division Lead, Dr. C.J. Van Slyke. See Van Slyke, C.J., op cit., p. 567. An earlier publication authored by the OSRD CMR and the PHS in May 1946 suggests a slightly different membership, composed of: Dr. J.W. Ferree (Navy), Dr. John F. Mahoney (Subcommittee on Venereal Diseases), Dr. Joseph E. Moore (Subcommittee on Venereal Diseases), Dr. Walter Schwartz (Navy), Dr. Harry C. Solomon (Harvard University), Dr. T.H. Sternberg (Army), Dr. John H. Stokes (University of Pennsylvania), and Dr. W.B. Wood, Jr. (Committee on Chemotherapeutics and Other Agents). See Committee on Medical Research and Public Health Service, op cit., p. 265.

[213] This description of the study is from a final letter from Chairman Moore to Dr. C.J. Van Slyke, with a copy to the entire Study Section, during deliberation of the reauthorization of the original grant. Joseph E. Moore to C.J. Van Slyke. (1947, May 26). Correspondence. PCSBI HSPI Archives, NARA-II_0000036.

[214] An abstract for this work was included in a group of "all new projects" circulated to members of the NAHC for review prior to its March meeting, but the abstracts have not been located. See Ernest Allen to R.E. Dyer. (1946, March 8). Correspondence. PCSBI HSPI Archives, NARA-II_0000129. See Van Slyke, C.J., op cit., pp. 556, 564. See also Fox, D.M., op cit., p. 450.

[215] Other members who were present at the NAHC meeting March 8-9, 1946 were: Gordon M. Fair (Harvard University), A. Baird Hastings (Harvard University), Carl S. Marvel (University of Illinois), Kenneth F. Maxcy (Johns Hopkins University), Karl F. Meyer (University of California, San Francisco), Harry S. Mustard (Columbia University), William C. Rose (University of Illinois), Henry F. Vaughan (University of Michigan), Harry W. Schoening (U.S. Department of Agriculture), Capt. O.L. Burton (U.S. Navy), R.E. Dyer (NIH Director), Col. Karl R. Lundeberg (U.S. Army). Absent members were Edwin B. Fred (University of Wisconsin), Lowell J. Reed (Johns Hopkins University), and John H. Musser (Tulane University). National Advisory Health Council Meeting, U.S. Public Health Service. (1946, March 8 and 9). PCSBI HSPI Archives, NARA-II_0000544; Van Slyke, C.J., op cit., pp. 559-567.

[216] Minutes of the National Advisory Health Council Meeting. (1946, March 8-9). PCSBI HSPI Archives, NARA-II_0000546. Meeting minutes show that this grant award was unusual in other ways. NAHC considered 30 grant applications during its two-day meeting, and meeting minutes list each proposal with the name of an institution as a grantee and the name of an individual as the principal investigator. The only exception is RG-65, which simply names "Guatemala" as the grantee and "Pan American Union" as the investigator. In addition, the amount recommended for RG-65 was conspicuously large, over five times greater than any other grant approved during the meeting. Just over a year later, on May 14-15, 1947, Dr. Parran presided over another NAHC meeting that recommended a continuing grant, RG-65(C), in the amount of $105,800, the largest amount for any grant recommended at the meeting. Members present at the May 14-15 meeting were George Baehr, Gordon Fair, A. Baird Hastings, Carl S. Marvel, Karl F. Meyer, John H. Musser, Harry S. Mustard, Henry F. Vaughan, Cpt. O.L. Burton, Col. Karl R. Lundeberg, Harry W. Schoening, and R.E. Dyer. Also present were non-members Deputy Surgeon General James A. Crabtree, C.J. Van Slyke, Ernest Allen, John D. Porterfield, David E. Price, and Mary Switzer (Assistant to the Administrator, Federal Security Agency). PCSBI HSPI Archives, NARA-II_0000473-74; Medical Research Grants. (1947, April 26). *JAMA* 17(133): 1289 (which reported, "of the 193 grants that supplement existing funds of universities and other research institutions, the largest, $105,800 was recommended for a study of syphilis by the Pan American Sanitary Bureau").

[217] In addition, PHS sent down materials and supplies. C.H. Morrison to John Cutler. (1946, November 4). Correspondence. PCSBI HSPI Archives, CTLR_0001262. The precise amount awarded and paid out for RG-65, 65(c) is unclear. Public Health Reports Supplement No. 205, revised shows that the total amount actually awarded for Grant 65, 65(c) as of August 31, 1948 was $171,950 ($44, 300 less than the total amount recommended by the NAHC). U.S. Public Health Service. (1948), *Research Grants Awarded by PHS*, *Public Health Reports,* Supplement No. 205, revised. p. 38. PCSBI HSPI Archives,

MISC_0000907. In addition to the grants funds that the PHS awarded to PASB, the PHS paid the salaries of five of researchers working on the STD studies in 1948 (John C. Cutler, Virginia Lee Harding, Sacha Levitan, Joseph Portnoy, and Alice Walker), worth $23,585.91 in services in kind. PASB. PASB Statement of Services in kind. (n.d.). PCSBI HSPI Archives PAHO_0000577-78. PASB salary records were not available for 1946 or 1947, but a conservative estimate for the combined years of 1946 and 1947 would be a $27,500 PHS contribution of services in kind. Combining these figures, the estimated amount that the PHS provided to PASB in direct funding and services for the purpose of conducting STD research in Guatemala is $223,032.91.

218 Pan American Sanitary Organization Executive Committee. Final Report of the Fourth Meeting of the Executive Committee of the Pan American Sanitary Bureau (1948, May 3-13). p. 9. PCSBI HSPI Archives, PITT_0000182.

219 Describing the construction in a 1951 publication, PASB serologist Genevieve Stout, on detail from the U.S. PHS, explained that it was "for the purpose of conducting an investigation of the serologic picture presented by the people in that area." Stout, G.W., Cutler, J.C. (1951). Serology problems (syphilis) in Central America. *Journal of Venereal Disease Information* 32(7): 237.

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

221 Dr. Spoto was doing work in Guatemala on onchocerciasis (a parasitic disease that causes blindness). Working with Guatemala's Dirección General de Sanidad Pública, Spoto and his colleagues examined more than 1,000 infected people around Guatemala City beginning in 1945. Clark, W.B. (1947). Ocular onchocerciasis in Guatemala: An investigation of 1,215 natives infected with onchocerca volvulus. *Transactions of the American Ophthalmological Society* 45:461-501.

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

223 John Cutler to John Mahoney. (1946, September 3). Correspondence. PCSBI HSPI Archives, CTLR_0001213.

224 Ibid.

225 John Cutler to John Mahoney. (1946, October 1). Correspondence. PCSBI HSPI Archives, CTLR_0001210.

226 John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000629. Joseph Portnoy followed in September 1946, Dr. Harlow arrived in winter 1947, and Dr. Levitan joined in spring 1947. John Cutler to John Mahoney (1946, September 3). Correspondence. PCSBI HSPI Archives, CTLR_0001213; John Cutler to John Mahoney. (1947, September 21). Correspondence. PCSBI HSPI Archives, CTLR_0001225; John Cutler to John Mahoney. (1947, February 4). Correspondence. PCSBI HSPI Archives, CTLR_0001047.

227 John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000641. Agreements and "commitments" were also referred to in contemporaneous Cutler correspondence. See e.g., John Cutler to John Mahoney. (1946, September 3). Correspondence. PCSBI HSPI Archives CTLR_0001213; and John Cutler to John Mahoney. (1947, September 20). Correspondence. PCSBI HSPI Archives, CTLR_0001225. Copies of these agreements were not included in the Cutler Documents and have not been located. Searches were conducted in the PAHO archives and the National Archives.

228 While the agreements may have given the researchers the authority claimed, it is clear that some of the specifics, e.g., use of "orphans and the insane," were undertaken well after his arrival in August 1946. See, e.g., John Cutler to John Mahoney. (1947, January 7). Correspondence. PCSBI HSPI Archives, CTLR_0001039. John Cutler to John Mahoney. (1946, September 3). Correspondence. PCSBI HSPI Archives, CTLR_0001213.

229 John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000642. Dr. Cutler added that they would have access to "excellent facilities for close follow-up on syphilis" in the Military Hospital and Penitentiary. John Cutler to John Mahoney. (1946, September 3). Correspondence. PCSBI HSPI Archives, CTLR_0001213.

230 Ibid. While these agreements could not be located, requests were made to PAHO (the successor organization of PASB) and the U.S. government.

[231] John Cutler. Final Syphilis Report. (1955, February 24). PCSBI HSPI Archives, CTLR_0000641.

[232] John Cutler to John Mahoney. (1946, September 3). Correspondence. PCSBI HSPI Archives, CTLR_0001213.

[233] In 1946 Dr. Mahoney told Dr. Cutler: "I have the highest regard for [Spoto's] judgement and ability..." John Mahoney to John Cutler. (1946, November 18). Correspondence. PCSBI HSPI Archives, CTLR_0001194.

[234] John Cutler to John Mahoney. (1946, October 17). Correspondence. PCSBI HSPI Archives, CTLR_0001208.

[235] John Cutler to John Mahoney. (1946, November 12). Correspondence. PCSBI HSPI Archives, CTLR_0001196.

[236] PCSBI. (2011). Subject Database.

[237] John Mahoney to John Cutler. (1946, October 15). Correspondence. PCSBI HSPI Archives, CTLR_0001200.

[238] John Mahoney to John Cutler. (1946, November 18). Correspondence. PCSBI HSPI Archives, CTLR_0001195.

[239] John Cutler to John Mahoney. (1946, November 30). Correspondence. PCSBI HSPI Archives, CTLR_0001192.

[240] [Translation]. Constantino Alvarez B. to John Cutler. (1946, December 26). Correspondence. PCSBI HSPI Archives, CTLR_0001068.

[241] [Translation]. John Cutler to Constantino Alvarez B. (1947, January 13). Correspondence. PCSBI HSPI Archives, CTLR_0001068.

[242] [Translation]. Carlos Tejeda to John Cutler. (1947, June 17). Correspondence. PCSBI HSPI Archives, CTLR_0001075.

[243] John Cutler to Carlos Tejeda. (1947, June 26). Correspondence. PCSBI HSPI Archives, CTLR_0001072-73.

[244] [Translation]. (1947). Primera Asamblea de Cirujanos Militares. *Diario de Centro America*. July 17, 1947.

[245] John Cutler to John Mahoney. (1947, January 20). Correspondence. PCSBI HSPI Archives, CTLR_0001041.

[246] Ibid.

[247] Ibid. In his 1955 Final Syphilis Report, Dr. Cutler noted that the researchers instituted a serologic screening program for all new prison admissions, and set up a system of "prophylaxis" for prisoners having sexual contact with a woman other than a wife. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000644. However, the January 20, 1947 letter from Dr. Cutler to Dr. Mahoney suggests that a comprehensive prophylaxis program was placebo-based. John Cutler to John Mahoney. (1947, January 20). Correspondence. PCSBI HSPI Archives, CTLR_0001041.

[248] PCSBI. (2011). Subject Database.

[249] John Cutler. (1955, February 24). Final Syphilis Report, PCSBI HSPI Archives, CTLR_0000628. Dr. Robles was also listed as a "Guatemalan Government Participant" in the syphilis experiments in Dr. Cutler's Final Syphilis Report. Ibid, PCSBI HSPI Archives, CTLR_0000629-30.

[250] PCSBI. (2011). Subject Database.

[251] John Cutler to John Mahoney (1947, January 10). Correspondence. PCSBI HSPI Archives, CTLR_0001040; John Mahoney to John Cutler (1947, January 20). Correspondence. PCSBI HSPI Archives, CTLR_0001049.

[252] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea Report. PCSBI HSPI Archives, CTLR_0001356; John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000629; John Cutler. (n.d.). Chancroid Experiment Report. PCSBI HSPI Archives, CTLR_0000947.

[253] John Cutler to John Mahoney. (1946, November 5). Correspondence. PCSBI HSPI Archives, CTLR_0001198.

[254] John Cutler to John Mahoney. (1946, November 5). Correspondence. PCSBI HSPI Archives, CTLR_0001198.

[255] Ibid; John Cutler to John F. Mahoney. (1946, November 30). Correspondence. PCSBI HSPI Archives, CTLR_0001192.

[256] John F. Mahoney to John Cutler. (1948, June 21). Correspondence. PCSBI HSPI Archives, CTLR_0001143; Falcone, H.H., Harris, A., Olansky, S., Salvado, C., Cutler, J.C. (1953). A study of the Neurath Inhibition Phenomenon in the serodiagnosis of syphilis. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* 37(3): 264-272. Memorandum to Mr. Gustavo An[i]rada to Mr. C.H. Morrison re: Pay-Consultants; Doctors Funes and Salvado. (1950, April 5). Correspondence. PCSBI HSPI Archives, NPRC_0001964.

[257] Dr. Aragon was appointed director of the Orphanage in January 1946. Nuevo Director del Hospicio Nacional. (1946). *Diario de Centro America*, January 24. Dr. Aragon was the director at the Orphanage until 1951 when he was transferred. Homenaje al Doctor Aragon en sus bodas de oro profesionales. (1971). *El Imparcial*. December 4.

[258] Stout, G.W., Cutler, J.C., op cit., p. 237; see generally Aragon, H.A. (1948, October). Estudio de la sifilis y pruebas de la serologia en el Hospicio Nacional de Guatemala. *Salubridad y Asistencia*; Levitan, S., et al. (1952, July). Clinical and serologic studies with reference to syphilis in Guatemala, Central America: I. Studies of comparative performance of the Kahn, Kolmer, Mazzini, and VDRL slide tests as carried out in the National Orphanage. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* 36:379.

[259] At the completion of the research Dr. Cutler concluded that the Kahn and Mazzini tests yielded yield high numbers of false positives whereas the Kolmer and VDRL slide tests had better specificity (accuracy). Funes, J.M., Cutler, J.C., Levitan, S., Portnoy, J., Funes, R. (1953). Estudios serológicos y clínicos con referencia a la sífilis in Guatemala, Centro America:II. Observaciones efectuadas en un grupo de niños de escuela en el Puerto de San José. *Boletín de la Oficina Sanitaria Panamericana* 34(1):14-18. The first two methods using lipoidal antigens resulted in significant numbers of false positives because the antibodies reacting with the antigen are not specific to syphilis. In fact, these antibodies can be present in numerous other conditions, including malaria and leprosy. Kahn, R.L. (1972). Syphilis serology with lipoidal antigen: The meaning of positive reactions. *Journal of the National Medical Association* 64(2):117-121. While cardiolipin antigens are also non-specific for syphilis, Dr. Cutler's Final Syphilis Report cites a lower level of false positives through empirical testing: "flocculation tests using crude lipoidal antigen [the Kahn and Mazzini tests]…give a much higher rate of serological positivity than complement fixation tests using crude lipoidal or cardiolipin-lecithin antigens [the Kolmer test], or flocculation tests using cardiolipin-lecithin antigens [the VDRL slide test]." John Cutler. Final Syphilis Report. (1955, February 24). PCSBI HSPI Archives, CTLR_0000675.

[260] Dugdale, D.C. (2009, December 1). National Library of Medicine and National Institutes of Health. Medline Plus, Serology. Available at http://www.nlm.nih.gov/medlineplus/ency/article/003511.htm.

[261] Dugdale, D.C. (2009, December 1). National Library of Medicine and National Institutes of Health. Medline Plus, Cerebral spinal fluid (CSF) collection. Available at http://www.nlm.nih.gov/medlineplus/ency/ article/003428.htm. (accessed September 8, 2011). Contemporaneous literature discusses the "fundamental importance" of spinal fluid examination in the detection of syphilis: "a guide to the effect of and need for treatment in both early and late neurosyphilis, the examination of the spinal fluid has become indispensable, and failure to insist on the test may rank as culpable negligence." Stokes, J.H., Beerman, H., Ingraham, N.R. (1944). *Modern Clinical Syphilology: Diagnosis, Treatment, Case Study.* Philadelphia: W.B. Saunders Company, pp. 1094-1114.

[262] John Cutler to John F. Mahoney. (1946, November 12). Correspondence. PCSBI HSPI Archives, CTLR_0001196.

[263] Stout, G.W. (1962). Personnel Files, Nomination for Departmental Honor Award. PCSBI HSPI Archives, PCSBI HSPI Archives, NPRC_0002555.

[264] John Cutler to John F. Mahoney. (1946, November 12). Correspondence. PCSBI HSPI Archives, CTLR_0001196.

[265] John Cutler to John F. Mahoney. (1946, December 6). Correspondence. PCSBI HSPI Archives, CTLR_0001253. The VDSPH was a hospital primarily for commercial sex workers in Guatemala who were required by law to report to Prophylactic Dispensaries twice a week for physical exams. Reglamento de la Seccion de profilaxia y de enfermedades venéreas: Leyes conexas con el mismo. (1938, June). PCSBI HSPI Archives, CTLR_0001692-1693. Dr. 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." John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000640. Dr. Cutler also performed several syphilis serology tests for the U.S. Air Base in San José, Guatemala, on men stationed there. John Cutler to the Commanding Officer, U.S.A. Air Base, San José Guatemala. (1946, December 21). Correspondence. PCSBI HSPI Archives, CTLR_0001245.

[266] Blood samples from the Air Force were used for a study on the "Neurath inhibition phenomenon," which was developed to aid in the serodiagnosis of syphilis. Originally tested by the VDRL Staten Island, the Neurath procedure was then carried out by the researchers in Guatemala "on a number of individuals in a population group giving a high percentage of positive reactions…" Blood specimens for this study were obtained from children in the Orphanage, school children in San José, and syphilitic adults in Guatemala City. U.S. men stationed at the Air Force Base in Guatemala were used as a control "to demonstrate whether reagents used and the performance of the procedure in Guatemala would elicit the same type of results as those obtained when the tests were performed in this country on individuals in the United States population." Falcone, V.H., et al., op cit., pp. 264-265, 269.

[267] Insofar as the serology experiments were part of medical care, conventional practices in the United States would not have mandated any written or formalized consent for testing. Faden, R.R., Beauchamp, T.L. (2009). The concept of informed consent. In Vaughn, L. (Ed.). (2009). *Bioethics: Principles, Issues, and Cases*. New York: Oxford University Press, p. 146. However, while available records show three children in the Orphanage received treatment for congenital syphilis, there is no record of treatment for the other children. Levitan, S., et al., op. cit., pp. 380-381.

[268] PCSBI. (2011). Subject Database.

[269] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000643.

[270] There were still outstanding questions regarding whether persons with untreated syphilis were resistant to infection with a different strain of syphilis, or whether persons with treated latent syphilis were immune to reinfection. If both of those questions held true, and many of the prisoners had syphilis already, there would be few men that would make adequate prophylaxis subjects. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000646.

[271] Ibid.

[272] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000648.

[273] Ibid.

[274] However, it does not appear as though the prisoners were subjected to more invasive serological testing methods used by the researchers later in other populations, such as lumbar or intra cisternal punctures.

[275] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000652.

[276] It is not clear when the research began, however Dr. Cutler wrote to Dr. Arnold in June 1947 to tell him they were going to San José to "work again" with the children. In the same letter, Dr. Cutler explained that testing in the Orphanage was more preliminary ("We have begun with the orphanage, but have barely touched it, so that there is nothing to report"). Unsigned [John Cutler] to Richard Arnold. (1947, June 5). Correspondence. PCSBI HSPI Archives, CTLR_0001240.

[277] Ibid; PCSBI HSPI Archives, CTLR_0001240; Levitan, S., et al., op cit., p. 379. Data analysis continued until the early 1950s. Stout, G.W., op cit.

[278] This number is made up of 515 children from the Orphanage, 151 children from the Port of San José, 277 "Indian" children from Totonicapan, and 441 "Ladino" children from the "highlands" of Guatemala. Stout, G.W., op cit., p. 238.

[279] Ibid, pp. 238-239.

[280] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000649. Dr. Cutler's records do not reflect why congenital syphilis would be readily apparent to the researchers, but there are many clinical symptoms of congenital syphilis that differentiate from sexually acquired syphilis. Stokes, J.H., op cit., pp. 1094-1114. Dr. Funes repeated this rational in his article on the children, arguing that "to study false positive reactions to the serologic tests, it is necessary to select a group that is not sexually mature and in which the probability of acquired syphilis is minimal" [translation]. Funes, J.M., et al., op cit., pp.14-18.

[281] Funes, J.M. (1949, enero). Avances venereológicos en la sección correspondiente de la Dirección General de Sanidad Pública de Guatemala. *Boletín de la Oficina Sanitaria Panamericana* 28(1):48-49.

[282] Aragon, H.A. (1948, October). Estudio de la sífilis y pruebas de la serología en el Hospicio Nacional de Guatemala. *Salubridad y Asistencia*: 187-190.

[283] The investigators reported that this was funded in part by the PHS grant to PASB, RG-65/65(C). Funes, J.M., et al., op cit.

[284] John Cutler to Willard H. Wright. (1948, February 13). Correspondence. PCSBI HSPI Archives, CTLR_0001173; This data was later published in Wright, W.H., Dobrovolny, C.G. (1953). Experiments in the control of schistosomiasis in Brazil. *Public Health Reports* 68(12):1156-1160. Willard H. Wright to John Cutler. (1948, February 18). Correspondence. PCSBI HSPI Archives, CTLR_0001174. Dr. Funes similarly writes of sending blood samples from school-aged children from Puerto de San Jose to the Laboratory of Tropical Disease in the United States for further analysis of suspected malaria. Funes, J.M., et al. (1953). Estudios serológicos y clínicos con referencia a la sífilis en Guatemala, Centro America: II. Observaciones efectuadas en un grupo de ninos de Escuela en el Puerto de San José. Boletín de la Oficina Sanitaria Panamericana 34(1):15. In mid-1948, the government of Guatemala, in cooperation with the U.S. Public Health Service and the Pan American Sanitary Bureau, began a large-scale malaria study in various locations across Guatemala. Schmidt, L.H. and Coatney, G.R. (1955). Review of investigations in malaria chemotherapy (U.S.A. 1946 to 1954). *American Journal of Tropical Medicine and Hygiene* 4(2):208-216; Dobrovolny, C.G., et al. (1953). Chloroquine and chlorguanide as suppressants of malaria in Guatemala. *American Journal of Tropical Medicine and Hygiene* 2(5): 808-845. Dr. Charles S. Dobrovolny, a parasitologist at the Tropical Disease Laboratory at NIH and a commissioned officer, was assigned to PASB for the malaria study in Guatemala. PASB Statement of Service in Kind. (n.d.). PCSBI HSPI Archives, PAHO_0000578; Wright, W.H., Dobrovolny, C.G., op cit. Dr. Dobrovolny and his supervisor in the malaria studies, Dr. Coatney, published a paper in 1953 detailing their malaria surveys and treatment studies across Guatemala. Dobrovolny, C.G., White, W.C., and Coatney, G.R. (1953). Chloroquine and chlorguanide as suppressants of malaria in Guatemala. *American Journal of Tropical Medicine and Hygiene*, 808-845. Dr. Coatney was the same physician who had discussed his observations of the Guatemala experiments with Dr. Parran and who wrote to Dr. Cutler in the winter of 1947 to inform him of Dr. Parran's "merry" reaction as described in the section on "Race and Secrecy in the Guatemala Experiments: Issues of Secrecy." G. Robert Coatney to John C. Cutler. (1947, February 17). Correspondence. PCSBI HSPI Archives, CTLR_0001051.

[285] John Cutler to John F. Mahoney (1947, June 6). Correspondence. PCSBI HSPI Archives, CTLR_0001070.

[286] Funes, J.M., et al., op cit.

[287] Ibid. There is no information indicating whether the children with confirmed syphilis were treated.

[288] [Unsigned] John Cutler to J. F. Mahoney. (1947, September 18). Correspondence. PCSBI HSPI Archives, CTLR_0001228. Completed research was published in 1953. Funes, J.M., Cutler, J.C., Levitan, S., Portnoy, J., Funes, R. Estudios serológicos y clínicos con referencia a la sífilis in Guatemala, Centro America: II. Observaciones efectuadas en un grupo de niños de escuela en el Puerto de San José. *Boletín de la Oficina Sanitaria Panamericana* 14-18.

[289] There are conflicting data in some of the articles regarding how many children were involved from the Orphanage, as well as their ages. Stout et al. reported that 515 children were involved, confirmed by the report from the director of the Orphanage, ages 1 to 18 years. Dr. Levitan et al. reported that 438 children were involved, ages 6 to 16. The reason for the discrepancies is unclear. See Stout, G.W., op cit., p. 238; but see Levitan, S., et al., op cit., p. 379. In published reports, the Ministry of Public Health is credited with sponsoring the study which was also "aided by a grant from the United States Public Health Service to the Pan-American Sanitary Bureau." Levitan, S. et al., op cit., p. 379.

[290] The Second Congress of Venereal Diseases in Central America, "an event that is singularly momentous for the country of Guatemala with regard to the fight against widely extended diseases," ran from April 26-May 1, 1948. [Translation]. (1948). Segundo Congreso de Venereologia el 25: Asistiran Observados de los Estados Unidos, Mexico y Cuba y Paises Centroamericanos. *El Imparcial.* April 5, 1948. The United States, Cuba, Mexico, Panama, and the republics of Central America were all participants. The organizing committee of the Second Congress included Drs. Galich, Funes, Aguilar, Tejeda, and Cutler. (1947). Guatemala sera sede del II Congress de Venereologia. *El Imparcial.* April 29, 1947. Dr. Arnold requested to Dr. Cutler that any papers the researchers wanted to present there be forwarded to VDRL Staten Island

for approval. R.C. Arnold to John Cutler. (1947, December 30). Correspondence. PCSBI HSPI Archives, CTLR_0001108. The topics of the congress included: "a) Valuation of penicillin in the treatment of syphilis; b) Evaluation of semi-intensive 20-day arsenotherapy; c) Study of the action of sodium, salicylate in the treatment of venereal lymphogranuloma and appreciation of other methods of treatment; d) Results obtained on the repressive system of prostitution in general and related studies on its economic aspect; e) Evaluation of the probability of marriage among syphilitics treated with intensive systems; f) Venereal disease in infancy; g) Open topics always related to the general topics" [Translation]. Other topics to be addressed by sub-committees included: "a) Social and legislative problems; b) Gonorrhea; c) Psychiatry of prostitution; d) Neurosyphilis; e) Serology; f) Intensive treatment; g) Other venereal diseases; h) Venereal diseases and infancy; i) Penicillin therapy" [Translation]. (1948). Segundo Congreso de Venereologia el 25: Asistiran Observados de los Estados Unidos, Mexico y Cuba y Paises Centroamericanos. *El Imparcial*. April 5, 1948. Attendants included Drs. Arnold and Spoto as well as "[f]our American doctors representing the army, navy, military and civil aviation…" [Translation]. (1948). Un acontecimiento sera el Congreso de Venereologia: Eminencias medicas de otros paises concurriran, ademas. *Diario de Centro America*. (April 15, 1948), p. 7. Pan American Sanitary Bureau. (1948). Expenditure Breakdown: Calendar Year 1948. PCSBI HSPI Archives, PAHO_0000568. Dr. Galich reported at this Congress that "trials or tests with penicillin are being conducted, up to now with the outstanding results, to prove conclusively that primary syphilis can be cured with only one ampoule or dose, just as is done in the United States seemingly with great success. [Translation]. (1948). Sistemas de Diagnostico al Congreso de Venereas. *El Imparcial*. April 29, 1948.

[291] Aragon, H.A. (1948). Estudio de la sifilis y pruebas de la serologia en el Hospicio Nacional de Guatemala. *Salubridad y Asistencia* 20:187-190.

[292] Ibid, p. 187.

[293] Levitan, S., et al., op cit., pp. 380-381.

[294] Ibid. ("By the time that 55 [children], called at random, had been checked, in addition to the 3 seropositive children, it was believed that a sufficient number of study cases had been assembled.") Thus, 34 children who had some sort of doubtful seropositive result were not examined further for clinical manifestations of syphilis.

[295] None of the 89 seroreactors exhibited obvious further clinical symptoms of syphilis during the observation period. In their study, the investigators concluded that the Kolmer and VDRL tests were best for routine use "under conditions such as exist in the region from which this group is drawn." Levitan, S., et al., op cit., p. 387. Lumbar punctures at the time would have been considered standard of care for diagnosis of syphilis. The risks associated with such a lumbar puncture include a post-procedure headache, which may be accompanied by nausea, vomiting, and dizziness. The children also faced the risk of experiencing radiating back pain, serious bleeding, and rarely infectious meningitis or brainstem herniation from this procedure, though there was no documentation of adverse events. Mayo Clinic. (2010). Lumbar puncture (spinal tap) – Definition. Available at http://www.mayoclinic.com/health/lumbar-puncture/MY00982 (accessed May 27, 2011).

[296] Stout, G.W., op cit., p. 239.

[297] Ibid.

[298] Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical Notebook. PCSBI HSPI Archives, CTLR_0000620.

[299] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000704.

[300] Unsigned [John Cutler] on PASB letterhead to Richard Arnold. (1947, June 5). PCSBI HSPI Archives, CTLR_0001240; Levitan, S. et al., op cit., p. 379. Data analysis continued until the early 1950s. Stout, G.W., op cit.

[301] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000649.

[302] While the study results were published in 1952, the dates of the research are not clear. The VDRL team for this work also included Ramiro Galvez (a bacteriologist from the VDRL stationed in Georgia). Portnoy, J., et al. (1952). Op cit., pp. 566-70.

[303] Portnoy, J., et al., op cit.

[304] Ibid.

[305] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000649. A contemporaneous newspaper article noted that the Psychiatric Hospital "is far from possessing all the characteristics inherent in a first-rate institution; nevertheless, as far as the scientific and material, little by little modifications and reforms have been introduced that have converted it into something of a bit of paradise in comparison to what it was three decades ago, when the institution merited the name 'house of the insane,' as it was nothing more than a place in which to pile all those who for any reason could be qualified as crazy." (1947). Servivio Quirurgico para el Hospital de Neuro-Psiquiatria. *Diario de Centro America*. July 21, 1947.

[306] Ibid.

[307] PCSBI. (2011). Subject Database.

[308] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000669.

[309] It is unclear whether the leprosy study could have provided a useful comparison. Furthermore, as with his retrospective claims about the decision to begin testing in children, the timeline for this statement is questionable. Intentional exposure work (requiring accompanying serological diagnostic testing) began in the Psychiatric Hospital in May 1947. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000694.

[310] Cutler Documents (1953). Report on Serologic Follow-up on Patients Done at CDC in 1953, Samples sent from Guatemala. PCSBI HSPI Archives, CTLR_0001433-76. These numbers are rough as there are subject data missing making an exact count impossible (e.g., for some subjects only the subject number [without a name] is included; as there are several subjects with the same number it is impossible to tell whether it is the same subject being tested twice or the data represents two different subjects).

[311] See, e.g., Cutler Documents. (1953). Report on Serologic Follow-up on Patients Done at CDC in 1953, Samples sent from Guatemala. PCSBI HSPI Archives, CTLR_0001436.

[312] Ibid.

[313] PCSBI. (2011). Subject Database.

[314] Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000611. Dr. Cutler's retrospective counts of his experiments, however, are inconsistent. According to his contemporaneous notes, subjects were exposed to gonorrhea on 67 different days. PCSBI. (2011). Subject Database.

[315] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000694-746. Dr. Cutler's retrospective counts of his experiments, however, are inconsistent. According to his contemporaneous notes, subjects were exposed to syphilis on 52 different days. PCSBI. (2011). Subject Database.

[316] John Cutler. (n.d.). Chancroid Experiment. Report. PCSBI HSPI Archives, CTLR_0000947. Dr. Cutler's retrospective counts of his experiments, however, are inconsistent. According to his contemporaneous notes, subjects were exposed to chancroid on four different days. PCSBI. (2011). Subject Database.

[317] Dr. Cutler's count of experiments is incomplete as it does not include several experiments conducted to assess infection methods and many individual observational inoculations presumably were excluded as they were not part of a larger controlled study. See, e.g., John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000885; and Cutler Documents. Insane Asylum Asilo Des Alienados and Prison Patient Records. (various Dates). Subjects Note Card. PCSBI HSPI Archives, CTLR_0004157. In addition, the contemporaneous notes Dr. Cutler took often contradict the data included in the reports he later wrote. See, e.g., Cutler Documents. (1947). [Subjects names]. Subjects Note Cards and Lists. PCSBI HSPI Archives, CTLR_0001806, CTLR_0001809, CTLR_0001810, CTLR_0001812, CTLR_0001813, CTLR_0001816; but see John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001299. For this reason, the Commission report will discuss *days* of experiments rather than *number* of experiments for accuracy. This day count will not include days on which commercial sex workers were infected as Dr. Cutler did not consider these instances experiments or the sex workers as subjects.

[318] PCSBI. (2011). Subject Database. "Exposure" to an STD is not the same as being "infected" with an STD. Subjects who were exposed to an STD by the researchers ran the risk of becoming infected with that STD—however many of the subjects that were exposed to an STD were not in fact infected.

[319] PCSBI. (2011). Subject Database. Overall, there were 18 subjects involved in the intentional exposure experiments who were under the age of 18 (including a 10 and 15-year-old soldier, a 16-year-old sex worker, a 15-year-old prisoner, and 14 psychiatric patients ranging in age from 14 to 17). The youngest subject involved in the STD exposure experiments was a 10-year-old soldier who was a member of the Honor Guard. As part of the experiments, he had sexual intercourse three times with a commercial sex worker infected with gonorrhea and was superficially inoculated in his penis with gonorrhea-infected pus once. The subject's age was recorded in two separate places. Cutler Documents. (1947). Gonorrhea Experiment #1. Clinical notes, protocols, and subject note cards. PCSBI HSPI Archives, CTLR_0001738, CTLR_0001743, CTLR_0001748, CTLR_0001769, CTLR_0001770; Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000561; and Cutler Documents. (1947-1948). Gonorrhea Experiments: Military. Lists and clinical notes. PCSBI HSPI Archives, CTLR_0001971. Studies have shown that sexual intercourse before the age of 13 is possible. CDC. (2010, June 4). Youth Risk Behavior Surveillance-United States, 2009. Available at http://www.cdc.gov/mmwr/pdf/ss/ss5905.pdf (accessed August 10, 2011).

[320] This is according to contemporaneous Cutler notes. PCSBI. (2011). Subject Database. While treatment with penicillin or sulfathiazole was recorded for many of the subjects, some of the subjects involved were released or escaped before treatment; homosexual contacts may have spread the disease further than the researchers charted; and some subjects not showing clinical manifestations of the disease were never treated, despite testing positive.

[321] For the original plan of Dr. Cutler's study, see Section "Initial Study Design."

[322] In addition, some studies were designed in a way that subjects in the active arm of the experiment, (testing the prophylaxis), were given a less effective form of inoculation than the control arm, thus making the prophylaxis appear more effective (see, e.g., experiment 31 in which the researchers used superficial inoculation for the active arm, but deep inoculation for the control group—a method they knew to be more likely to transfer gonorrhea). Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000602.

[323] PCSBI. (2011). Subject Database.

[324] Ibid. This number excludes several subjects for whom the records reflect confusion as to whether the subject died or not. See, e.g. Cutler Documents. (n.d.). Penitentiary, Alphabetical Lists of Patients by Number. PCSBI HSPI Archives, CTLR_0001500. Seventy-six of the 83 subjects that the researchers recorded as having passed away were involved in the STD exposure experiments.

[325] These deaths occurred "either during the inoculation stage, during the active phase of the disease, or post treatment." John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000672.

[326] Ibid. The researchers offered staff at the Psychiatric Hospital "a few extra dollars" to notify them of subject deaths so that autopsies could be performed. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000674. This practice is consistent with the PHS/Venereal Disease Division activities in the Tuskegee Syphilis Study, where Dr. R.A. Vonderlehr coordinated with a wide variety of agencies and individuals, including Dr. Eugene Dibble, a physician at the Tuskegee Institute to whom he offered a PHS appointment, to ensure that researchers were notified of subject deaths to facilitate autopsies. Jones, J.H. (1993). *Bad Blood: The Tuskegee Syphilis Experiment.* New York: The Free Press, pp. 132-150. No autopsy reports were found in the Cutler Documents, but there are records of tissue samples from seven subjects being sent to Dr. James D. Thayer at the Venereal Disease Experimental Laboratory in Chapel Hill, North Carolina in April 1957. The Venereal Disease Experimental Laboratory was part of the PHS Venereal Disease Branch and was also associated with the University of North Carolina, Chapel Hill. John Cutler to L.L. Ashburn. (1957, January 7). Correspondence. PCSBI HSPI Archives, CTLR 0001531; L.L. Ashburn to James Thayer. (1957, April 3). PCSBI HSPI Archives, CTLR 000152.

[327] PCSBI. (2011). Subject Database.

[328] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001299.

[329] Ibid, PCSBI HSPI Archives, CTLR_0001285.

[330] John Cutler to R.C. Arnold. (1947, September 16). Correspondence. PCSBI HSPI Archives, CTLR_0001230.

[331] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001285. This dosage meets the standard of care treatment for gonorrhea at the time. Perkins G.E., Brewster, H.N. (1947). Penicillin in the treatment of gonorrhea in women: Results of treatment as reported and by twelve co-operating venereal-disease clinics in Massachusetts during 1945. *New England Journal of Medicine* 236(8):280.

[332] See e.g., Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC), Notebook 4. Clinical notebook. PCSBI HSPI Archives, CTLR_0000505.

[333] PCSBI. (2011). Subject Database.

[334] Cutler Documents. (1947). Gonorrheal experiment #1. Clinical notes, protocols, and subject notecards. PCSBI HSPI Archives, CTLR_0001736-79.

[335] Gram staining and culture were used, sometimes individually and sometimes together, to detect the bacteria that causes gonorrhea. The Gram stain test required samples from swabs of the urethra (in males) or cervix (in females) to be stained and microscopically examined for *Neisseria gonorrhoeae*. Although Gram stain tests are relatively accurate for males, they are only accurate in 40 percent to 60 percent of infected females. The bacterial culture test, which was more accurate but also more time consuming, required the samples to be placed onto culture medium specific for *Neisseria gonorrhoeae* to determine if the bacteria was present. Oxtoby, M., et al. (1982). Potential shortcuts in the laboratory diagnosis of gonorrhea: a single stain for smears and nonremoval of cervical secretions before obtaining test specimens *Sexually transmitted diseases*. 9(2):59-62.

[336] PCSBI. (2011). Subject Database.

[337] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001285.

[338] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001356; John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000629.

[339] While no syphilis experiments were actually conducted in the Guatemalan Army, Dr. Cutler still listed these men as participants in his Final Syphilis Report. It is possible that they became involved as they were overseeing syphilitic patients of their own. In addition, some syphilis human passage material (i.e., chancres) was taken from Guatemalan Army patients. John Cutler, Final Syphilis Report. (1955, February 24). PCSBI HSPI Archives, CTLR_0000629.

[340] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001302.

[341] Unsigned [John Cutler] to Richard Arnold. (1947, September 16). Correspondence. PCSBI HSPI Archives, CTLR_0001230. The Guardia de Honor (Presidential Honor Guard) was a unit created for the President of Guatemala's personal protection. Gleijeses, P. (1991). *Shattered Hope: the Guatemalan Revolution and the United States*, 1944-1954. Princeton, N.J.: Princeton University Press, p. 16.

[342] See, e.g., Cutler Documents. (1948, June 28-29). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000602.

[343] PCSBI. (2011). Subject Database.

[344] See, e.g., Cutler Documents. (1947, February 14). Gonorrheal experiment #1. Clinical notes, protocols, and subject note cards. PCSBI HSPI Archives, CTLR_0001749-1778.

[345] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001280.

[346] John Cutler to John Mahoney. (1947, September 16). Correspondence. PCSBI HSPI Archives, CTLR_0001126.

[347] See, e.g., Cutler Documents. (1947-1948). Gonorrhea Experiments: Military. Lists and clinical notes. PCSBI HSPI Archives, CTLR_0001878.

[348] John Mahoney to John Cutler. (1947, June 30). Correspondence. PCSBI HSPI Archives, CTLR_0001078.

[349] Ibid.

[350] See Cutler Documents. (1947). Gonorrheal experiment #1. PCSBI HSPI Archives, CTLR_0001736-79 and Cutler Documents. (1947). Gonorrheal experiment #2. Clinical notes and subject note cards. PCSBI HSPI Archives, CTLR_0001780-1801; but see John Cutler. (1952, October 29). Experimental studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001299.

[351] PCSBI. (2011). Subject Database.

[352] The Venereal Disease and Sexual Prophylaxis Hospital still stands today in Guatemala City and a delegation from the Commission visited it in May 2011. A 1937 plaque on the building dedicated it to three people including Mr. John D. Rockefeller and Dr. Hugh S. Cumming, former U.S. Surgeon General (1920-1936) and PASB Director from 1937 to 1947.

[353] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001279-80.

[354] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000640.

[355] The copy he retained was of the regulations in 1938. It is not clear how the regulations changed, if at all, before Dr. Cutler undertook his experiments.

[356] Reglamento de la Seccion de profilaxia y de enfermedades venéreas: Leyes conexas con el mismo. (1938 June). PCSBI HSPI Archives, CTLR_0001691.

[357] Ibid, PCSBI HSPI Archives, CTLR_0001686-735.

[358] Ibid, PCSBI HSPI Archives, CTLR_0001692; Funes, J.M. (1949, enero). Avances venereológicos en la sección correspondiente de la Dirección General de Sanidad Pública de Guatemala. *Boletín de la Oficina Sanitaria Panamericana* 28(1):46. The treatment with arsenical drugs was not related to the U.S. PHS STD experiments, which predominently used penicillin as a treatment.

[359] The intentional infection procedures are discussed below.

[360] Cutler Documents. (1947). Gonorrheal experiment #1. Clinical notes, protocols, and subject note cards. PCSBI HSPI Archives, CTLR_0001737.

[361] However, "[i]t was not feasible to carry on further studies with respect to alcohol on rate of infection." John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001287.

[362] Ibid.

[363] PCSBI. (2011). Subject Database.

[364] This payment was documented on one day for one experiment involving multiple exposures. Cutler Documents. (1947). Gonorrheal experiment #2. Clinical notes and subject note cards. PCSBI HSPI Archives, CTLR_0001781-97. In 1947, $25 had the same buying power as $253 in 2011.

[365] See, e.g., Cutler Documents. (various dates). Gonorreal experiment #1. Clinical notes, protocols, and subject note cards. PCSBI HSPI Archives, CTLR_0001736-1800.

[366] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001280.

[367] Ibid.

[368] Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000620.

[369] Cutler Documents. (1947). Gonorrheal Experiment #1. Clinical notes, protocols, and subject note cards. PCSBI Archives, CTLR_0001736-79. The placebo used in most experiments was an injection of 0.5 cc of sterile, distilled water. See, e.g., Ibid, PCSBI HSPI Archives CTLR_0001751.

[370] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001286.

[371] It is unclear from Dr. Cutler's notes whether these deviations were intentional. See Cutler Documents. (1947). Gonorrheal Experiment #1. Clinical notes, protocols, and subject note cards. PCSBI HSPI Archives, CTLR_0001749-78.

[372] Referred to as "exposures" by Dr. Cutler. John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001280.

[373] Cutler Documents. (1947). Gonorrheal Experiment #1. Clinical notes, protocols, and subject note cards. PCSBI HSPI Archives, CTLR_0001749-78. The failure to confirm that the sex workers were infected at the time of the experiment may have undermined the validity of the study.

[374] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001280.

[375] See Cutler Documents. (1947). Gonorrheal Experiment #1. Clinical notes, protocols, and subject note cards. PCSBI HSPI Archives, CTLR_0001761-75.

[376] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives CTLR_0001286.

[377] Ibid, PCSBI HSPI Archives, CTLR_0001299.

[378] John Mahoney to John Cutler. (1947, February 10). Correspondence. PCSBI HSPI Archives, CTLR_0001048.

[379] John Cutler to John Mahoney. (1947, March 12). Correspondence. PCSBI HSPI Archives, CTLR_0001054.

[380] John Cutler to John Mahoney. (1947, January 2). Correspondence. PCSBI HSPI Archives, CTLR_0001034.

[381] John Cutler to John Mahoney. (1947, January 7). Correspondence. PCSBI HSPI Archives, CTLR_0001037. After the trip, Dr. Arnold wrote to Dr. Cutler that the rabbit inoculations were a failure and that none exhibited pinto. Richard Arnold to John Cutler. (1947, April 10). Correspondence. PCSBI HSPI Archives, CTLR_0001037.

[382] Richard Arnold to John Cutler (1947, April 10). Correspondence. PCSBI HSPI Archives, CTLR_0001190.

[383] Ibid. Most likely meaning that Dr. Cutler should stretch the truth.

[384] Ibid.

[385] Richard Arnold to John Cutler. (1947, April, 11). Correspondence. PCSBI HSPI Archives, CTLR_0001061.

[386] Culter Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clnical notebook. PCSBI HSPI Archives, CTLR_0000513.

[387] Cutler Documents. (1947). Gonorrheal Experiment #4. Clinical notes and subject note cards. PCSBI HSPI Archives, CTLR_0001823; Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSP I Archives, CTLR_0000513.

[388] Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSP I Archives, CTLR_0000513.

[389] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001299. Dr. Cutler published that result nearly three decades later: "[s]tudies in gonorrhea have indicated that the risk to the male in contact with an infected female is roughly one in 20 for a single contact." Dr. Cutler cites an "[u]npublished observation" by Dr. Funes and himself for this data. Cutler, J.C. et al. (1973, February). Op cit., p. 89.

[390] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001299-1302.

[391] Ibid, PCSBI HSPI Archives, CTLR_0001282.

[392] Ibid, PCSBI HSPI Archives, CTLR_0001283.

[393] Ibid.

[394] John Cutler to John Mahoney. (1947, May 17). Correspondence. PCSBI HSPI Archives, CTLR_0001121.

[395] Ibid, PCSBI HSPI Archives, CTLR_0001121-22.

[396] Unsigned [John Cutler] on PASB letterhead to Richard Arnold. (1947, June 5). Correspondence. PCSBI HSPI Archives, CTLR_0001240.

[397] John Cutler to John F. Mahoney. (1947, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001242.

[398] Reports to a Conference Held Under the Auspices of the Subcommittee on Venereal Diseases 9 February 1944, on the Chemical Prophylaxis of Venereal Disease. (1944, February 9). PCSBI HSPI Archives, NAS_0003113-18.

[399] John Mahoney to John Cutler. (1947, June 30). Correspondence. PCSBI HSPI Archives, CTLR_0001077. However, Mahoney's opinion with regard to artificial inoculation reflects some uncertainly as well. Mahoney, J.F., Van Slyke, C.J., Cutler, J.C., Blum, H.L. (1946). Op cit., 24. Dr. Mahoney's stated preference for "contact" methods as a mode of inoculation apparently applied to both the gonorrhea and syphilis studies, as described in "Syphilis Experiments: Psychiatric Hospital: Scarification and Abrasion" section regarding the contact method for syphilis transmissions, and in his syphilis research in rabbits. Mahoney, J. (1936). An experimental resurvey of the basic factors concerned in prophylaxis in syphilis. *The Military Surgeon* 352-353.

[400] John Mahoney to John Cutler. (1947, August 11). Correspondence. PCSBI HSPI Archives, CTLR_0001086. Dr. Mahoney sent this letter to Dr. Cutler through the Director of PASB, and forwarded to Assistant Director, John Murdock.

[401] John Cutler to John Mahoney. (1947, August 25). Correspondence. PCSBI HSPI Archives, CTLR_0001085.

[402] PCSBI. (2011). Subject Database. Separate experiments for this section are defined as a group of exposures done with the same population and the same STD on the same day. How Dr. Cutler defined his own use of numbering the experiments is unclear, and he does not account for all of his data.

[403] It is not clear to whom the term "authors" refers, as it appears that only Dr. Cutler wrote up the Experimental Studies in Gonorrhea report. In the report, after the word "authors," a citation is added to the Terre Haute article, "Experimental Gonococci Urethritis in Human Volunteers" by Drs. Mahoney, Van Slyke, Cutler, and Blum. John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001286.

[404] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001286.

[405] Ibid, PCSBI HSPI Archives, CTLR_0001288.

[406] Minutes of the Twenty-First Meeting of the Subcommittee on Venereal Diseases. (1943, November 11). PCSBI HSPI Archives, NAS_0002782; Reports to a Conference Held Under the Auspices of the Subcommittee on Venereal Diseases 9 February 1944, on the Chemical Prophylaxis of Venereal Disease. (1944, February 9). PCSBI HSPI Archives, NAS_0003114-18.

[407] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001303-4.

[408] Ibid, PCSBI HSPI Archives, CTLR_0001290.

[409] Ibid.

[410] Ibid, PCSBI HSPI Archives, CTLR_0001286.

[411] PCSBI. (2011). Subject Database.

[412] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. CTLR_0001302. In 1948, after Dr. Cutler concluded that sexual intercourse experiments with sex workers were ineffective for experimental transmission of disease, Dr. Funes and Casta Luz Aguilar (who succeeded Dr. Galich as the Chief of the Guatemalan Ministry for Public Health) decided to test the effectiveness of the orvus-mapharsen prophylaxis in sex workers. While Dr. Arnold and Dr. Mahoney concluded in their 1948 animal study of orvus-mapharsen that "the preparation should be suitable for use in a douche" for women, Dr. Funes and Aguilar decided to test its use as a post-coital prophylactic douche in female commercial sex workers "under legal supervision" in a Guatemalan brothel [translation]. In their published article, they argued that commercial sex-regulating bureaus and agencies in the Americas relied too heavily on the condom (which clients of sex workers often refused to use) to both protect sex workers and prevent the spread of the disease. Dr. Funes and Aguilar used six sex workers in the experiment that "had previously been followed for a long time by the first author [Dr. Funes]…" [translation]. These are possibly some of the same women used in the U.S. PHS normal exposure experiments, although it is unclear. After recording the women's sexual activities for six months, Dr. Funes and Aguilar determined that use of the orvus-mapharsen douche produced a decrease in the incidence of gonorrhea. There is no record of them intentionally inoculating the sex workers for this experiment; however, if these women had been used in the U.S. PHS's normal exposure experiments, they may have already been inoculated for those purposes. There is also no record of the researchers determining the rates of STD infection in the men with

whom the sex workers had contact, indeed "precise observations were not made" of the women's sexual contacts [translation]. Arnold, R.C., Mahoney, J.F. (1948). Local prophylaxis in experimental syphilis of the rabbit. *Journal of Venereal Disease Information* 29:138-41; Funes, J. Aguilar, C.L. (1952 agosto). La solución de mafarside-orvus en la profilaxis de la blenorragia de la mujer. *Boletín de la Oficina Sanitaria Panamericana* 33(2):121-125. Dr. Cutler discussed this study in a later article on STD prophlaxis; however, he added "[s]tudies involving the exposure of non-infected volunteers to infected contacts in order to observe relative rates of protection have become increasingly difficult, due to the rigid medical research ethics now operative." Cutler, J.C., et al., (1973). Op cit., p. 89.

413 PCSBI. (2011). Subject Database.

414 Ibid.

415 The idea to infect in subjects' eyes possibly came from Dr. Arnold's letter in which he had written to Dr. Cutler about another experiment "that could be done" involving "the actual infection or [an] attempt to infect the eye with [gonococcal] pus…" He was curious whether the eye became infected easily as "[j]ust a thought for the future." Richard Arnold to John Cutler. (1947, April 19). Correspondence. PCSBI HSPI Archives, CTLR_0001220.

416 Cutler Documents. Insane Asylum Asilo de Alienados and Prison Patient Records. (Various dates) Subject note cards. PCSBI HSPI Archives, CTLR_0004155-57; Cutler Documents. (1947-1948) Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000617; Cutler Documents. (1948, February 8). Asylum Asilo de Alienados and Prison Patient Records. (Various dates) Subject note cards. PCSBI HSPI Archives, CTLR_0004158.

417 PCSBI. (2011). Subject Database.

418 Arnold, R.C., Mahoney, J.F. (1948, May). Op cit., pp. 138-141; John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000759.

419 John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000782.

420 These strains include the Nichols strain, the Frew Strain, and a "street strain" of Dr. Cutler's own making. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000684-86.

421 *Treponema pallidum* cannot be maintained adequately in culture and can only be maintained in the testes of rabbits. To produce *Treponema pallidum* for research purposes, rabbits are inoculated intra-testicularly with the organism and, after a month, are killed. Emulsions are then prepared from the testes. The researchers had "access to large quantities of the organism more or less at will" because "an animal colony was maintained at the VDRL Staten Island to use in experimental work." See John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000688.

422 John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000711.

423 Ibid, PCSBI HSPI Archives, CTLR_0000675.

424 Ibid, PCSBI HSPI Archives, CTLR_0000687.

425 Ibid, PCSBI HSPI Archives, CTLR_0000686.

426 As of 1946, as evidenced by a statement by Dr. Moore at a Penicillin Conference held under the Auspices of the U.S. PHS, FDA, and NRC, the U.S. Armed Forces were treating patients with syphilis with 2.4 million units of penicillin, but data indicated that amount was insufficient. As a result, penicillin researchers were testing other amounts, as high as 9.6 million units, but there were insufficient data to determine which amount was most effective. Penicillin Conference Under the Auspices of the U.S. Public Health Service, Food and Drug Administration, and National Research Council. March 27, 1946, at 158-159. The researchers defined "adequate" treatment as ≥ 3,400,000 units of penicillin administered over seven to eight days, with aqueous preparations every two hours and 12 to 24 hours for the POB and Duracillin, which fit within the standard of care guidelines at the time. Crawford, G.M. (1947). Syphilis. *New England Journal of Medicine* 236(8):283.

427 PCSBI. (2011). Subject Database. Several patients in the Psychiatric Hospital without serological or clinical evidence of syphilis were also treated with penicillin "for *political* reasons only (emphasis in original)." See, e.g, Cutler Documents. Insane Asylum Asilo de Alienados and Prison Patient Records. (Various dates). Subject note cards. PCSBI HSPI Archives, CTLR_00006321.

[428] It was not clear that his death was caused by penicillin; the subject "developed status epileptiaus during the course of therapy with aqueous penicillin for primary syphilis on the 6th day, and despite efforts to control the condition, died," but, Dr. Cutler reported, the subject had a history of severe epileptic attacks prior to his exposure to penicillin during the experiment. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000748. Dr. Cutler and his staff also made a number of clinical observations in the Final Syphilis Report. With regard to lesions, the researchers found that: "…it can be said that absence of lesion signifies with a high degree of certainly the absence of infection. This statement had subsequently been confirmed with respect to the group of patients initially treated for latent syphilis or late symptomatic syphilis in the Sing Sing study." John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000925. As Dr. Cutler points out in his Final Syphilis Report, he was also involved in the U.S. PHS-sponsored Sing Sing Correctional Facility study conducted from 1953 to 1954. To develop a syphilis vaccine, researchers inoculated volunteers with a very high level of syphilis spirochetes. Investigators discussed "the study, the objectives, and the details of its day-to-day conduct" with the volunteers. Patients received follow-up for a year (monthly checkups) through the study and then were treated as part of the general "syphilitic" prison population. The details of this research were widely published in the medical and popular press. Syphilis vaccine gains: Sing Sing tests held raising hopes for finding preventive. (1954). *New York Times*, December, 9; Sing Sing study confirms rabbit tests. (1955, February). *Public Health Reports (1896-1970)*, 70(2):214; Magnuson, H., et al. (1956, February). Inoculation syphilis in human volunteers. *Medicine* 35(1):33-82; Reverby, S. (2009). *Examining Tuskegee: The Infamous Syphilis Study and its Legacy.* Chapel Hill: University of North Carolina Press, p. 146.

[429] This date is taken from the day that two commercial sex workers were exposed to syphilis via intra-cervical injection on May 10, 1947 "to send to the penitentiary as part of the study to determine normal rate of infections." Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000620. While there are no contemporaneous clinical notes of Penitentiary subjects having sexual intercourse with sex workers on that date and it is not included in the summary section of the Final Syphilis Report, Dr. Cutler does discuss this "risk of infection" study in the "Immunity" section of his final report. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000885.

[430] PCSBI. (2011). Subject Database. Five prison guards were also included in the researchers' intentional exposure experiments (see, e.g., Cutler Documents. Insane Asylum Asilo de Alienados and Prison Patient Records. (Various dates). Subject note cards. PCSBI HSPI Archives, CTLR_0003401); for the sake of brevity, they will be included with the data of the "prisoners."

[431] PCSBI. (2011). Subject Database.

[432] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000662.

[433] Ibid. PCSBI HSPI Archives, CTLR_0000667.

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

[435] Ibid.

[436] John Cutler to John Mahoney. (1947, January 7). Correspondence. PCSBI HSPI Archives, CTLR_0001039. When Dr. Cutler wrote that the papers were already complaining about prison conditions, he is probably referring to articles such as the one published later that year reporting that "the prison system in Guatemala, like the infamous Bastille to the French and the horrible Romada to the Venezuelans, has not fulfilled the purpose outlined by national law, but has been a pit for vengeance, for suffering and for crime that has served dictators in satisfying their basest instincts on defenseless enemies, who in reality have been the best friends of democratic institutions and the joyful march to civilization and culture" [translation]. Editorial. (1947, August, 9). La Reforma Penitenciaria. *Diario de Centro America*.

[437] PCSBI. (2011). Subject Database. There is one day on which the method of exposure is unclear.

[438] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000723.

[439] Ibid, PCSBI HSPI Archives, CTLR_0000724.

[440] Ibid, PCSBI HSPI Archives, CTLR_0000699.

[441] Ibid.

[442] Ibid, PCSBI HSPI Archives, CTLR_0000704. The contemporaneous literature defines the "abortive cure" of syphilis as "essentially the systematic speculative under-estimation of the amount of treatment required by the seronegative primary stage," which was a dated treatment from the turn of the century. Stokes, J.H., Beerman, H., Ingraham, N. R. (1944). *Modern Clinical Syphilology: Diagnosis, Treatment, Case Study.* Philadelphia: W.B. Saunders Company, pp. 1094-1114.

[443] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000731.

[444] Ibid, PCSBI HSPI Archives, CTLR_0000741.

[445] See Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives CTLR_0000620 and John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives CTLR_0000885.

[446] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000640.

[447] Ibid, PCSBI HSPI Archives, CTLR_0000885.

[448] Ibid, PCSBI HSPI Archives, CTLR_0000648. The researchers were having such a difficult time causing infections through the sex workers that Dr. Harlow conveyed his amusement to Dr. Mahoney that the only person they managed to infect in the prison was the "prisoner-secretary" of the Penitentiary hospital who "had contact" with "one of our female hirelings whom we thought was non-infected." Dr. Harlow "could not help laughing at the irony of the situation" and even asked the secretary not to take sulfa or penicillin as treatment which "he unfortunately had access to." The next day the discharge and symptoms abated and Dr. Harlow "fear[ed] he may have treated himself." John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000762.

[449] Ibid, PCSBI HSPI Archives, CTLR_0000640.

[450] Ibid, PCSBI HSPI Archives, CTLR_0000762.

[451] Ibid, PCSBI HSPI Archives, CTLR_0000722-23.

[452] Ibid, PCSBI HSPI Archives, CTLR_0000699.

[453] Ibid, PCSBI HSPI Archives, CTLR_0000764.

[454] Ibid, PCSBI HSPI Archives, CTLR_0000696. It is also possible that they wanted to avoid giving the prisoners time to speak with each other and the opportunity to decline to participate in future experiments.

[455] Dr. Cutler did not later report any evidence of transmission of jaundice or other infection. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000679.

[456] John Cutler to John Mahoney. (1947, January 7). Correspondence. PCSBI HSPI Archives, CTLR_0001039.

[457] Richard Arnold to John Cutler. (194[7], April 19). Correspondence. 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 letter that Dr. Cutler forwarded to them on April 10, 1947) and that the letter should have been dated April 19, 1947. See e.g., John Cutler to John Mahoney. (1947, April 10). Correspondence. PCSBI HSPI Archives, CTLR_0001059.

[458] Richard Arnold to John Cutler. (1947, April 19). PCSBI HSPI Archives, CTLR_0001220.

[459] Ibid.

[460] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000648.

[461] Ibid, PCSBI HSPI Archives, CTLR_0000658.

[462] PCSBI. (2011). Subject Database.

[463] Ibid. This data also includes at least one nurse who worked at the Psychiatric Institution who was exposed to syphilis twice through injection. Cutler Documents. (1948, May 9). Asilo de Alienados: Immune Experiment No 14. Protocols. PCSBI HSPI Archives, CTLR_0002224; Cutler Documents. Insane Asylum Asilo des Alienados and Prison Patient Records. (various dates). Subject Notecard. PCSBI HSPI Archives, CTLR_0003885.

[464] See, e.g., Cutler Documents. (n.d.). Insane Asylum Asilo de Alienados and Prison Patient Records. (Various dates). Subject note cards. PCSBI HSPI Archives CTLR_0002635.

[465] "[I]t was known by the staff that homosexual practices were very common." John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000659.

[466] "It is worth mentioning that although supervision of the patients within the institutions was minimal and although it was known by the staff that homosexual practices were very common (several epidemics of homosexual gonorrhea were treated) no clinical evidence of syphilis by this route was observed." John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000659.

[467] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001356; John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000629.

[468] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000653.

[469] It is not clear to what study Dr. Cutler is referring.

[470] Dr. Cutler is possibly referencing the Stateville prison study of 1942, in which 432 inmates in the Illinois Federal Penitentiary in Stateville were intentionally infected with malaria, while confined for 18 months in a segregated part of the prison, through a mosquito vector. Informed consent was obtained from each subject. Five days after exposure, the subjects were treated with an experimental intervention. Comfort, N. (2009, September). The prisoner as model organism: Malaria research at Stateville Penitentiary," *Studies in History and Philosophy of Biological and Biomedical Science* 40(3):190–203.

[471] Dr. Cutler is possibly referencing the Lynchburg Colony studies conducted during World War I at the Virginia Colony for the Epileptic and Feebleminded, where 190 patients between the ages of 15 and 57 were given the "Rockefeller vaccine," known to cause hepatitis and jaundice in a significant number of administrations, so the military could use the data on infectious hepatitis occurrences and treatment in the relevant arenas of war. See Lombardo, P.A. (2004). 'Of Utmost Urgency': The Lynchburg Colony Hepatitis Study, 1942. In Moreno, J.D. (Ed.). *In the Wake of Terror: Medicine and Morality in a Time of Crisis.* Cambridge: MIT Press, pp. 3-15.

[472] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000655.

[473] Ibid, PCSBI HSPI Archives, CTLR_0000654.

[474] Ibid.

[475] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000673.

[476] Ibid, PCSBI HSPI Archives, CTLR_0000673-74.

[477] Ibid, PCSBI HSPI Archives, CTLR_0000674.

[478] John Cutler to John Mahoney (1948, May 19). Correspondence. PCSBI HSPI Archives, CTLR_0001141.

[479] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000657.

[480] John Cutler to John Mahoney (1948, May 19). Correspondence. PCSBI HSPI Archives, CTLR_0001141.

[481] See, John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000552; but see John Cutler to [Fred L. Soper] Director, Pan American Sanitary Bureau. (1948, November 15). Correspondence. PCSBI HSPI Archives, CTLR_0001172.

[482] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000673.

[483] John Cutler to John Mahoney. (1948, February 6). Correspondence. PCSBI HSPI Archives, CTLR_0001139.

[484] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000652.

[485] John Cutler to Richard Arnold. (1947, June 5). Correspondence. PCSBI HSPI Archives, CTLR_0001240.

[486] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000706. Also, many subjects were noted as being "uncooperative." See, e.g. Cutler Documents. Insane Asylum Asilo Des Alienados and Prison Patient Records. (Various dates). Subject Note Card. PCSBI HSPI Archives, CTLR_0005103.

[487] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000657.

[488] Ibid, PCSBI HSPI Archives, CTLR_0000666.

[489] Ibid, PCSBI HSPI Archives, CTLR_0000845.

[490] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000694.

[491] Richard Arnold to John Cutler. (1947, April 11). Correspondence. PCSBI HSPI Archives, CTLR_0001061.

[492] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000766.

[493] Ibid, PCSBI HSPI Archives, CTLR_0000679.

[494] Ibid, PCSBI HSPI Archives, CTLR_0000766.

[495] Ibid, PCSBI HSPI Archives, CTLR_0000706.

[496] John Mahoney to John Cutler. (1947, September 8). Correspondence. PCSBI HSPI Archives, CTLR_0001234. He was most likely referring to his published work on the effectiveness of the orvus-mapharsen prophylaxis in rabbits. Arnold, R.C., Mahoney, J.F. (1948, May). Local prophylaxis in experimental syphilis of the rabbit. *The Journal of Venereal Disease Information* 29:138-141.

[497] John Mahoney to John Cutler. (1947, September 8). Correspondence. PCSBI HSPI Archives, CTLR_0001234. Dr. Mahoney had been arguing that the contact method of syphilis inoculation (i.e., with a pledget soaked in syphilis spirochetes placed upon intact skin) was the best practice in syphilis research. See Mahoney, J. (1936, May). An experimental resurvey of the basic factors concerned in prophylaxis in syphilis. *The Military Surgeon* 352-353.

[498] John Mahoney to John Cutler. (1947, September 8). Correspondence. PCSBI HSPI Archives, CTLR_0001234.

[499] In addition, in order to perform "a comprehensive study of the reliability of serology as a diagnostic instrument among aboriginal peoples in tropical America," it "would require a different approach than the one being used at the present." They would "be obligated to canvass the South and Central American natives, the Mexican Indians, the Indian tribes in the United States and, finally, the southern negro." This type of study would require "mobile teams capable of doing medical work as well as serology," and Dr. Mahoney was "not at all sure that we could make the necessary financial arrangements." John Mahoney to John Cutler (1947, September 8). Correspondence. PCSBI HSPI Archives, CTLR_0001233.

[500] John Cutler to John Mahoney. (1947, September 18). Correspondence. PCSBI HSPI Archives, CTLR_0001231.

[501] Ibid. Between 1924 and 1927, Drs. Alan Chesney and Jarold Kemp, both of the Johns Hopkins University Department of Medicine, published a series of articles regarding syphilis experiments done on rabbits. The experiments included reinoculation and reinfection, treatment with arsphenamine, and the relationship between the dose of inoculum given and the incubation period of the infection induced. Chesney, A.M., Kemp, J.E. (1924). Experimental observations on the "cure" of syphilis in the rabbit with arsphenamine. *Journal of Experimental Medicine* 39(4):553-564; Chesney, A.M., Kemp, J.E. (1925). Studies in experimental syphilis: I. The influence of the size of inoculum on the course of experimental syphilis in the rabbit. *Journal of Experimental Medicine* 41(4):479-485; Chesney, A.M., Kemp, J.E. (1925). Studies in experimental syphilis: II. The influence of a non-specific inflammatory reaction upon the development of the chancre. *Journal of Experimental Medicine* 41(4):487-502; Chesney, A.M., Kemp, J.E. (1925). Studies in experimental syphilis: III. Further observations on the possibility of cure of syphilis in the rabbit with arsphenamine. *Journal of Experimental Medicine* 42(1):17-31; Chesney, A.M., Kemp, J.E. (1925). Studies in experimental syphilis: IV. The survival of *Treponema pallidum* in the internal organs of treated and untreated rabbits. *Journal of Experimental Medicine* 42(1): 33-42; Chesney, A.M., Kemp, J.E. (1926). Studies in experimental syphilis: VI. On variations in the response of treated rabbits to reinoculation; and on cryptogenetic reinfection with syphilis. *Journal of Experimental Medicine* 44(5):589-606; Chesney, A.M., Kemp, J.E. (1927). Studies in experimental syphilis: VII. Reinoculation of treated and untreated syphilitic rabbits with heterologous strains of *Treponema pallidum*. *Journal of Experimental Medicine* 46(2):223-237.

[502] John Cutler to John Mahoney. (1947, September 18). Correspondence. PCSBI HSPI Archives, CTLR_0001231.

[503] Ibid, PCSBI HSPI Archives, CTLR_0001229. Dr. Mahoney had already addressed this heroic challenge method counterargument in his Terre Haute publication, and he pointed out that the "usefulness of the experimental approach" required "that the experimental routine reasonably approximate the mode of transmission which is operative in female to male infection of human beings—this, *in order that the burden placed upon the prophylactic agent might not be greatly in excess of that imposed by natural exposure* (emphasis added)." Mahoney, J.F., et al. (1946). Op cit., 3.

[504] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000933. "Challenge methods" is a term used to describe intentional infection studies. Which involve deliberately inducing infection in order to study preventative measures and disease pathogenesis. Though controversial, challenge experiments are still conducted today. Some ethicists have argued that they are not necessarily unethical and that they may be ethically justified when conducted by competent investigators and according to scientifically sound protocols that incorporate safeguards to ensure the safety of volunteers. Miller, F.G., Grady, C. (2001). The ethical challenge of infection-inducing challenge experiments. *Clinical Infectious Diseases* 33(7):1028-1033.

[505] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000701.

[506] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001290.

[507] John Cutler to Richard Arnold. (1947, September 16). Correspondence. PCSBI HSPI Archives, CTLR_0001230.

[508] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000727.

[509] John Cutler to Richard Arnold. (1947, September 16). Correspondence. PCSBI HSPI Archives, CTLR_0001230.

[510] John Cutler to John Mahoney. (1947, September 18). Correspondence. PCSBI HSPI Archives, CTLR_0001228.

[511] John Cutler. (1989, June). Stemming the AIDS epidemic: Drawing on past experience with VD control. *Consultant* 26(6):62-63.

[512] Ibid.

[513] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000705.

[514] John Cutler to John Mahoney. (1947, September 18). Correspondence. PCSBI HSPI Archives, CTLR_0001228.

[515] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000734.

[516] Ibid, PCSBI HSPI Archives, CTLR_0000680.

[517] Ibid, PCSBI HSPI Archives, CTLR_0000763.

[518] Ibid, PCSBI HSPI Archives, CTLR_0000680.

[519] Ibid, PCSBI HSPI Archives, CTLR_0000712.

[520] Ibid, PCSBI HSPI Archives, CTLR_0000729. In other words, Dr. Cutler decided that instead of allowing the time necessary for future experiments to build on knowledge gained from the first experiments, the researchers should assume results based on incomplete data and move forward with new experiments nonetheless.

[521] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000728.

[522] Ibid, PCSBI HSPI Archives, CTLR_0000681.

[523] Ibid, PCSBI HSPI Archives, CTLR_0000705.

[524] Ibid, PCSBI HSPI Archives, CTLR_0000836.

[525] Ibid, PCSBI HSPI Archives, CTLR_0000669.

[526] Ibid, PCSBI HSPI Archives, CTLR_0000732.

[527] Ibid, PCSBI HSPI Archives, CTLR_0000681.

[528] Medline. (n.d.). Cerebral spinal fluid (CSF) collection. Available at http://www.nlm.nih.gov/ medlineplus/ ency/article/003428.htm (accessed May 11, 2011). Damage to the brain stem can cause loss of control over autonomic functions such as breathing, digestion, and heartbeat, and a mishap would result in death. The University Hospital. (n.d.). Anatomy of the Brain. Available at http://www.theuniversity hospital.com/ stroke/anatomy.htm (accessed May 11, 2011).

[529] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000669.

[530] Ibid, PCSBI HSPI Archives, CTLR_0000793.

[531] Ibid.

[532] Ibid.

[533] Cutler Documents. Insane Asylum Asilo de Alienados and Prison Patient Records. (Various dates). Subject note cards. PCSBI HSPI Archives, CTLR_0005823, CTLR_0005777.

[534] Curth, W. (1933). Syphilis in the highlands of Guatemala. *American Journal of Syphilis* 2(xvii):166.

[535] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000669.

[536] John Mahoney to John Cutler. (1948, February 19). Correspondence. PCSBI HSPI Archives, CTLR_0001223.

[537] Ibid. It is not clear from the letter what the "innocuous stage" of the Guatemala project would have included.

[538] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000718.

[539] Ibid, PCSBI HSPI Archives, CTLR_0000744.

[540] Ibid, PCSBI HSPI Archives, CTLR_0000746.

[541] John Mahoney to John Cutler. (1948, June 21). Correspondence. PCSBI HSPI Archives, CTLR_0001143.

[542] Risks involved in the application of chancroid in this manner include painful pustular lesions and redness of the skin. Al-Tawfiq, J.A., et al. (1998). Standardization of the experimental model of *Haemophilus ducreyi* infection in human subjects. *Journal of Infectious Diseases* 178(6):1684–1687; Heyman, H. (1950). Chancroid. In Harrison, T.R., et al. (Eds.). *Principles of Internal Medicine.* Philadelphia: The Blakiston Company, pp. 861-863..

[543] John Cutler. (n.d.). Chancroid Experiment. Report. PCSBI HSPI Archives, CTLR_0000969.

[544] PCSBI. (2011). Subject Database.

[545] See, e.g. Cutler Documents. (1947-1948) Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000621-22.

[546] PCSBI. (2011). Subject Database.

[547] John Cutler. (n.d.). Chancroid Experiment. Report. PCSBI HSPI Archives, CTLR_0000947.

[548] Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives, CTLR_0000621-622.

[549] Ibid, PCSBI HSPI Archives, CTLR_0000621.

[550] John Cutler. (n.d.). Chancroid Experiment. Report. PCSBI HSPI Archives, CTLR_0000969.

[551] PCSBI. (2011). Subject Database.

[552] John Cutler. (n.d.). Chancroid Experiment. Report. PCSBI HSPI Archives, CTLR_0000969.

[553] Ibid.

[554] The names of the physicians are included in the original draft of the Chancroid Experiment report, but are then crossed out by hand and not included in the final draft. (See Appendix II: Chancroid Experiment Report). Ibid, PCSBI HSPI Archives, CTLR_0000980.

[555] Ibid, PCSBI HSPI Archives, CTLR_0000970.

[556] Ibid, PCSBI HSPI Archives, CTLR_0000967. This film was not in the University of Pittsburgh Archives and has not been located.

[557] John Mahoney to John Cutler. (1948, June 21). Correspondence. PCSBI HSPI Archives, CTLR_0001143.

[558] Ernest Allen to John Murdock. (1948, June 28). Correspondence. PCSBI HSPI Archives, CTLR_0001182.

[559] John Cutler to John Mahoney, forwarded by William J. McAnally, Jr. (1948, August 26). Correspondence. PCSBI HSPI Archives, CTLR_0001163.

[560] John Mahoney to John Cutler, forwarded by [Fred L. Soper] Director, Pan-American Sanitary Bureau. (1948, September 3). Correspondence. PCSBI HSPI Archives, CTLR_0001161.

[561] Ibid.

[562] John Cutler to John Mahoney. (1948, June 21). Correspondence. PCSBI HSPI Archives, CTLR_0001142.

[563] John Cutler to John Mahoney. (1948, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001144.

[564] John Murdock to John Cutler, forwarded by William J. McAnally, Jr. (1948, June 30). Correspondence. PCSBI HSPI Archives, CTLR_0001151.

[565] John Mahoney to John Cutler. (1948, July 16). Correspondence. PCSBI HSPI Archives, CTLR_0001148.

[566] Parran, T. (1937). *Shadow on the Land.* New York: Reynal & Hitchcock, p. 175.

[567] Ibid.

[568] Dr. Cutler led the Tuskegee Syphilis Study in conjunction with Dr. Sidney Olansky and Dr. Stanley Schuman. Reverby, S. (2009). Op cit., p.69.

[569] Jones, J.H. (1993) *Bad Blood: The Tuskegee Syphilis Experiment.* New York: The Free Press, p. 28.

[570] John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001287-88.

[571] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000852. Dr. Cutler cites to: Shattuck. G.C. (1930). Preliminary communication on syphilis in Yucatan. *American Journal of Tropical Medicine and Hygiene* S1-10(3):177-182.; Curth, W. (1933). Op cit.; and Shattuck, G.C. (1933). Syphilis in Yucatan and related immunological questions.

[572] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000852.

[573] Curth, W. (1933). Op cit. This article is cited by Dr. Cutler in his Final Syphilis Report.

[574] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000809.

[575] Ibid, PCSBI HSPI Archives, CTLR_0000809. When Commission staff traveled to Guatemala and spoke with the Guatemalan Commission investigating these experiments, the Guatemalan Commission informed them that words used to describe the indigenous population in contemporaneous documents (that the Guatemalan Commission possesses) were derogatory and offensive.

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

[577] Richard Arnold to John Cutler. (1947, April 10). Correspondence. PCSBI HSPI Archives, CTLR_0001190.

[578] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000858.

[579] Ibid, PCSBI HSPI Archives, CTLR_0000809.

[580] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000655.

[581] G. Robert Coatney to John Cutler. (1947, February 17). Correspondence. PCSBI HSPI Archives, CTLR_0001051

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

[583] Kaempffert, W. (1947). Notes on science: syphilis prevention. *New York Times,* April 27. Several months before the *New York Times* publication, Dr. Eagle had been working with the Surgeon General of the U.S. Navy, Rear Admiral Clifford A. Swanson, on testing an oral penicillin prophylaxis in the Navy stemming from the above research. Surgeon General Swanson wrote to the NRC that "we are very much interested in the possibility of trying [penicillin by mouth] in the Navy on an experimental basis." He solicited "[s] uggestions for setting up the experiment…if the Council considers that this can be accomplished *without seriously jeopardizing the health of the men involved"* [emphasis added]. Clifford A. Swanson to Lewis H. Weed. (1947, February 13). Correspondence. PCSBI HSPI Archives, NAS_0001991. As described in a 1949 article, Eagle did indeed conduct this research in "a small body of military personnel with an extraordinarily high morbidity of gonorrhea." This study did not involve artificial exposure. In fact, "no attempt was made to ascertain whether the men had been exposed." Instead, subjects were divided into an experimental group, who received a single tablet of penicillin each time they returned from leave, and a control group, who received a placebo. Eagle then compared the general rate of infection of both groups over two 24-week periods. Eagle, H. (1949). The prophylactic use of penicillin. *Trans Assoc Am Physicians* 62:59-60.

[584] Waldemar B. Kaempffert Dies; Science Editor of The Times, 79. (1956). *New York Times*, November 28. PCSBI HSPI Archives, MISC_0000070.

[585] Kaempffert, W. (1947). Notes on science: syphilis prevention. *New York Times,* April 27..

[586] John Mahoney to John Cutler. (1947, May 5). Correspondence. PCSBI HSPI Archives, CTLR_0001243.

[587] Most likely because the prophylaxis was intended to be included in the Army pro kit for soldiers to treat themselves, which would rule out injections. John Mahoney to John Cutler. (1947, May 5). Correspondence. PCSBI HSPI Archives, CTLR_0001243. It is also worth noting that Drs. Arnold and Mahoney had first discovered the use of the orvus-mapharsen prophylaxis, a competitor to the use of penicillin as a prophylaxis. Arnold, R.C., Mahoney, J.F. (1948). Local prophylaxis in experimental syphilis of the rabbit. *Journal of Venereal Disease Information* 29(5):138-41.

[588] John Mahoney to John Cutler. (1947, May 5). Correspondence. PCSBI HSPI Archives, CTLR_0001243. Dr. Mahoney does not specifically say in this letter why he thought that an oral preparation of penicillin was less important; however, he most likely was concerned about the use of penicillin as a prophylaxis creating penicillin-resistant bacteria. As Dr. Cutler discussed in the Experimental Studies in Gonorrhea report, "the fact that patients may become, or be sensitive to penicillin and the danger inherent in creating a penicillin-resistant bacterial flora in the patient that might later prove pathogenic…suggests that it is inadvisable to use oral penicillin as a mass prophylaxis against venereal disease." John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001298.

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

[590] Ibid.

[591] John Mahoney to John Cutler. (1947, May 5). Correspondence. PCSBI HSPI Archives, CTLR_0001243. There is no further information in the Cutler Documents regarding the formation of an advisory group.

[592] Ibid.

[593] Ibid.

[594] John Cutler to John Mahoney. (1947, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001242.

[595] John Mahoney to John Cutler. (1947, June 30). Correspondence. PCSBI HSPI Archives, CTLR_0001078.

[596] John Cutler to John Mahoney. (1947, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001241.

[597] Ibid.

[598] John Mahoney to John Cutler. (1947, June 30). Correspondence. PCSBI HSPI Archives, CTLR_0001077. It appears that this confidence was indeed later entrusted, as in a later letter written by Dr. Soper, he lauds Dr. Cutler's excellent job leading the Venereal Disease Program in Guatemala, which included studies in "transmission, serology and treatment of venereal diseases." Dr. Soper goes on to say that "[d]uring [Dr. Cutler's] detail in Guatemala, which required not only technical skill but the ability to deal with authorities and handle patients under extremely difficult conditions, he conducted his work in an outstanding manner, got along well with every one, and demonstrated his administrative capacity." Fred L. Soper to Ernest L. Stubbins. (1950, April 20). Correspondence. PCSBI HSPI Archives, JHU_0000007.

[599] John Cutler to John Mahoney. (1947, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001241.

[600] Ibid.

[601] Ibid.

[602] It is not clear who Dr. Cutler is including in the four. In addition to himself, Dr. Levitan, and Dr. Harlow, he is also possibly including Dr. Spoto.

[603] John Cutler to John Mahoney. (1947, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001241.

[604] Ibid.

[605] Strickland, S.P. (1989). Op cit.

[606] John R. Murdock to John Cutler, forwarded by William J. McAnally, Jr. (1947, December 26). Correspondence. PCSBI HSPI Archives, CTLR_0001102.

[607] John Cutler to John Mahoney. (1947, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001241.

[608] See e.g., John Cutler to John Mahoney. (1947, February 4). Correspondence. PCSBI HSPI Archives, CTLR_0001047. Copies of these reports were not included in the Cutler Documents.

[609] John Cutler to John Mahoney. (1947, June 22). Correspondence. PCSBI HSPI Archives, CTLR_0001241.

[610] John Mahoney to John Cutler. (1947, June 30). Correspondence. PCSBI HSPI Archives, CTLR_0001077.

[611] Ibid.

[612] Ibid.

[613] Ibid.

[614] Stout, G.W., Guzmán, M., Scrimshaw, N.S. (1952, marzo). Reacciones serológicas para sífilis presuntamente positivas falsas en la América Central. *Boletín de la Oficina Sanitaria Panamericana* 32(3): 206-213; Stout, G.W., Guzmán, M., Scrimshaw, N.S. (1952, junio). Reacciones serológicas para sífilis presuntamente positivas falsas en la América Central: II. Relación con el acido ascórbico, riboflavina, fosfatasa alcalina, carotina y vitaminas A y E en el suero sanguíneo. *Boletín de la Oficina Sanitaria Panamericana* 32(6): 521-526; Stout, G.W., Méndez, J., Guzmán, M., Scrimshaw, N.S. (1952, agosto). Reacciones serológicas para sífilis presuntamente positivas falsas en la América Central: III. Relación con el contenido de proteina, albumina y globulina en el suero. *Boletín de la Oficina Sanitaria Panamericana* 33(2):110-115; Stout, G.W., Aguirre, F., Scrimshaw, N.S. (1953, enero). Reacciones serológicas para sífilis presuntamente positivas falsas en la América Central: IV. Relación con las reacciones positivas a la prueba de floculación de cefalina colesterol (hanger). *Boletín de la Oficina Sanitaria Panamericana* 34(1): 9-13.

[615] John R. Murdock to William J. McAnally, Jr.. (1948, July 26). Correspondence. PCSBI HSPI Archives, CTLR_0001155; Report of the Director of the Pan American Sanitary Bureau to the Member Governments of the Pan American Sanitary Organization. (n.d.). PCSBI HSPI Archives, NLM_0000033. Dr. Stout was a microbiologist who had worked with Dr. Mahoney at Staten Island and had, prior to joining Mahoney's team, been in charge of the Serological Department for the Navy at Bethesda. Genevieve W. Stout Personnel Files, Nomination for Departmental Honor Award, 1962. PCSBI HSPI Archives, NPRC_0002573.

[616] John R. Murdock to William J. McAnally, Jr. (1948, July 26). Correspondence. PCSBI HSPI Archives, CTLR_0001155-56; Stout, G.W., Cutler, J.C. (1951). Serology problems (syphilis) in Central America. *Journal of Venereal Disease Information* 7(32): 240.

[617] John R. Murdock to William J. McAnally, Jr. (1948, July 26). Correspondence, PCSBI HSPI Archives, CTLR_0001155-56.

[618] Stout, G.W. Personnel Files, Nomination for Departmental Honor Award, 1962, PCSBI HSPI Archives, NPRC_0002555; Pan American Sanitary Bureau. (1948). Expenditure Breakdown: Calendar Year 1948. PCSBI HSPI Archives HSPI, PAHO_0000574.

[619] Thome, J.V. (1955, agosto). Encuestas serológicas centroamericanas realizadas durante los años 1950, 1951, 1952, y 1953. *Boletín de la Oficina Sanitaria Panamericana* 39(2):131-145.

[620] Ibid.

[621] Ibid. One of Stout's articles indicates that did serological testing in Guatemala, El Salvador, Costa Rica, and Panama. Stout, G.W., Cutler, J.C. (1951). Op cit,. p. 240. This work was conducted in conjunction with investigators in the United States. The VDRL in Chamblee, Georgia, the institute to which Funes's continuing observation samples were sent, co-sponsored the studies, and "the PASB solicited the cooperation of the United States Public Health Service to have the VDRL in Chamblee…serve as a co-control lab" for at least two of the studies. Thome, J.V., op cit., pp.131-145. Their results showed a high incidence of false-positive reactions in most of the countries involved (Panama, like the United States, did not show the elevated incidence of false-positives), which mirrored the staff's prior results. Stout, G.W., Cutler, J.C. (1951). Op. cit., p.240.

[622] John Mahoney to John Cutler. (1948, June 21). Correspondence. PCSBI HSPI Archives, CTLR_0001143; Memorandum to Gustavo An[i]rada to C.H. Morrison re: Pay-Consultants; Doctors Funes and Salvado. (1950, April 5). Correspondence. PCSBI HSPI Archives, NPRC_0001964. Dr. Carlos A. Salvado received a "special research" fellowship from the Public Health Service to study Psychiatry at New Jersey State Hospital in 1949. Research Grants Awarded by the Public Health Service. Supplement 205 Public Health Reports. (1950). PCSBI HSPI Archives, MISC_0000900.

[623] John Mahoney to John Cutler. (1948, July 26). Correspondence. PCSBI HSPI Archives, CTLR_0001157.

[624] John Cutler to Fred L. Soper, forwarded by William J. McAnally, Jr. (1948, August 27). Correspondence. PCSBI HSPI Archives, CTLR_0001183.

[625] John Cutler to John Mahoney, forwarded by William J. McAnally, Jr. (1948, August 26). Correspondence. PCSBI HSPI Archives, CTLR_0001162; Juan M. Funes Personnel Files. (1948, December 10). PCSBI HSPI Archives, NPRC_0000807.

[626] Ibid.

[627] Report on Serologic Follow-up on Patients Done at CDC in 1953, Samples sent from Guatemala. (n.d.). PCSBI HSPI Archives, CTLR_0001466.

[628] Ibid, PCSBI HSPI Archives, CTLR_0001433-76. These numbers are rough as there are data missing for many patients, which makes an exact count impossible (e.g., for some patients only the patient number [without a name] is included; as there are several patients with the same number it is impossible to tell whether it is the same patient being tested twice or two different patients).

[629] See, e.g., Report on Serologic Follow-up on Patients Done at CDC in 1953, Samples sent from Guatemala. (n.d.). PCSBI HSPI Archives, CTLR_0001436.

[630] This is the latest date for which there is evidence of samples sent to the VDRL at Chamblee, Georgia.

[631] Levitan, S., et al. (1952). Op. cit, pp. 379-387.

[632] John Cutler. (1950, September 1). Summary Report of the WHO Venereal Disease Demonstration Team in India, PCSBI HSPI Archives, MISC_0000426.

[633] John Cutler, Curriculum Vitae. (1990, February). PCSBI HSPI Archives, UOFM_0000021.

[634] John Cutler. (n.d.). Chancroid Experiment, Report. PCSBI HSPI Archives, CTLR_0001003.

[635] E.g., the country in which the experiment was conducted and the physicians involved. John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI Archives, CTLR_0001278-79.

[636] John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR 0000632.

[637] Aragon, H.A., (1948, October). Estudio de la sifilis y pruebas de la serologia en el Hospicio Nacional de Guatemala. *Salubridad y Asistencia*; Stout, G.W., Cutler, J.C. (1951). Op cit., pp. 238-239; Levitan, S., et al. (1952, July). Op cit.; Funes, J.M., et al., (1953). Op cit., pp. 14-18; Portnoy, J., Galvez, R., Cutler, J.C. (1952). Op cit., pp. 566-570; Falcone, V.H., Harris, A., Olansky, S., Salvado, C., Cutler, J.C. (1953). Op cit.

[638] Cutler, J.C., et al. (1972, February). Studies on development of a vaginal preparation providing both prophylaxis against venereal disease, other genital infections, and contraception. I. Venereal disease prophylaxis, past experience, present status and plans for future studies. *Military Medicine* 138(2):89; Cutler, J.C. (1989, June). Op cit., p. 63.

[639] For example, Cutler cites a Funes orvus-mapharsen study on sex workers as support for the statement that "the male's risk for [gonorrheal] infection through vaginal contact was only one in 20 contacts" in several of his articles. See e.g., Cutler, J.C., (1989, June). Op cit., pp. 60-61. This Funes study, however, did not include data from male contacts and just followed the rate of infection of the sex workers. Funes, J., Aguilar, C.L. (1952 agosto). La solución de mafarside-orvus en la profilaxis de la blenorragia de la mujer. *Boletín de la Oficina Sanitaria Panamericana* 33(2):121-125. The Studies in Gonorrhea Report *does* draw this 1 in 20 conclusion from the Guatemala data. John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001303.

[640] See, e.g., Arnold, R.C., Cutler, J.C., Wright, R.D., Levitan, S. (1952). Studies in penicillin treatment of syphilis – from 1943 to 1950. *Public Health Reports* 67(1):78-89; Cutler, J.C. (1972). Prophylaxis in the venereal diseases. *Medical Clinics of North America* 56(5): 1211-1216; and Cutler, J.C., Arnold, R.C. (1988). Venereal disease control by health departments in the past: Lessons for the present. *American Journal of Public Health* 78(4):372-376. As Dr. Cutler concluded in 1973, however: "[a]lthough both syphilis and gonorrhea are accepted as completely curable in the early stages, they are certainly never trivial, and rarely self-limiting. It is highly questionable whether it would be acceptable to deliberately expose volunteers to the risk of such infection. The required experimental circumstances, i.e. of deliberate sexual intercourse by volunteers with a person known to have active gonorrhea and/or infectious syphilis

present problems of social, political, and ethical concern, which must be weighed against national attitudes and practices and the seriousness of the problem to be studied." In addition, Cutler continues that Terre Haute and Sing Sing could be carried out with volunteer cooperation "because of the certainty of cure and consequent low risk to the patient, and because of the fact that the technique for infection was experimental inoculation," presumably as opposed to sexual intercourse. Cutler, J.C., et al. (1972, February). Op cit., p. 90.

641 See, e.g., Mahoney, J.F., Van Slyke, C.J., Cutler, J.C., Blum, H.L. (1946). Op cit. John Cutler. (1952, October 29). Experimental Studies in Gonorrhea. Report. PCSBI HSPI Archives, CTLR_0001286; Magnuson, H.J., et al. (1956). Inoculation syphilis in human volunteers. *Medicine* 35(1):33-82. In addition, the VDRL staff went back to publishing regarding syphilis prophylaxis in rabbits. See, e.g., Arnold, R.C., Cutler, J.C. (1956). Experimental studies to develop local prophylactic agents against syphilis. *British Journal of Venereal Disease* 32(1):34-35.

642 Reverby, S. (2009). Op cit., p. 144; John Cutler, Curriculum Vitae. (1990 February). PCSBI HSPI Archives, UOFM_0000020.

643 "Syphilis vaccine gains." (1954). *New York Times*, December 9.

644 John Cutler, Curriculum Vitae. (February 1990). PCSBI HSPI Archives, UOFM_0000020.

645 Ibid.

646 Project for the Development of a Combined Agent for Disease Prophylaxis and Contraception. PCSBI HSPI Archives, NLM_0001832.

647 Contract No. AID/csd-2822. (1971, December 8). Allegheny County Field Efficacy Trial of Prophylaxis-Contraceptive Compound, Experimental Design Document. PCSBI HSPI Archives, NLM_000240. In this study, female subjects were selected from local STD clinics, and were self-identified as high risk of contracting an STD by "repeated visits for treatment at this clinic." In the experiment, a health educator interviewed patients, the purpose of the trial was explained, and if the patients agreed to participate, they were asked to sign a consent form. No intentional infection protocol was employed. Singh, B., Cutler, J. (1979). Vaginal contraceptives for prophylaxis against sexually transmissible diseases. Workshop on New Developments in Vaginal Contraception, Guatemala City, Guatemala, April 25-27, 1979.

648 Ackerman, J. (2003). Obituary: John Charles Cutler / Pioneer in Preventing Sexual Diseases. *Pittsburgh Post-Gazette.* February 12. Available at http://www.post-gazette.com/obituaries/20030212cutler0212p3.asp (accessed Sept. 1, 2011).

649 Richard Arnold personnel form. (n.d.). PCSBI HSPI Archives, NPRC_0000132.

650 Ibid.

651 Roster of Workshop Consultants (n.d.). PCSBI HSPI Archives, NLM_0001920.

652 Richard C. Arnold Obituary. (n.d.). PCSBI HSPI Archives, MISC_000319.

653 See Funes, J., et al. (1953). Serological and clinical studies of syphilis in guatemala, central america: Part 2, observations of a group of schoolchildren in Puerto San Jose. *Pan-American Sanitation Bulletin* 34(1):14-18.

654 Juan M. Funes Personnel Files, Notification of Personnel Action. (1956). PCSBI HSPI Archives, NPRC_0000799.

655 Venereal Disease Control. (1950, Oct. 14). *JAMA* 7(144): 556.

656 Wilcox, R.R. (1954). A WHO Study of Treatment Schedules of Treatment Schedule for Early Syphilis in use Throughout the World. *World Health Organization Bulletin*, 10: 579-617.

657 John F. Mahoney Obituary. (1957). PCSBI HSPI Archives, MISC_0000071.

658 T. Parran Personel File, PCSBI HSPI Archives, NPRC_0001601-662.

659 Cassius J. Van Slyke Personnel Files. (Various dates). PCSBI HSPI Archives, NPRC_0002844-57.

660 For other examples, see Beecher, H.K. (1966). Ethics and clinical research. *New England Journal of Medicine* 274(24):1354-1360.

[661] See Drug Amendments of 1962, Public Law No. 87-781 (1962), codified at 21 U.S.C. 355 (requiring informed consent in certain FDA-regulated research); 21 C.F.R. 50 (same); National Research Act of 1974, Public Law No. 93-348 (1974), codified at 42 U.S.C. 218 (requiring informed consent and independent review in HHS-sponsored research); 45 C.F.R. 46 (same); Emanuel, E.J., Wendler, D., Grady, C. (2000). What makes clinical research ethical? *JAMA* 283(20):2701-2711; World Medical Association. (1964). *Code of Ethics of the World Medical Association: Declaration of Helsinki.* Helsinki, Finland: World Medical Association.

[662] See Section "Guatemala Experiments 1946-48" in this report.

[663] See Section "Guatemala Experiments 1946-48: Race and Secrecy in the Guatemala Experiments: Issues of Secrecy."

[664] See Section "Guatemala Experiments 1946-48: Intentional Exposure Experiments: Overview."

[665] 45 C.F.R. 46, Subparts B, C, D; Council for International Organizations and Medical Sciences and World Health Organization. (2002). *International Ethical Guidelines for Biomedical Research involving Human Subjects.* Geneva: World Health Organization, pp. 64-66; The 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, D.C.: Department of Health, Education, and Welfare, DHEW Publication OS 78-0012; Ruof, M.C. (2004). Vulnerability, vulnerable populations, and policy. *Kennedy Institute of Ethics Journal* 14(4):411-425; Levine, R.J. (1988). *Ethics and Regulation of Clinical Research*, 2nd ed. New Haven: Yale University Press.

[666] See Section "Guatemala Experiments 1946-48: Race and Secrecy in the Guatemala Experiments: Issues of Secrecy."

[667] The Nuremberg Code. (1949). In *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10, Volume 2.* Washington, D.C.: U.S. Government Printing Office, pp. 181-182.

[668] Ibid.

[669] See, e.g., Kant, I. (1959). *Foundations of the Metaphysics of Morals*, trans. Lewis White Beck. Indianapolis: Bobbs-Merrill Company, pp. 37-42.

[670] For prominent discussions of bioethical principles and moral rules, Beauchamp, T.L., Childress, J.F. (2001). *Principles of Biomedical Ethics.* New York: Oxford University Press; Gert, B., Culver, C.M., Clouser, K.D. (Eds.) (1997). *Bioethics: A Return to Fundamentals.* New York: Oxford University Press. The Advisory Committee on Human Radiation Experiments (1995) alludes to these rules as well.

[671] de Kruif, P. (1926). *Microbe Hunters.* New York: Harcourt, pp. 303-325.

[672] *Schloendorff v. Society of N.Y. Hospital*, 211 N.Y. 125, 129, 105 N.E. 92, 93 (1914) ("Every human being of adult years and sound mind has a right to determine what shall be done with his own body."); Katz, J. (1984). *The Silent World of Doctor and Patient.* New York: The Free Press. See also Lederer, S.E. (1995). *Subjected to Science: Human Experimentation in America before the Second World War.* Baltimore: Johns Hopkins University Press.

[673] Advisory Committee on Human Radiation Experiments. (1996). *Final Report of the Advisory Committee on Human Radiation Experiments.* New York: Oxford University Press, p. 502.

[674] Ibid. See also Beecher, H.K. Op. cit.

[675] Advisory Committee on Human Radiation Experiments, op cit., p. 502.

[676] Moreno, J.D., Hurt, V. (1996). How the Atomic Energy Commission discovered 'informed consent.' In DeVries, R., Subedie, J. (Eds.). *Bioethics and Society: Constructing the Ethical Enterprise*. Upper Saddle River, N.J.: Prentice Hall; Bonham, V.H., Moreno, J.D. (2008). Research with captive populations: Prisoners, students, and soldiers. In Emanuel, E.J., et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics.* New York: Oxford University Press, pp. 461-474; Harkness, J.M. (1996). *Research Behind Bars: A History of Nontherapeutic Research on American Prisoners*, Ph.D. dissertation, University of Wisconsin-Madison, pp. 102-110 discussing Nathan Leopold's experiences in the Stateville malaria experiments; Ethics governing the service of prisoners as subjects in medical experiments: Report of a committee appointed by Governor Dwight H. Green of Illinois. (1948). *JAMA* 136(7):457-458.

[677] Advisory Committee on Human Radiation Experiments, op cit., pp. 53-54.

[678] Mahoney, J.F., Van Slyke, C.J., Cutler, J.C., Blum, H.L. (1946). Experimental gonococcic urethritis in human volunteers. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* 30:3.

[679] See, e.g., Akrawi, F. (1949). Is bejel syphilis? *British Journal of Venereal Disease* 25:119; Alving, A.S., et al. (1948). Procedures used at Stateville Penitentiary for the testing of potential antimalarial agents. *Journal of Clinical Investigation* 27:2-5; Rein, C.R., Kent, J.F. (1947). False positive tests for syphilis: A study of their incidence in sporozite-induced *vivax malaria*. *JAMA* 133(14):1001-1003.

[680] Advisory Committee on Human Radiation Experiments, op cit., p. 92, n.2; Lifton, R.J., (1986). *The Nazi Doctors: Medical Killing and the Psychology of Genocide.* New York, Basic Books; Proctor, R. (1988). *Racial Hygiene: Medicine Under the Nazis.* Cambridge, MA: Harvard University Press.

[681] American Medical Association, Board of Trustees. Minutes of the May 1946 meeting, pp. 156-157.

[682] Moreno, J.D. (2000). *Undue Risk: Secret State Experiments on Humans.* New York: Routledge, pp. 63-71.

[683] Coventry, W.A. (1947). Report of the Reference Committee on Miscellaneous Business, proceedings of the House of Delegates Meeting, 9-11 Dec. 1946. *JAMA* 133(1): 35.

[684] Advisory Committee on Human Radiation Experiments, op cit., p. 76.

[685] Ibid. Of course, conventions such as the Hippocratic Oath, which is widely known to admonish physicians to "abstain from all intentional wrong-doing and harm," informed the understanding of a physician's duties well before the written declarations of the mid 20th century. See Rieser, S.J., Dyck, A.J., Curran, W.J. (Eds.). (1977). *Ethics in Medicine: Historical Perspectives and Contemporary Concerns.* Cambridge, MA: MIT Press, p. 5.

[686] Ivy, A.C. (1947, May). Nazi war crimes of a medical nature. *Federation Bulletin* 33:133. Ivy also discussed his views several months earlier at an annual meeting of the Federation of State Medical Boards of the United States in February 1947. See Advisory Committee on Human Radiation Experiments, op cit., p. 93, n.5.

[687] John C. Cutler to John F. Mahoney. (1947, May 17). Correspondence. PCSBI HSPI Archives, CTLR_0001122.

[688] *United States v. Karl Brandt et al*. (1949). The Medical Case, Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Washington, D.C.: U.S. Government Printing Office.

[689] Ibid.

[690] Ibid.

[691] The veracity of this claim was challenged by many developments in the history of human subjects research in the decades that followed. See, e.g., Beecher, H.K., op cit. Scholars have argued that the Nuremberg Code itself had little if any effect on mainstream researchers in the United States until the 1960s. See Faden, R.R., Lederer, S.E., Moreno, J.D. (1996). US medical researchers, the Nuremberg Doctors Trial, and the Nuremberg Code: A review of findings of the Advisory Committee on Human Radiation Experiments. *JAMA* 276(20):1667-1671.

[692] Moreno, J.D. (2000). Op cit., pp. 64-80.

[693] See Section "Guatemala Experiments 1946-1948: Syphilis Experiments: Overview."

[694] Advisory Committee on Human Radiation Experiments, op cit., pp. 121-124.

[695] See Section "Background: Developments in the Science of Sexually Transmitted Disease." As Parran pointed out: "You know, we couldn't do such an experiment in this country." G. Robert Coatney to John C. Cutler. (1947, February 17). Correspondence. PCSBI HSPI Archives, CTLR_0001051. See also Moreno, J.D. (2000). Op cit., pp. 28-32.

[696] As noted, it may be that the researchers viewed moral concerns not as meaningful requirements but rather as pragmatic boundaries beyond which they might receive unwanted attention from the press, the public, or government. See, e.g., 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.

[697] See Section "Guatemala Experiments 1946-1948: Race and Secrey During the Guatemala Experiments: Issues of Secrecy."

[698] Advisory Committee on Human Radiation Experiments, op cit., p. 501.

[699] Brandt, A.M. (1987). *No Magic Bullet: A Social History of Venereal Disease in the United States Since 1880.* New York: Oxford University Press.

[700] See section "Background."

[701] See, e.g., Jonas, H. (1969). Philosophical reflections on experimenting with human subjects. *Daedalus* 98(2):219-247; Arras, J.D. (2005). Rationing vaccine during an avian influenza pandemic: Why it won't be easy. *Yale Journal of Biology and Medicine* 78:287-300.

[702] Indeed, a high rate of infection within a local population would make a prophylaxis study ill-suited to that locality, since researchers primarily sought uninfected subjects in order to test methods to prevent infection. John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives, CTLR_0000646.

[703] See Section "Guatemala Experiments 1946-1948: Initial Experiment Design."

[704] The 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, D.C.: Department of Health, Education, and Welfare, DHEW Publication OS 78-0012.

[705] See Section "Guatemala Experiments 1946-1948: Syphilis Experiments: Psychiatric Hospital: Scarification and Abrasion."

[706] For a complete list of documents, please see Table I: The Cutler Documents.

[707] See John Cutler. (1955, February 24). Final Syphilis Report. PCSBI HSPI Archives CTLR_0001299; but see PCSBI. (2011). Subject Database.

[708] Cutler Documents. (1947-1948). Guatemala Journal Studies with the Military (GC). Clinical notebook. PCSBI HSPI Archives CTLR_ 0000516.

Index

Italic numbers indicate pages bearing illustrations

P

R

S

T

U

V

W

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