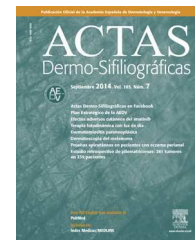




ACTAS Derma-Sifiliográficas

Full English text available at
www.actasdermo.org



HISTORY AND HUMANITIES IN DERMATOLOGY

Syphilis and Human Experimentation From the First Appearance of the Disease to World War II: A Historical Perspective and Reflections on Ethics[☆]



E. Cuerda-Galindo,^{a,*} X. Sierra-Valentí,^b E. González-López,^c F. López-Muñoz^d

^a *Departamento de Anatomía y Embriología Humana, Universidad Rey Juan Carlos, Madrid, Spain*

^b *Institut Català de la Salut, Terrassa, Barcelona, Spain*

^c *Departamento de Medicina, Universidad Autónoma, Madrid, Spain*

^d *Facultad de Ciencias de la Salud, Universidad Camilo José Cela, Madrid, Spain*

Received 25 April 2013; accepted 6 September 2013

Available online 8 September 2014

KEYWORDS

Syphilis;
Nazis;
Prisons;
Japan;
Unit 731

Abstract Physicians have conducted research on syphilis for centuries, seeking to understand its etiology and the means of transmission as well as find ways to prevent and cure the disease. Their research practices often strayed from today's ethical standards. In this paper we review ethical aspects of the long history of research on syphilis with emphasis on the experiments performed in the 20th century. The description of research around the time of World War II covers medical experiments carried out in US prisons and in the experimentation centers established by Japanese doctors in occupied territory, as well as experiments in Nazi Germany and the treatment of syphilitics there.

© 2013 Elsevier España, S.L.U. and AEDV. All rights reserved.

PALABRAS CLAVE

Sífilis;
Nazis;
Prisiones;
Japón;
Unidad 731

Experimentación en sífilis hasta la Segunda Guerra Mundial: historia y reflexiones éticas

Resumen Durante siglos la sífilis ha sido objeto de investigación por parte de los médicos, dado que la etiología, la forma de contagio, la profilaxis y el tratamiento eran desconocidos. En muchas ocasiones las investigaciones se han alejado de los estándares éticos actuales. En este artículo hemos revisado desde un punto de vista histórico y ético las investigaciones que sobre esta enfermedad se han ido realizando a lo largo de los siglos, centrándonos sobre todo en aquellos experimentos realizados en el siglo xx. Describimos con detalle los estudios realizados en los años que tuvieron lugar alrededor de la Segunda Guerra Mundial: experimentos realizados por los médicos norteamericanos en prisiones de Estados Unidos, la sífilis en la Alemania nazi o

[☆] Please cite this article as: Cuerda-Galindo E. Experimentación en sífilis hasta la Segunda Guerra Mundial: historia y reflexiones éticas. Actas Dermosifiliogr. 2014;105:762–767.

* Corresponding author.

E-mail address: esther.cuerda@urjc.es (E. Cuerda-Galindo).

los ensayos realizados por los japoneses en centros de experimentación creados a tal fin en los territorios ocupados.

© 2013 Elsevier España, S.L.U. y AEDV. Todos los derechos reservados.

Introduction to the History of Syphilis

The first cases of syphilis in Europe were detected toward the end of the 15th century. The physician Ruy Díaz de Isla claimed to have first seen the disease in Barcelona in 1493 and he surmised that the crew who traveled with Columbus had brought it back from the Caribbean. At a time when no known cure was at hand, syphilis spread across the world and the manner of transmission associated it with social disgrace. With the emergence of venereology in the 19th century, many scientists began to look further into the means of contagion and possible treatments, and in some cases their experiments were clearly improper when viewed in the light of today's ethical standards. In this article we will review the best known studies and their repercussions.

Experiments Involving Self-Inoculation or Inoculation of Patients

In attempting to confirm theories about the etiology of syphilis, some physicians resorted to self-inoculation. In 1767 the surgeon John Hunter apparently inoculated himself with secretions from a patient's urethra in an experiment intended to shed light on the relative merits of the "unicist" and "dualist" theories of sexually transmitted diseases (STDs).¹ Once syphilis was understood to be sexually transmitted, venereologists could address the question of whether or not it could be distinguished from another STD: the blennorrhagia of gonorrhoea. Defenders of the unicist theory hypothesized a single venereal disease that caused all symptoms. Dualists, on the other hand, argued that various STDs were at work. In 1812 in Toulon, Jean-François Hernández managed to confirm the dualist hypothesis when he inoculated 17 prison inmates with gonorrhoeal pus only and saw that syphilis did not develop.¹ The literature records similar experiments by 2 others. One was William Wallace, who infected healthy subjects with syphilis. Another was Joseph-Alexandre Auzias-Turenne, who practiced syphilization, a procedure in which the patient was inoculated with syphilitic material with the intention of inducing a curative response. Auzias-Turenne infected prostitutes held at the Saint Lazare prison.² At this time—the middle of the 19th century—syphilization was being hotly debated by respected physicians such as Joseph-François Malgaigne, who defended the practice, and Philippe Ricord, who opposed it. Similarly respected physicians in Spain, such as Matías Nieto y Serrano, were radically opposed to Auzias-Tourenne's method, arguing that there was no evidence that it provided any benefits, whereas it did lead to complications and worsening of the disease in certain patients. Syphilization was even discussed in doctoral theses, such as one completed in 1877 in Nuevo León in Mexico by Evaristo Sepúlveda.³

The conviction that syphilis was caused by a still unidentified microorganism was widespread by the early years of the 19th century. In a talk on dermatology at a Spanish medical conference in Madrid in 1864, dermatologist José Eugenio Olavide spent some time discussing the case for syphilis as a contagious, infectious disease.⁴

Twentieth-Century Experiments

Doubts about the distinct natures of the various STDs were dispelled by the end of the 19th century thanks to the contributions of bacteriology, which helped to clarify the etiology of individual clinical entities.⁵

In 1905 in Berlin, Fritz Schaudinn and Erich Hoffman discovered the causative agent of syphilis by means of dark-field microscopy. The name they gave the pathogen, *Treponema pallidum*, was a reference to the pale staining they observed. The Bordet-Wassermann reaction for diagnosing syphilis was described in 1906. Other serology techniques introduced later were the Meinike reaction (1917), the US Venereal Disease Research Laboratory (VDRL) test (1941), the Nelson-Mayer test (1949), and the fluorescent treponemal antibody absorption test.

Alexander Fleming discovered penicillin in 1928, and by the 1930s it was being used to treat humans. Only a decade later, during World War II, improvements in the manufacture of penicillin made it available in larger quantities for wider use.

The 2 world wars in the first half of the 20th century led to large-scale movements of troops and civilians. Military authorities understood that STDs were epidemic among soldiers and prevention, diagnosis, and treatment were high priorities. The pathogen had been identified, several serologic tests were available, and penicillin had been discovered: this combination created the basis for carrying out the studies of transmission, diagnosis, and treatment that will be discussed below.

Syphilis in Germany and Under the Nazis: Sterilization, Euthanasia, and Experimentation

In 1898, Albert Neisser carried out experiments on German prostitutes, who he injected with serum from patients with syphilis in an attempt to develop an antisiphilitic serum therapy.⁶ Most of the women contracted the disease, which Neisser attributed to their prostitution rather than the injected serum.⁷ Under pressure from public opinion once the experiment became known, the German Health Ministry issued a directive in 1900 to formally recognize the rights of individuals involved in scientific experiments.

Neisser then traveled to Java between 1905 and 1907 to conduct tests on the etiology, course, and treatment of

syphilis in monkeys; the experimental use of these animals was prohibited in Germany at the time.⁸

When a series of tests of the bacille Calmette-Guérin in the children of working-class families in Lübeck became known in the 1930s, the German public was once again shaken.⁹ In response, new rules governing human experimentation and the development of new therapies were established in 1931, probably inspired by the thinking of Julius Moses (1868-1942), spokesman for the Social Democrats in the Reichstag.¹⁰ The new legislation, which protected even animals from the excesses researchers might commit, strengthened the directives that had been issued several years earlier.¹¹

Such laws were no longer respected by 1933, when the Nazi Party began to eradicate whatever might weaken the so-called Aryan race. The Nazis targeted those with mental disabilities and diseases (including syphilis) as well as alcoholics, prostitutes and Jews, who represented the maximum expression of biological degeneration according to Nazi ideology.¹² Physicians and other professionals in Germany between 1933 and 1945¹³⁻¹⁵ practiced forced sterilization and caused the death of patients in experiments¹⁶⁻¹⁸ they had not consented to; they also participated in the extermination of many for religious, political, cultural or other reasons of personal identity.

Many health problems considered social diseases today—such as alcoholism or STDs—and disabilities were thought to be transmissible to society according to Nazi medical theory. Eliminating elements of society classified as degenerate would prevent contagion, the Nazis claimed, and would also eliminate the cost of caring for the afflicted persons.

A law to prevent hereditary diseases, enacted in 1933, allowed for the forced sterilization of German citizens if they had defects considered hereditary or transmissible.¹² Syphilis was not itself a primary indication for sterilization but patients with neurosyphilis were targeted on the basis of principles stated in the general sections of the 1933 law.^{12,20} Approximately 350 000 to 400 000 persons were sterilized, although euthanasia or racial hygiene (defined as selective reproduction of the human race in order to improve it) was an international current that found fertile ground for its most radical expression in Hitler's Germany, initially through sterilization programs and later through extermination.¹²

The Marital Health Law passed in Germany in 1935 required anyone wishing to marry to undergo a medical examination to confirm they were not carriers of some genetic defect. Although syphilis was not mentioned specifically, individuals applying to marry were advised to ask each other about common ancestors and the possibility that they might have communicable diseases. This type of legislation was not peculiar to Germany, however. A similar law was passed in the United States to require medical tests, including serology for syphilis, of anyone applying for a marriage licence.²¹

In 1939 Hitler authorized certain physicians to undertake mercy killings, and a network of companies and facilities for eliminating patients was created. The physicians were required to fill in forms and send them to number 4 Tiergartenstrasse in Berlin, giving the program a name: Action, or Operation, T4.²²⁻²⁴ The forms made specific mention of "refractory paralysis and other sequelae of syphilis."



Figure 1 Dissection room at the Sachsenhausen concentration camp in Germany. Prisoners with advanced neurosyphilis were euthanized here. Source of photograph: Esther Cuerda.



Figure 2 Concentration camp for women in Ravensbrück, Germany. Promised freedom, the prisoners were transferred to other camps to work as prostitutes. None were freed and many contracted venereal diseases. Source of photograph: Esther Cuerda.

Patients were euthanized in 6 facilities masquerading as hospitals. Some 70 000 individuals were killed by carbon monoxide inhalation until pressure from Christian churches stalled the program in 1941. Afterwards, the more clandestine practice of so-called wild euthanasia commenced and another 110 000 patients were eventually killed with morphine and barbiturates in institutions and hospitals located away from population centers.

Documents record the inclusion of patients with neurosyphilis in both sterilization and euthanasia programs (e.g., at the Sachsenhausen concentration camp, Fig. 1).^{19,20,25} Little is known of how syphilis-related experiments were conducted in such camps, but there are records of prison serology tests performed.²⁶ Brothels operated in concentration camps from the summer of 1943. Women who were recruited at the Ravensbrück camp (Fig. 2) on the promise of freedom in 6 months underwent complete physical examinations. None, of course, were freed and witnesses have told of how the women were later subjected to syphilis experiments when their brothel services ended or

else were allowed to die while the course of their disease was studied.^{27,28}

At this point it is worth mentioning Karl Herxheimer, a German Jewish dermatologist who discovered the Jarisch-Herxheimer reaction that develops when syphilis is treated with penicillin. Herxheimer died of dysentery at the Theresienstadt camp near Prague in 1941.²⁹

When the atrocities committed by physicians working for the Nazis were revealed at the end of World War II, the Nuremberg Code was established and additional ethical guidelines were developed later.^{30,31}

Experiments on Prison Inmates in the United States

It was argued during the Nuremberg trials of Nazi physicians that US physicians were carrying out similar experiments in the United States.³¹ One example mentioned before the tribunal was the work of Richard Pearson Strong, who inoculated prisoners with cholera.³² Another was Joseph Goldberger's research on pellagra among prisoners in Mississippi.³³ The US scientific community excused these colleagues of blame, however, and continued to insist that the actions of the Nazi doctors were instances of unmitigated wrongdoing.

In fact, using prisoners or other institutionalized individuals as the subjects of experiments was nothing new in the United States.³⁴ Such studies were carried out during the 1940s; encouraged by US participation in World War II, many were designed to meet military goals. Prison experimentation expanded tremendously during this period with studies on tinea pedis, histoplasmosis, hepatitis, malaria, and dysentery.^{35–37}

In spite of the Nuremberg Code, most scientists did not feel the rules applied to them, alleging that the requirements of war and the social situation of the moment legitimized their prison experiments.

Nearly half the clinical trials performed during this period have been found to have defects of form and substance with regard to the requirement of patient informed consent.³⁸ Syphilis research was also entangled in this web of political, ethical, social, and scientific interests.

The researcher mentioned most often in connection with syphilis is John Cutler, a surgeon who worked for the US Public Health Service. Cutler conducted studies at the Sing Sing Correctional Facility in New York State,³⁹ where he infected prisoners with the disease. The US VDRL, organized there in 1939 and 1940, set out to standardize the diagnosis and treatment of STDs, in a prison where inmates underwent thorough physical examinations before transfer to other facilities. Experimentation on syphilis was a key reason the VDRL was created at Sing Sing.^{40,41}

Social and political indifference to human experimentation began to shift by the early 1970s, however, following the thalidomide birth defects crisis and after the public was alerted to the Tuskegee experiments. Numerous articles and books about medical ethics appeared as more and more people began to denounce the use of prisoners and other institutionalized individuals in experiments; next, the practice was condemned and studies were closed down.⁴²



Figure 3 Manchuria, China: Unit 731 physicians performing routine work.

Source of photograph: British Broadcasting Corporation.

Experiments in a Japanese Research Facility

At the outbreak of the Second Sino-Japanese War in 1937 the Japanese Imperial Army launched an ambitious experimental research program with the main purpose of enhancing their biological warfare capabilities. The operation was headed by the future Lieutenant General Shiro Ishii, a physician who specialized in microbiology. That same year he set up a research facility in Ping Fang, Manchuria, near the city of Harbin. Euphemistically called the Epidemic Prevention and Water Purification Department—or the Boeki Bu or the Togo Unit—it came to be more sadly referred to as Unit 731 (Fig. 3). Housed in more than 150 buildings in a complex that occupied some 6 km², the unit remained in operation until World War II ended in 1945. Some 3000 workers staffed the facility, which would go down in history as one of the largest death factories ever created in the name of science. The program experimented on thousands of human guinea pigs (Chinese, Mongols, and Koreans accused of spying or working for the resistance, along with prisoners of war from Western countries and the physically or mentally disabled) and is estimated to have killed over 10 000 human beings between 1937 and 1945.^{43,44} The subjects were called *marutas*, a word that denotes logs or firewood.

The main function of Unit 731 was microbiological research for developing biological weapons. Our knowledge of the unit's activity comes mainly from the testimony of survivors—including staff and military personnel assigned to the unit, who told of experiments in which healthy individuals were inoculated with germs causing anthrax, yellow fever, typhoid and paratyphoid fevers, typhus, chicken pox, cholera, dysentery, scarlet fever, encephalitis, hemorrhagic fever, whooping cough, diphtheria, pneumonia, meningitis, tuberculosis, salmonella, gonorrhoea, and of course syphilis.⁴⁴

Most of the experiments were designed to meet clearly military goals, leading to weapons that could be used in armed conflicts. In the case of syphilis, however, different aims were pursued. The researchers sought to understand the disease better in order to optimize the treatment of

Japanese troops, among whom the prevalence of syphilis was high due to the systematic rape of women and the widespread use of sex slaves.^{45,46}

Given that both health and military authorities at Unit 731 and other facilities expressed great interest in syphilis, subjects were deliberately infected so that the course of disease could be studied.⁴⁷ The staff looked not only at external signs—such as changes in genital organs—but also the effects on internal organs; they therefore killed subjects for dissection at specified intervals or practiced vivisection.⁴⁷ There are even reports of the deliberate infection of pregnant women so that both mother and fetus could be dissected to study vertical transmission.⁴³ The cadavers were later incinerated in a large oven within the unit, an image that recalls Nazi extermination methods.

Unfortunately, most records of the experiments were destroyed. Activity at Unit 731 had to be quickly abandoned in August of 1945, when Russian troops crossed into Manchuria and Mengjiang.

The staff fled to Japan but not before destroying the facility and nearly all the material it contained. What few documents survived destruction were kept by the Japanese physicians and sold to the Allied commanders in exchange for immunity.⁴⁸

Conclusions

From the time syphilis was first described through the end of World War II, it attracted the interest of scientists who often acted outside ethical boundaries and who even broke laws that were already in place in their societies. The end of the war was a turning point in medical ethics, above all because of the world's reaction on learning of the atrocities committed by Nazi physicians. In spite of the establishment of the Nuremberg Code, however, medical researchers continued to transgress the boundaries set by even the most basic moral principles.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- Sierra X. Historia de las enfermedades de transmisión sexual. In: Vilata JJ, editor. *Enfermedades de transmisión sexual*. Barcelona: Ed. Proust; 1993. p. 1–18.
- Sierra X. Ética e investigación médica en humanos: perspectiva histórica. *Actas Dermosifiliogr*. 2011;102:395–401.
- Medina GCE, Ortiz GAH. Tesis del siglo XIX. Primeros egresados de la Escuela de Medicina de Nuevo León Medicina Universitaria. 2008;10:114–25.
- Actas de las sesiones del Congreso Médico Español celebrado en Madrid en setiembre de 1864. Madrid: Ducazcal; 1865.
- García Pérez A. *Enfermedades de transmisión sexual*. Madrid: Eudema; 1992.
- Vollman J, Winau R. Informed consent in human experimentation before the Nuremberg code. *BMJ*. 1996;313:1445–9.
- Schirren C. Versuche am Menschen in der dermatologie vor 100 jahren und heute. *Hautarzt*. 2001;52:537–41.
- Bendick C, Scholz A. Albert Neissers expeditionen nach Java 1905 und 1907. *Syphilisforschung und reiseerfahrung*. *Hautarzt*. 2005;56:116–23.
- Roelcke V, Maio G, editors. *Twentieth century ethics of human subjects research: Historical perspectives on values, practices, and regulations*. Stuttgart: Franz Steiner Verlag; 2004.
- Nadav DS. *Medicine and nazism*. Jerusalem: The Hebrew University Magnes Press; 2009.
- Seidelman WE. Animal experiments in Nazi Germany. *Lancet*. 1986;1:1214.
- Bachrach S. In the name of public health—Nazi racial hygiene. *N Eng J Med*. 2004;351:417–20.
- Hanuske-Abel HM. Not a slippery slope or sudden subversion: German medicine and national socialism in 1933. *BMJ*. 1996;313:1453–63.
- Adam YG. Aide memoire—the role of the German medical establishment in the Holocaust: A retrospective on the 60th anniversary of the liberation of Auschwitz. *Isr Med Assoc J*. 2005;7:139–42.
- Lifton RJ. *The Nazi doctors: Medical killing and the psychology of genocide*. New York: Basic Books; 2000.
- González-López E. Medicina y nazismo. *Aprender de la historia*. *Rev Clin Esp*. 2011;211:199–203.
- Seidelman WE. Mengele medicus: Medicine's Nazi heritage. *Milbank Q*. 1988;66:221–39.
- Spitz V. *Doctores del Infierno. Un cruel relato de los experimentos que los nazis practicaron con humanos*. Barcelona: Tempus Editorial; 2009.
- Slater E. German eugenics in practice. *Eugen Rev*. 1936;27:285–95.
- Weisz GM. Nazi medicine and racial policy. Hektoen International [cited 2013 Jun 28]. Available from: http://www.hektoeninternational.org/Nazi_medicine_&_racial_policy.html
- Eventos históricos del 10 de abril [cited 2013 Jun 29]. Available from: <http://www.historyorb.com/events/april/10>
- Platen-Hallermund A. *Exterminio de enfermos mentales en la Alemania nazi*. 1.ª ed. Buenos Aires: Nueva Visión SAIC; 2007.
- García Marcos JA. *La eutanasia en la Alemania nazi y su debate en la actualidad*. Valencia: Ed. Centro Francisco Tomás y Valiente; 2009.
- Barondess JA. Care of the medical ethos: Reflections on social darwinism, racial Hygiene, and the Holocaust. *Ann Intern Med*. 1998;129:891–8.
- Ley A, Morsch G. *Medizin und Verbrechen. Das Krankenrevier des KZ Sachsenhausen 1936-1945*. Berlin: Metropol Verlag; 2007.
- Material de archivo. International Trace Service, Bad Arolsen, Alemania.
- Hayes P, editor. *Lessons and legacies VII: The Holocaust in international perspective*. USA: Northwestern University Press; 2006.
- Kogon E. *El Estado de la SS*. Barcelona: Alba Editorial; 2005. p. 259–61.
- Cuerda Galindo E, González López E, López Estebanz JL. Dermatología en la Alemania nazi. *Actas Dermosifiliogr*. 2011;102:423–8.
- Pressel DM. Nuremberg y Tuskegee: Lessons for contemporary American medicine. *J Natl Med Assoc*. 2003;95:1216–25.
- United States v Karl Brandt. *Trials of war criminals*. In: *The Medical Case*. Washington, DC: Government Printing Office; 1949.
- Chernin E. Richard Pearson Strong and the iatrogenic plague disaster in Bilibid Prison, Manila, 1906. *Rev Infect Dis*. 1989;11:996–1004.
- Etheridge EW. *The butterfly caste*. Westport, CN: Greenwood; 1972. p. 7.
- Stanley LL. An analysis of one thousand testicular substance implantations. *Endocrinology*. 1922;6:787–8.
- Kaplan M. Tests on convicts curb vaccine ills. *New York Times*; 1947.

36. Butterfield WJH. Memorandum on observations on volunteers from penitentiary 1951 and letters to Richard W Copeland October 30, 1951 and Major WF Smyth, October 30, 1951. Richmond, VA: Archives of Medical College of Virginia.
37. Garcia-Guerrero J. Los presos como sujetos de investigación biomédica. *Cuad Bioet.* 2010;21:185–98.
38. Beecher HK. Ethics and clinical research. *New Eng J Med.* 1966;274:1354–60.
39. Magnuson HJ, Thomas EW, Olansky S, Kaplan BI, de Mello L, Cutler JC. Inoculation syphilis in human volunteers. *Medicine (Baltimore).* 1956;35:33–82.
40. Kaplan BI, Ryan J, Thomas E, Cutler JC, Jenkins KH. Results of therapy of latent and asymptomatic syphilis in a prison population. II. Clinical outcome with reference to cardiovascular and central nervous system syphilis and related to a nonsyphilitic control population. *J Chronic Dis.* 1958;7:300–11.
41. Kaplan BI, Ryan J, Thomas E, Cutler JC, Jones O. Results of therapy of latent and asymptomatic syphilis in a prison population. II. Seroreversal following definitive treatment as shown by the New York State complement fixation test. *J Chronic Dis.* 1958;7:312–20.
42. Hornblum AM. They were cheap and available: Prisoners as research subjects in twentieth century America. *BMJ.* 1997;315:1437–41.
43. Williams P, Wallace D. *Unit 731: Japan's secret biological warfare in World War II.* New York: Free Press; 1989.
44. Harris SH. *Factories of death: Japanese biological warfare, 1932-1945, and the American cover-up.* 2nd ed. New York: Routledge; 2002.
45. Stetz M, Oh BBC, editors. *Legacies of the comfort women of World War II.* Armonk. New York: M.E. Sharp; 2003.
46. Gold H. *Unit 731 Testimony.* Singapore: Tuttle Publishing; 2004.
47. Hudson C. Doctors of depravity. *Daily Mail* (March 2, 2007). Associated Newspapers Ltd [cited 2013 Apr 24]. Available from: <http://www.dailymail.co.uk/news/article-439776/Doctors-Depravity.html>
48. Nie JB. The United States cover-up of Japanese wartime medical atrocities: Complicity committed in the national interest and two proposals for contemporary action. *Am Journal Bioet.* 2006;6:W21–33.