Original Scholarship

From *in vivo* to *in vitro*: How the Guatemala STD Experiments Transformed Bodies into Biospecimens

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Policy Points:

- While most scholarship regarding the US Public Health Service's STD experiments in Guatemala during the 1940s has focused on the intentional exposure experiments, secondary research was also conducted on biospecimens collected from these subjects.
- These biospecimen experiments continued after the Guatemala grant ended, and the specimens were used in conjunction with those from the Tuskegee syphilis experiments for ongoing research.
- We argue there should be a public accounting of whether there are still biospecimens from Guatemala and Tuskegee held in US government biorepositories today, and if such specimens exist, they should be retired from research archives because they were collected unethically as understood at the time.

Context: The US Public Health Service's Guatemala STD experiments (1946-1948) included intentional exposure to pathogens and testing of postexposure prophylaxis methods for syphilis, gonorrhea, and chancroid in over 1,300 soldiers, sex workers, prison inmates, and psychiatric patients. Though the experiments had officially ended, the biospecimens collected from these subjects continued to be used for research at least into the 1950s.

Methods: We analyzed historical documents—including clinical and laboratory records, correspondence, final reports, and medical records—for information relevant to these biospecimen experiments from the US National Archives. In addition, we researched material from past governmental investigations into the Guatemala STD experiments, including those of the US Presidential Commission for the Study of Bioethical Issues and the Guatemalan Comisión Presidencial para el Esclarecimento de los Experimentos Practicados con Humanos en Guatemala.

Findings: Identified spinal fluid, blood specimens, and tissue collected during the Guatemala diagnostic methodology and intentional exposure experiments were subsequently distributed to laboratories throughout the United States for use in ongoing research until at least 1957. Five psychiatric patient subjects involved in the biospecimen experiments died soon after exposure to STDs. The same US government researchers working with the Guatemala biospecimens after the exposure experiments ended were also working with specimens taken from the Tuskegee syphilis study.

Conclusions: There should be a complete public accounting of whether biospecimens from the Guatemala and Tuskegee experiments are held in US government biorepositories today. If they still exist, these specimens should be retired from such biorepositories and their future

disposition determined by stakeholders, including representatives from the communities from which they were derived.

Keywords: research ethics, Guatemala STD experiments, Tuskegee syphilis experiments, Common Rule

On January 7, 1957, Dr. John C. Cutler, then a senior surgeon in the United States Public Health Service's (PHS) Venereal Disease Division, requested 9 tissue samples from his colleague Dr. Llewellyn Lee Ashburn, chief of the section on pathology and anatomy at the National Institutes of Health (NIH). Cutler described the material as "autopsy and biopsy material" connected to his "former research project."[1] Cutler listed all of the donors by full name and subject number and identified whether the sample was from the subject's urethra, skin, or cervix. He asked that the biospecimens be sent to Dr. James D. Thayer at the University of North Carolina, Chapel Hill's (UNC) Venereal Disease Experimental Laboratory (VDEL) for use in his gonorrhea research.[1] (See Table 1 for a list of the key players and their affiliations.)

Cutler would later become notorious for his involvement in the PHS STD experiments conducted in Guatemala from 1946 to 1948, which drew media attention and public ire in 2010 when the records were disclosed.[2] Ashburn would have been familiar with this research, as he was in Guatemala conducting his own research on river blindness at the same time as Cutler.[3] The intentional exposure experiments were initially designed to test postexposure prophylaxis for syphilis, gonorrhea, and chancroid. These experiments ultimately involved exposing more than 1,300 soldiers, sex workers, prison inmates, and psychiatric patients without their consent or sometimes even knowledge. PHS and Guatemalan researchers used injections and other invasive interventions to intentionally expose these subjects to infectious disease; only half of the subjects received any subsequent treatment for potential infection.[4]

Thayer, the recipient of the samples in 1957, had previously worked at the Venereal Disease Research Laboratory (VDRL) in Staten Island with Cutler and his supervisors.[5] The samples Thayer requested were collected during the Guatemala STD experiments from 4 men

and 4 women—all patients from the Asilo de Alienados, a psychiatric hospital in Guatemala City.[6] Cutler sent these tissue samples from Guatemala to the NIH. He noted in 1956 that they had been "up to eight years in formaldehyde," indicating they were collected before he left Guatemala in 1948.[7]

The Guatemala intentional exposure experiments have already been scrutinized in several publications. Analysis of those experiments by historian Susan Reverby resulted in government-led investigations by the US Centers for Disease Control and Prevention (CDC),[8] President Obama's Presidential Commission for the Study of Bioethical Issues (Bioethics Commission),[4] and the government of Guatemala.[9-11] Other related scholarship has explored how the intentional exposure experiments were approved,[12] critiqued the Bioethics Commission's report,[13] reviewed the history of the NIH's regulatory structure,[14] called for compensation for victims,[15] and evaluated the legacy of associated physicians.[16] But there were actually 3 types of experiments being conducted by US government officials and their Guatemalan counterparts during this time period:

1. **Diagnostic methodology experiments**: Taking blood and spinal fluid to test the sensitivity and specificity of syphilis diagnostic methodologies.

2. **Intentional exposure experiments**: Intentionally exposing subjects to syphilis, gonorrhea, and/or chancroid as part of a larger protocol to test the effectiveness of prophylaxis and treatment methods.

3. **Biospecimen experiments**: Collecting and experimenting with identified spinal fluid, blood, and tissue specimens from research subjects in the diagnostic methodology and intentional exposure experiments, even after the Guatemala STD experiment grant funding ended.

The Bioethics Commission discussed the diagnostic methodology and intentional exposure experiments in its 2011 report, but only briefly acknowledged the biospecimen experiments.[4(p83)] This article is the first to explore how the subjects from the diagnostic methodology and intentional exposure experiments played one last role in the Guatemala STD experiments—as unknowing secondary research subjects in blood, tissue, and/or spinal fluid research. The biospecimens collected from the Guatemalan subjects during both the diagnostic methodology and intentional exposure experiments were subsequently distributed to laboratories throughout the United States for use in this ongoing research.[7,17]

The current disposition of the Guatemala biospecimens is particularly significant, as in January 2017, 16 US federal departments and agencies released revisions to the current US human subjects protection research regulations.[18] This was the first major revision of regulations initially conceived in the 1970s as a response to federally funded research scandals, most notably the Tuskegee syphilis experiments (in which PHS researchers observed poor black sharecroppers with syphilis in Macon County, Alabama, for decades and prevented them from receiving treatment).[19] The most significant controversy surrounding the revisions to the research regulations involved informed consent to research with human specimens.[20]

Here we review the relevance of the Guatemala intentional exposure and diagnostic methodology experiments to the subjects who later became part of the biospecimen experiments, secondary research which extended at least through 1957. The US government researchers who conducted those experiments in Guatemala were the leaders of the venereal disease research movement for the first two-thirds of the twentieth century; many of the same men who approved the intentional exposure experiments as members of the NIH Syphilis

Study Section later benefited from that approval by engaging in the biospecimen experiments,[12] and some of those scientists were also simultaneously working with samples taken from the Tuskegee syphilis study.

While the Guatemala biospecimen experiments are historically important in their own right, we believe they can also inform current policy discussions concerning research involving biospecimens. Our ethical and regulatory entities still struggle with the appropriate normative framework with which to approach the research use of such specimens—particularly those that have been obtained through improper means. Here we argue that there should be a complete public accounting of whether biospecimens from the Guatemala and Tuskegee experiments are held in US government biorepositories today. If they still exist, these specimens should be retired from such biorepositories and their future disposition determined by stakeholders, including representatives from the communities from which they were derived.

The Guatemala STD Experiments

Intentional Exposure Experiments

The original research grant for the "Guatemala study dealing with the experimental transmission of syphilis to human volunteers and improved methods of prophylaxis"[21] supported intentional exposure experiments that ran from February 1947 through October 1948.[4(p127)] During this time period, Cutler collected from psychiatric patients the biospecimens that Thayer would later request. It is possible to review the de-identified research records of these subjects via the Bioethics Commission's "Guatemala Subject Data Spreadsheet,"[6] as well as from material published by the Guatemalan government's Comisión Presidencial para el Esclarecimento de los Experimentos Practicados con Humanos en

Guatemala.[9-11] Through these records we know that these subjects endured some of the most severe experimental exposure interventions documented.

Subjects who later were involved in the Guatemala biospecimen experiments were exposed to syphilis, gonorrhea, or chancroid during the intentional exposure experiments; 2 of the subjects were exposed to more than one STD (Table 2). Methods of exposure included inserting a toothpick coated in gonorrheal pus (taken from another patient) deep into the urethra or into the eyes. Syphilitic emulsion was injected into subjects' arms (Figure 1) or rubbed into their intentionally abraded genitals. Only 2 of the 8 subjects have any record of being treated for these exposures. Five of the subjects died during the experiments and were given autopsies by staff at the psychiatric hospital. No information regarding death or autopsy results is available for 2 patients. One patient was discharged from the institution, with the record indicating that she had been "freed" (see Table 2).

Of the 5 patients whose deaths were recorded, all died proximate to the time in which they were involved in the intentional exposure experiments (see Table 2). The Bioethics Commission reported 83 deaths of subjects during the Guatemala STD experiments, but found that "the exact relationship between the experimental procedures and the subject deaths is unclear."[4(p42)] Cutler claimed in his later report that this "steady loss of patients by death" was primarily due to high rates of tuberculosis and the fact that "acute and chronically ill patients were used" (Figure 2).[4(p42)]

Diagnostic Methodology Experiments

In addition to biospecimens that Cutler collected himself during the intentional exposure experiments, specimens were also mailed to the United States by additional PHS and

Guatemalan researchers.[4(p83)] For example, Genevieve Stout, a PHS microbiologist and serologist who worked for VDRL director John F. Mahoney, moved from the VDRL to act as the director of the Guatemala laboratory, where she conducted diagnostic methodology experiments of her own.[4(p82), 23-27] The VDRL in Chamblee, Georgia, cosponsored this research and served as a control laboratory for some of the work.[28]

In addition to Stout, the PHS continued to support several local Guatemalan staff after the Guatemala STD grant ended. Cutler wrote that he and Dr. Sacha Levitan (also a PHS senior surgeon and the "assistant director" of the intentional exposure experiments) felt that continued observation of the Guatemala intentional exposure subjects was critical.[29] Cutler recommended Dr. Juan Funes (his former PHS fellow and chief of the VD Section of the Guatemalan Ministry of Public Health), as well as Dr. Carlos Salvado (the director of the Guatemalan psychiatric hospital), to supervise the ongoing research.[29] These doctors and several staff were offered part-time salaries from the PHS Division of Venereal Disease for "post-treatment" observation of the subjects, and additional funds were set aside to pay for cigarettes to reward subjects and to support autopsies.[29-30] Medical records were also updated and provided to Cutler, who kept them in a personal record collection.[31] Funding was specifically allocated for preparation and shipment of biospecimens to the Staten Island VDRL.[30] Payments from the Division of Venereal Diseases to the Guatemalan physicians ended in May/June 1950,[32] although they shipped biospecimens to the United States until at least 1953.[17]

While the PHS employment contract for Funes indicated that the ongoing research would be with patients—including orphans, schoolchildren, prisoners, indigenous communities, and those *released* from the psychiatric institution[30]—the single available contemporaneous report is actually a record of diagnostic methodology experiments

involving 243 blood draws and 170 lumbar punctures collected exclusively from 248 *institutionalized* psychiatric patients.[4(p83n628)] While all of these subjects were described as "post-treatment," the diagnostic records provided with the samples demonstrate that 30 patients still tested positive for syphilis by at least one diagnostic metric (Online Appendix).[17] There is no record that these patients received any additional treatment.

Biospecimen Experiments

Biospecimens from people with STDs, such as the ones sent from Guatemala, were a highly valued commodity during Cutler's time in Guatemala and the decade thereafter. Serologic testing of blood was the backbone of syphilis diagnosis and control, but—as in Guatemala—researchers were still studying appropriate diagnostic methodologies into the 1950s and beyond.

In a 1995 article, Benjamin Roy argued that the primary goal of the Tuskegee syphilis experiments had not been, in fact, to observe the natural progression of syphilis, as the clinical publications claimed—but rather to develop serological testing for the US commercial market.[33] As a result of significant increases in federal funding for syphilis eradication from the 1930s through the 1950s, the market for STD testing grew into a lucrative business during the years that encompassed the Tuskegee and Guatemala experiments, as the number of people being tested rose rapidly.[33] Laws requiring syphilis testing for "marriage certificates, newborns, military recruits, industrial physical examinations, and admissions to hospitals" ensured steady work for laboratories.[33(p64)] To support the diagnostic research necessary to do this kind of testing, Tuskegee syphilis experiment researchers sent biopsy material, medical records, X-rays, and autopsy spinal/brain samples to researchers at the NIH and universities like Johns Hopkins and UNC–Chapel Hill (where Thayer worked using PHS funds).[7,19(p148-149),34] In 1970, James Lucas,

assistant chief of the venereal disease branch of PHS, claimed that the only scientific benefit of the Tuskegee syphilis experiments was the development of STD diagnostic methodologies.[19(p202)]

Stout, Funes, and Cutler also sent several different kinds of biospecimens from the Guatemala experiments to the same biorepositories that housed the Tuskegee materials. But, unlike the Tuskegee syphilis experiments which resulted in many publications (one of which included Cutler as a coauthor [35]), data from the Guatemala intentional exposure experiments were never published.[4(p86)] We also found no evidence that work from the biospecimen experiments was described in peer-reviewed publications.

One of the few extant records confirms that Funes, the Guatemalan physician paid by the US government to conduct diagnostic methodology experiments, mailed blood and spinal fluid specimens to the Chamblee, Georgia, VDRL in 1953. There, the biospecimens were received by VDRL associate director Dr. W.F. Edmundson, assistant director Ad Harris, and Cutler.[17] VDRL director Dr. Sidney Olansky—who at the time was the director of the Tuskegee syphilis experiments[19]—was also listed on the Guatemala biospecimen manifest.[17] Edmundson was simultaneously working on "serologic reactions in untreated syphilitic male Negroes" to determine "specific morbidity and mortality of latent syphilis in a group of untreated male Negros" in Macon County, Alabama (ie, Tuskegee).[36] In another study, Edmundson, Olansky, Harris, Cutler, and Dr. Harold J. Magnuson—the director of the UNC VDEL who recruited Thayer—coauthored a paper on a protocol of US prisoners who were experimentally exposed to syphilis—evidence of the close working relationship of these researchers and overlapping use of STD specimen collections.[37]

In October 1956, 3 years after the biospecimens were sent from Guatemala, Thayer met with his former VDRL colleague Cutler at a scientific conference in Washington, DC.[38-39] At that meeting, Cutler informed Thayer that biospecimens obtained from 9 subjects in

Guatemala and brought back to the United States were available for research.[7] Upon return to the UNC VDEL in 1957, Thayer requested access via letter to these biospecimens for his "studies in gonorrhea related to the possible intra-cellular location of the gonoccus [sic], the durcrey bacillus and the treponema pallidum as affecting response to therapy."[1] Ashburn responded to Thayer's request by providing 8 biospecimens stored in paraffin (one specimen had been misplaced) from the NIH biorepository, in addition to related medical records to help "put the single tissue in perspective."[1,40] It is unclear from Thayer's UNC VDEL records whether he ever used these Guatemalan tissue samples for his own experiments.

Policy Implications for Contemporary Biospecimen Research

Just as it was in Cutler's time, use of biospecimens and related data remains a critical component of current medical research. Programs such as the "Precision Medicine Initiative," which promise individually tailored therapies, require vast amounts of data and health information from hundreds of thousands of people in order to advance medical science.[41] The banking of biospecimens and data for future research has become almost as important as conventional clinical trials and provides a springboard for thousands of secondary research protocols.[20] Despite their value, however, our ethical and regulatory response to the uses of human biospecimens has struggled to keep up with the public's normative expectations.

Debate Over Use of Cadavers, Biospecimens, and Unethically Obtained Data

Infamous crimes committed by the Nazis under the guise of medical research provide another classic example of egregious experimentation clearly in violation of research ethics standards at the time.[42] The actions of the physician researchers involved were publicly condemned in the subsequent "Nazi Doctors Trial," in which 16 defendants were found guilty of murder and torture and 7 were sentenced to death.[42] Although the opening statement for the

prosecution argued at trial that the Nazi experiments "revealed nothing which civilized medicine can use,"[43] cadavers, biospecimens, and data from the Nazi era have in fact been integrated into ongoing medical education and scientific research for decades.[44] For example, Tubingen Medical School received 1,077 cadavers from a Holocaust execution site and, along with other West German medical schools, used skeletons and biospecimens from Holocaust victims in anatomy classes until the 1990s.[45] However, after public outcry in Israel and elsewhere over the continued use of these biospecimens and cadavers, "[t]he pendulum swung from retention to disposal," and many anatomical specimens were given a religious burial.[44-45]

It is worth clarifying the distinction between using artifacts and data to educate people about past atrocities, to honor the victims, and to attempt to prevent similar occurrences versus using them for general medical or science education or ongoing research purposes. On one end of the spectrum, the use of unethically obtained Holocaust cadavers or biospecimens for ongoing research purposes is inappropriate because it uses the victims as a means to scientific ends and can even be considered a re-victimization.[46] The use of Nazi victim cadavers and biospecimens by West German medical schools for general anatomy education is inappropriate, because by treating them similarly to those obtained via legitimate means (eg, donation after natural death), it fails to acknowledge in any way the indignity, affront, and pain that they experienced. The use of de-identified *data* to advance future scientific research, such as that gathered by the Nazis during torturous hypothermia experiments, has also been controversial.[46]

On the other end of the spectrum is a third type of application that involves using data, biospecimens, or other artifacts for education about the unethical event itself. For example, museums like the one at Auschwitz-Birkenau display collections of shoes, personal

possessions, and art to "bear testimony" to the atrocities that occurred there.[47] Similarly, in 2011, the Bioethics Commission released its "Subject Data Spreadsheet" of the de-identified medical and experimental records of the Guatemala STD victims on its website along with its report.[6] These data were released for ethical and educational use to help "researchers and bio-ethicists better understand the exploitation of some research subjects in the past to protect the contribution of all research participants in the future."[48]

US Human Subjects Research Regulations

Despite this agreement regarding use of biological samples derived during the Holocaust, the normative debate over appropriate standards of consent for general secondary research use of biospecimens is ongoing. In January 2017, the Department of Health and Human Services and other major stakeholders released the first comprehensive update to the US human subjects research regulations' "Common Rule" since its codification in 1991.[18] These revisions grew out of an almost 6-year process, which is still ongoing,[49] with one of the major points of controversy being informed consent to biospecimen research.[20]

Under the original Common Rule conceptualization, informed consent and Institutional Review Board approval are required for federally funded research involving a living individual from whom the research obtains data or specimens via "intervention or interaction" or "identifiable private information."[50] This means that while researchers can currently experiment with human biospecimens without consent, as long as they are de-identified —they cannot do research with data or specimens associated with personal identifiers without consent or waiver. The Notice of Proposed Rulemaking (NPRM) for the regulatory revisions, which gave interested parties a legally required notice and comment opportunity, proposed changing the definition such that research with *all* biospecimens (whether they included "identifiable private information" or not) would trigger informed

consent requirements, so as to "acknowledge and give appropriate weight to this distinct autonomy interest in research using biospecimens…"[51(p53942)] A previous iteration of this notice, the Advance Notice of Proposed Rulemaking (ANPRM), cited the popular nonfiction book about secondary research on clinical biospecimens without consent—*The Immortal Life of Henrietta Lacks*—as highlighting these underpinning concerns.[52(p44524)] The ANPRM had originally posed the question of whether existing collections of biospecimens should be "grandfathered in" so that any new rule requiring consent for all biospecimens would not apply to them,[52] but as the final rule did not require informed consent for de-identified biospecimens, the question became moot.[18]

In addition to these debates in federal law, US case law protecting human biospecimens is scarce and is largely focused on the property interests such specimens might represent rather than the privacy and dignitary harms at the forefront of current debate.[53-55] Empirical data have demonstrated that while research participants are willing to donate biospecimens and data, there is disagreement over how much control donors should retain over the specific purposes for which their donations are used.[56]

Moving Forward

Curators of contemporary biorepositories are grappling with the challenge of responding in ethically appropriate ways to these evolving normative public and professional standards.[57] On one hand, many commentators critiquing the proposed revisions to the Common Rule noted major practical limitations and great losses to the research community if biospecimens were required to be destroyed retroactively.[18] On the other hand, indefinitely archiving human biospecimens collected under egregious circumstances such as the Tuskegee and Guatemala experiments raises other concerns.

As was the case for the Nazi medical experiments, the consensus is that—under professional research norms *at the time of collection*—material gathered during the Guatemala and Tuskegee experiments was done so unethically. [4(p86),19] These experiments were a gross violation of the subjects' autonomy interests as well as social justice considerations and caused profound and indefinite harm that continues to engender anger, fear, and mistrust.[58-59]

Whether or not the Guatemala or Tuskegee biospecimens still exist in government archives is not a matter of public knowledge, although it appears likely that they do. For example, in 2008, the senior advisor for laboratory science for the Coordinating Center for Infectious Diseases at the CDC testified before the US House of Representatives that the CDC's archived biospecimens are only destroyed in "extremely rare circumstances," such as "when required by an Institutional Review Board."[60] The majority of CDC laboratories have no uniform destruction protocols in place, although destruction occurs only "after study and consultation and in a very controlled and documented manner."[60] In addition, after a vial of live smallpox virus was found in an unsecure storage room at the NIH in July 2014,[61] all US government departments and agencies that work with infectious agents were urged to conduct a "safety stand-down" to ensure laboratory safety practices.[62] As part of this procedure, the CDC searched 1,000 of its own laboratory rooms and inventoried and documented over 8 million stored samples.[62]

However, an initial search requested by the authors[63] and conducted by the CDC's Agency for Toxic Substances and Disease Registry, failed to turn up *any record* regarding biospecimens collected during the Tuskegee or Guatemala studies—or even any documents that apply to the "reevaluation, review, retention, or destruction" of any such specimens.[64] Given the plethora of public government documentation available regarding PHS

involvement in both studies and the retention and discussion of the specimens they generated,[4,17,19] a more thorough public accounting of whether or not these biospecimens are still in the possession of the US government as well as their current location is warranted. If these biospecimens still exist, they should be retired from the government's biorepositories and their disposition determined by independent stakeholders—including representatives of the communities from which they were derived. As was the case for the Nazi medical experiment specimens, destruction is one possibility. Another option is donation to a museum to represent the physical remains and sacrifices of the victims, much like the human hair on display at the Auschwitz-Birkenau Museum.[47]

One counterargument to this call for retiring the specimens is that access for secondary research use honors the victims. "The suffering is done—let someone benefit from all the pain," argued Lucien A. Ballin, who helped publicize data from Nazi hypothermia experiments at the Dachau concentration camp.[65] However, we believe that this line of reasoning—while perhaps appropriate for anonymous data[66] or research ethics pedagogy[48]—does not apply to biospecimens (either identified or de-identified) in research biorepositories. It became clear in the recent debate over the human subjects research regulations that some members of the public believe that de-identified biospecimens have a different normative value than does data. People ascribe a higher sense of identity and ownership to biospecimens that is ethically compelling on the basis of respect for persons as well as encouraging trust in the research enterprise. Moreover, while the US Bioethics Commission did not release any identifying information about victims of the Guatemala experiments, the government of Guatemala released identified medical information and some photographs.[9-11] Therefore, victims have been identified.

Ultimately, the federal government declined to regulate research with de-identified human biospecimens as some advocates had demanded. Whether or not this was the correct balance to strike between the protection of participant autonomy and public beneficence and justice, many parties came away from the compromise disappointed. Retirement of the Tuskegee and Guatemala biospecimens would be a worthy response to some of the ongoing criticisms of continued research use of biospecimens. It would also constitute a clear acknowledgment of the reprehensible nature of the Tuskegee syphilis and Guatemala intentional exposure experiments.

Conclusion

While the Guatemala STD intentional exposure experiments occurred over only a two-year period, biospecimens collected during these and the Guatemala diagnostic methodology experiments remained part of US research protocols for at least a decade following the completion of the original research. These biospecimens, along with the Tuskegee samples, became part of a critical federal biorepository of syphilitic blood and tissue used for serology research for both public health and lucrative business purposes. Though the appropriate research use of biospecimens is still a matter of debate, ethicists have roundly condemned the continued use of cadavers and specimens obtained during the Holocaust. We call as well for the retirement of any biospecimens collected from the Guatemala and Tuskegee experiments still in existence in federal biorepositories today.

References

1. Cutler J to Ashburn LL. Procurement of Unstained Sections. January 7, 1957. PCSBI HSPI Archives. National Archives at Atlanta, Morrow, Georgia. CTLR_0001531 (hereafter cited as PCSBI HSPI Archives with Bates page numbering).
2. Reverby S. "Normal exposure" and inoculation syphilis: a PHS "Tuskegee" doctor in Guatemala, 1946-1948. *J Policy Hist*. 2011;23(1):6-28.
3. Burch TA, Ashburn LL. Experimental therapy of onchocerciasis with suramin and hetrazan: results of a three-year study. *Am J Trop Med Hyg.* 1951;31(5):617-623.
4. Presidential Commission for the Study of Bioethical Issues. *"Ethically Impossible": STD Research in Guatemala from 1946 to 1948*. Washington, DC: Government Printing Office; 2011.
5. Magnuson HJ to McGavran EG. June 25, 1951. Collection 40120, Records of the School of Public Health, 1930-1998. University Archives at the Louis Round Wilson Special Collections Library, University of North Carolina at Chapel Hill, School of Public Health.
6. Presidential Commission for the Study of Bioethical Issues. *Guatemala Subject Data Spreadsheet*. https://bioethicsarchive.georgetown.edu/pcsbi/node/650.html. Published February 17, 2012. Accessed July 21, 2017.
7. Cutler JC to Thayer JD. *Autopsy and Biopsy Material from Patients with Syphilis and Gonorrhea*. November 15, 1956. PCSBI HSPI Archives: CTLR_0001533.
8. Centers for Disease Control and Prevention. *Report on Findings from the U.S. Public Health Service Sexually Transmitted Disease Inoculation Study of 1946-1948, Based on Review of Archived Papers of John Cutler, MD, at the University of Pittsburgh*. Washington, DC: Department of Health and Human Services; 2010.

9. La Comisión Presidencial para el Esclarecimento de los Experimentos Practicados con Humanos en Guatemala 1946-48. *Consentir el Daño: Experimentos Médicos de Estados Unidos en Guatemala, 1946-1948*. Guatemala City, Guatemala: Government of Guatemala; 2011. https://www.cityprojectca.org/blog/wp-content/uploads/2012/07/Guatemala-Report-Consentir-Spanish-201110.pdf. Accessed July 21, 2017.
10. La Comisión Presidencial para el Esclarecimento de los Experimentos Practicados con Humanos en Guatemala 1946-48: Comisión Técnica. *Experimentos en Seres Humanos el Caso Guatemala, 1946-48*. Guatemala City, Guatemala: Government of Guatemala; 2011. https://www.cityprojectca.org/blog/wp-content/uploads/2012/07/technical-report-Spanish-201104.pdf. Accessed July 21, 2017.
11. Archivo Historico de la Policia Nacional, Archivo General de Centro América, and the Dirección de los Archivos de la Paz. *Investigación Archivística Sobre Experimentos Practicados en Seres Humanos en Guatemala, 1947-1948*. Guatemala City, Guatemala: Government of Guatemala; 2011. https://www.cityprojectca.org/blog/wp-content/uploads/2012/07/archival-report-Spanish-13052011.pdf. Accessed July 21, 2017.
12. Spector-Bagdady K, Lombardo PA. "Something of an adventure": postwar NIH research ethos and the Guatemala STD experiments. *J Law Med Ethics*. 2013;41(3):697-710.
13. Galarneau C. "Ever vigilant" in "*Ethically Impossible*": structural injustice and responsibility in PHS research in Guatemala. *Hastings Cent Rep*. 2013;43(3):36-45.

14. Frieden TR, Collins FS. Intentional infection of vulnerable populations in 1946-1948: another tragic history lesson. *JAMA*. 2010;304(18):2063-2064.

15. Cohen IG, Lynch HF. Guatemalans used in experiments deserve compensation. *The New York Times*. July 4, 2012. http://mobile.nytimes.com/2012/07/05/opinion/guatemalans-used-in-experiments-deserve-compensation.html. Accessed May 12, 2016.

16. Lombardo PA. When heroes stumble. *Sex Transm Dis*. 2013;40(12):280.

17. Venereal Disease Research Laboratory. *Report on Serologic Follow-up on Patients Done at CDC in 1953, Samples Sent from Guatemala.* 1953. PCSBI HSPI Archives:CTLR_0001433-76.

18. Department of Homeland Security, Department of Agriculture, Department of Energy, et al. Federal policy for the protection of human subjects. Final rule. *Fed Regist.* 2017;82(12):7149-7274.

19. Jones JH. *Bad Blood.* New York: Free Press; 1993.

20. Smith JD, Birkeland AC, Goldman EB, et al. The immortal life of the Common Rule: ethics, consent, and the future of cancer research. *J Clin Oncol.* 2017;35(17):1879-1883.

21. Moore JE to Van Slyke CJ. May 26, 1947. PCSBI HSPI Archives: NARA-II_0000036.

22. National Archives Records Administration. Records of Dr. John C. Cutler. *Prison and Insane Asylum Photographs to Accompany Final Report.* Photos 1:71. Published March 28, 2011. Accessed July 24, 2017.

23. Stout GW, Cutler JC. Serology problems (syphilis) in Central America. *J Vener Dis Inf*. 1951;32(9):237-241.

24. Stout G, Guzman M, Scrimshaw NS. Presumptive false positive serologic reactions for syphilis in Central America. *Am J Syph Gonorrhea Vener Dis*. 1952;36(1):41-48.

25. Stout G, Guzman M, Scrimshaw NS. Presumptive false positive serologic reactions for syphilis in Central America. II. Relation to serum ascorbic acid, riboflavin, alkaline phosphatase, carotene, and vitamins A and E in blood serum. *Am J Syph Gonorrhea Vener Dis*. 1952;36(1):49-54.

26. Stout G, Mendez J, Guzman M, Scrimshaw NS. Presumptive false positive serologic reactions for syphilis in Central America. III. Relation to serum protein, albumin, and globulin. *Am J Syph Gonorrhea Vener Dis*. 1952;36(1):55-59.

27. Stout G, Aguirre F, Scrimshaw NS. Presumptive false positive serologic reactions for syphilis in Central America. IV. Relation to positive reactions for cephalin cholesterol (Hanger) flocculation test. *Am J Syph Gonorrhea Vener Dis.* 1952;36(1):60-63.

28. Thome JV. Encuestas serológicas centroamericanas realizadas durante los años 1950, 1951, 1952, y 1953. *Bol Oficina Sanit Panam*. 1955;39(2):131-145.

29. Cutler JC to Mahoney JF. August 26, 1948. PCSBI HSPI Archives:CTLR_0001162-3.

30. Funes JM. *Special Consultant Appointment Recommendation*. December 10, 1948. PCSBI HSPI Archives:NPRC_0000807.

31. Subject Notecards: Box 6. December 12, 1949. PCSBI HSPI Archives:CTLR_0006098.

32. Morrison CH to Andrada G. April 5, 1950. PCSBI HSPI Archives:NPRC_0001964.

33. Roy B. The Tuskegee syphilis experiment: biotechnology and the administrative state. *J Natl Med Assoc.* 1995;87(1):56-67.

34. Fletcher JC. A case study in historical relativism. In: Reverby S, ed. *Tuskegee's Truths: Rethinking the Tuskegee Syphilis Study*. Chapel Hill, NC: University of North Carolina Press; 2000:276-298, 277.

35. Olansky S, Harris A, Cutler JC, Price EV. Untreated syphilis in the male Negro: twenty-two years of serologic observation in a selected syphilis study group. *AMA Arch Derm.* 1956;73(5):516-522.

36. Andrews JM to Division Chiefs, Bureau of State Services. November 15, 1954. Summary of operational research projects for calendar year 1953. Summary of Projects File. RG 442-56A172, 1/1, National Archives Records Administration, College Park, MD:10-11, 14.

37. Magnuson HJ, Thomas EW, Olansky S, Kaplan BI, De Mello L, Cutler JC. Inoculation syphilis in human volunteers. *Medicine (Baltimore)*. 1956;35(1):33-82.

38. Symposium on Antibiotics. *J Pharm Sci*. 1956;45(6):388.

39. Faculty members present technical health papers. *The Daily Tar Heel*. October 19, 1956.

40. Ashburn LL to Thayer JD. April 3, 1957. PCSBI HSPI Archives:CTLR_0001532.

41. Obama B. *The Precision Medicine Initiative*. https://obamawhitehouse.archives.gov/node/333101. Accessed July 21, 2017.

42. Shuster E. Fifty years later: the significance of the Nuremberg Code. *N Engl J Med.* 1997;337:1436-1440.

43. Moe K. Should the Nazi research data be cited? *Hastings Cent Rep*. 1984;14(6):5-7.

44. Weindling PJ. The Nazi medical experiments. In: Emanuel EJ, Grady CC, Crouch RA, Lie LK, Miller FG, Wendler D, eds. *The Oxford Textbook of Clinical Research Ethics*. New York: Oxford University Press; 2011:18-30.

45. Dickman S. Scandal over Nazi victims' corpses rocks universities. *Nature*. 1989;337(19):195.

46. Post SG. The echo of Nuremberg: Nazi data and ethics. *J Med Ethics.* 1991;17(1):42-44.

47. Auschwitz-Birkenau Memorial and Museum. *Historical Collection*. Oświęcim, Poland: Auschwitz-Birkenau State Museum; 2017. http://auschwitz.org/en/museum/historical-collection/. Accessed May 16, 2017.

48. Spector-Bagdady K. Public Health Service research in Guatemala: toward new scholarship. *Hastings Cent Rep.* 2013;43(4):3.

49. Department of Homeland Security, Department of Agriculture, Department of Energy, et al. Federal policy for the protection of human subjects: delay of the revisions to the federal policy for the protection of human subjects. *Fed Regist*. 2018;83(14):2885-2894.

50. 45 CFR § 46. 101-102 (2009).

51. Department of Homeland Security, Department of Agriculture, Department of Energy, et al. Federal policy for the protection of human subjects. *Fed Regist.* 2015;80(173):53933-54061.

52. Department of Health and Human Services. Human subjects research protections: enhancing protections for research subjects and reducing burden, delay, and ambiguity for investigators. *Fed Regist.* 2011;76(143):44512-44531.

53. *Moore v. Regents of the University of California*, 793 P.2d 479 (Cal. 1990).

54. *Greenberg v. Miami Children's Hosp. Research Inst., Inc*., 264 F. Supp. 2d 1064 (S.D. Fla. 2003).

55. *Washington University v. Catalona*, 490 F.3d 667, 675 (8th Cir. 2007).

56. Grady C, Eckstein L, Berkman B, et al. Broad consent for research with biological samples: workshop conclusions. *Am J Bioeth.* 2015;15(9):34-42.

57. Henderson GE, Edwards TP, Cadigan RJ, et al. Stewardship practices of U.S. biobanks. *Sci Trans Med*. 2013;5(215). doi:10.1126/scitranslmed.3007362.

58. Aultman JM. Abuses and apologies: irresponsible conduct of human subjects research in Latin America. *J Law Med Ethics*. 2013;41(1):353-368.

59. Newkirk VR II. A generation of bad blood. *The Atlantic.* June 17, 2016. https://www.theatlantic.com/politics/archive/2016/06/tuskegee-study-medical-distrust-research/487439/. Accessed July 18, 2017.

60. Statement of Janet Nicholson, PhD, Senior Advisory, Laboratory Science Coordinating Center for Infectious Diseases, CDC, before the U.S. House of Representatives Committee on Science and Technology, Subcommittee on Investigations and Oversight. September 9, 2008.

61. Sun LH, Dennis B. Smallpox vials, decades old, found in storage room at NIH campus in Bethesda. *Washington Post*. July 8, 2014. https://www.washingtonpost.com/national/health-science/smallpox-vials-found-in-storage-room-of-nih-campus-in-bethesda/2014/07/08/bfdc284a-06d2-11e4-8a6a-19355c7e870a_story.html?utm_term=.0acd0d8b432c. Accessed November 5, 2017.

62. CDC. *Next Steps: Biosafety and Biosecurity at the CDC*. Washington, DC: CDC; December 16, 2014. https://www.cdc.gov/about/lab-safety/nextsteps.html. Accessed November 5, 2017.

63. Lombardo PA, Spector-Bagdady K. Request for information regarding the Tuskegee syphilis experiment and Guatemala STD experiment biospecimens. November 10, 2017 (on file with authors).

64. Andoh R. RE: CDC/ATSDR Freedom of Information Act Request of November 10, 2017. #18-00155-FOIA. December 4, 2017 (on file with authors).
65. Siegel B. Can evil beget good? Nazi data: a dilemma for science. *Los Angeles Times*. October 30, 1988. http://articles.latimes.com/1988-10-30/news/mn-958_1_nazi-data-issue. Accessed July 18, 2017.
66. Kor EM. Nazi experiments as viewed by a survivor of Mengele's experiments. In: Caplan AL, ed. *When Medicine Went Mad: Bioethics and the Holocaust*. New York, NY: Springer Science and Business Media; 1992:3-8.*Funding/Support:* Kayte Spector-Bagdady receives ongoing support from the Center for Bioethics & Social Sciences in Medicine at the University of Michigan Medical School.

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Table 1: Key Players in the Biospecimen Experiments[a]

Name	Affiliation
Cutler, John C.	Director, Guatemala STD Experiments Senior Surgeon, Venereal Disease Research Laboratory (VDRL), US Public Health Services (PHS)
Funes, Juan M.	Chief, Venereal Disease Section, National Department of Health, Guatemala Ministry of Public Health Special Consultant with the Venereal Disease Division, Bureau of State Services, PHS (1948-1956)
Levitan, Sacha	Assistant Director, Guatemala STD experiments Senior Surgeon, PHS
Magnuson, Harold J.	Director, University of North Carolina (UNC), Venereal Disease Experimental Laboratory (VDEL)
Mahoney, John F.	Member, Syphilis Study Section (which recommended the Guatemala experiments for approval) Principal Investigator, Research Grant-65 for the Prophylaxis and Treatment of Gonorrhea and Syphilis (ie, the Guatemala STD experiments grant) Director, VDRL (1929-1949)
Olansky, Sidney	Senior Surgeon, Director, PHS Director, Tuskegee syphilis study (1950-57)
Salvado, Carlos	Director, Guatemala National Psychiatric Hospital Special Consultant with the Venereal Disease Division, Bureau of State Services, PHS (Dec. 1948-May 1950)
Stout, Genevieve	Serologist, PHS Director, Venereal Disease Laboratory and Training Center, Guatemala City, Guatemala (Aug. 1948- Aug. 1951)
Thayer, James D.	Chief, UNC VDEL

[a]Adapted from: Bioethics Commission. *"Ethically Impossible": STD Research in Guatemala from 1946 to 1948*. Washington, D.C.: Government Printing Office; 2011.

Figure 1. Photo of Syphilitic Chancre on Arm of Female Psychiatric Patient and Subject of the Biospecimen Experiments

Photo of syphilitic chancre (dated 12.30.47) on right arm of female psychiatric patient 0341 after exposure to syphilis via injection during the intentional exposure experiments (public domain);[22] related clinical notes state she was "freed" in December of 1949; a sample of her skin was later requested for the biospecimen experiments (Table 2).

Figure 2. Portrait of Male Psychiatric Patient and Subject of the Biospecimen Experiments

Portrait of male psychiatric patient 0432[11(p228)] (public domain); he was exposed to syphilis 8 times via the contact method and injection over the period of a year during the intentional exposure experiments; a sample of his skin was later requested for the biospecimen experiments.

Table 2. Key Players in the Guatemala Biospecimen Experiments

PCSBI ID[b]	Cutler ID	Biospecimen Type	Sex	Dates of Intervention(s)	STD Exposure	STD Test	Treatment	Notes
n/s[b]-0889	A-4789	Cervix	F	June 4, 1948	Gonorrhea via deep inoculation[d]	Positive for gonorrhea	None recorded	
				October 6, 1948				"Died and autopsied"
PP[e]-0059	A-4785	Urethra	M	August 2, 1948	Gonorrhea via deep inoculation		None recorded	
				August 3, 1948				"Died"
				August 4, 1948		Positive for gonorrhea (post-mortem)		
PP-0075	A-4782	Urethra	M	March 19, 1948	Syphilis via scarification of the penis[f]	Negative	None recorded	
				June 4, 1948	Gonorrhea via deep inoculation	Positive for gonorrhea		
				June 12, 1948				"Patient died, autopsy performed"
PP – 0164	A-4780	Skin	F	October 10, 1948	Chancroid via scarification on left arm		None recorded	
				October 11, 1948	Chancroid via scarification on right arm			"Sites inoculated on 10/10 showed nothing"
				October 12, 1948	Chancroid via scarification on right arm			"No results from inoculation

					"using material taken from…patient"			s on 10/10 or 10/11"
				October 22, 1948		Positive for chancroid		
				October 23, 1948				"Died"
PP-0211	A-4783	Urethra and cervix	F	February 2, 1948	Intracutaneous injection of syphilis		None recorded	None
				June, 1948	Gonorrhea via deep inoculation with material taken from another psychiatric patient			
				July 3-8, 1948		Positive for gonorrhea in both eyes, urethra, and "meatus"		
PP-0341	S-3216	Skin	F	November 30, 1947	Syphilis via intracutaneous injection into right arm	Positive for syphilis		
				December 5, 1947		No clinical evidence of syphilis		
				January 11, 1948	Chancre from her arm used to produce serum used in another syphilis experiment	Chancres		

				March 1, 1948			Treatment with penicillin	
				December 12, 1949				Freed
PP-0432	S-3218	Skin	M	May 13, 1947	Exposed to syphilis via contact method[g] four times, and injection into right forearm			
				June 13, 1947	Exposed to syphilis via contact method and "subcutaneous method"[h]	Conflicting data for syphilis test		
				June 18, 1947				"Biopsy taken and sent to Dr.Sofian at USMH, S.I.[i]
				July 19, 1947			Treatment with penicillin	
				May 9, 1948	Injection of syphilis into left forearm			
				June 23, 1948			Treatment with penicillin	
				July 7, 1948 and October 18, 1949		Spinal tap		
PP-0438	A-4784	Urethra	M (45 yrs)	January 11, 1948	Exposure to syphilis via scarrification of penis, six applications of pledgets, removed after	None recorded	None recorded	Epileptic patient

					2 hours			
				February 25, 1948				Died and autopsy performed

a. Adapted from the Presidential Commission for the Study of Bioethical Issues, *Guatemala Subject Data Spreadsheet*.[6]
b. PCSBI = Presidential Commission for the Study of Bioethical Issues.
c. The Bioethics Commission had been unable to categorize the subject population of this subject in its own empirical analysis, but given her inclusion in the biospecimen set, we concluded she must have been a psychiatric patient.
d. In the **deep inoculation** method a toothpick was moistened with pus from an "acute case of gonorrhea in the male" and then "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." PCSBI. *"Ethically Impossible": STD Research in Guatemala from 1946 to 1948*. Washington, D.C.: Government Printing Office; 2011, 48-49.
e. PP = Psychiatric Patent.
f. In the **scarification** method researchers abraded the penis of the subject so as to break the skin and then applied a pledget soaked in syphilitic material to the injured area. PCSBI. *"Ethically Impossible": STD Research in Guatemala from 1946 to 1948*. Washington, D.C.: Government Printing Office; 2011, 62.
g. In the "**contact method**" a "cotton pledget was placed at the frenum [of the penis] and moistened with varying amounts of suspension and at intervals…The foreskin was replaced to normal position concealing the pledget entirely." PCSBI. *"Ethically Impossible": STD Research in Guatemala from 1946 to 1948*. Washington, D.C.: Government Printing Office; 2011, 61.
h. "Subcutaneous method" likely means injection.
i. Dr. L. Sofian at the United States Marine Hospital, Staten Island.