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INVITED HISTORICAL REVIEW

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Penicillin: Origin, Health Issues,
Cultural Representation and
Ethical Challenges**

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The Syphilis Pandemic Prior to Penicillin: Origin, Health Issues, Cultural Representation and Ethical Challenges

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Syphilis is currently a treatable disease, with a low incidence in most developed countries, although the prevalence has increased recently, especially among men-who-have-sex-with-men. In many of the least developed countries, however, syphilis is still a major health problem, although the problem is not comparable to the desperate situation worldwide less than 80 years ago. At that time, and for many centuries previously, syphilis dramatically affected the lives and health of individuals and threatened the well-being of many societies. This review examines the aetiology, transmission, and many manifestations of syphilis from a historical perspective, emphasizing morbidity, treatment, psychosocial and cultural manifestations, as well as ethical issues uncovered in the clinical search for knowledge about the manifestations of the disease.

Key words: ethics, medical; history of medicine; medicine in the arts; pandemics; syphilis.

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Syphilis has had an enormous impact on humankind, including on the development of medicine as a science and as an art. In 1897, Sir William Osler, one of the fathers of internal medicine, is quoted as having advised his students that syphilis was the only disease they needed to study thoroughly. He said: “*Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you*” (1). The reasons for this statement were that syphilis has a myriad of expressions and, at the time, was a burden for a significant proportion of the population in some countries.

This review examines the diverse impacts of syphilis from medieval times onwards. It is important to reflect on the almost apocalyptic impact of early syphilis in Europe and its gradual transition to a disease with long-term rather than acute consequences for the individual, a situation that continued until around 1950 when penicillin therapy became widely available. A central theme of this review is the impact on society of this chronic disease, which for centuries crippled so many countries and for which the mode of transmission

SIGNIFICANCE

Syphilis has many guises, and, historically, it was crucial that medical professionals were knowledgeable about its manifestations. However, after being a scourge to humanity for centuries, the advent of penicillin almost eradicated the syphilis pandemic, and awareness of its characteristics has largely faded away. However, syphilis is currently increasing globally. A virtual absence of resistance of syphilis to penicillin is no guarantee for the future. With the possibility of antibiotic resistance and in the absence of a vaccine against syphilis, there is a risk that the disease could once again become epidemic. An understanding of collected knowledge about syphilis is, therefore, invaluable.

was related to behaviours that were strongly outside the religious and moral norms of the time. A further theme of this review is to examine how society acted when the spread of syphilis was out of control, and how the need to regain control led to measures that contravened human rights.

This review also highlights the rich artwork that has accompanied syphilis. Recent publications (e.g. (2–7)) cover this aspect of syphilis from a wider art-history perspective than we can present here.

FIRST APPEARANCE OF SYPHILIS IN EUROPE

Origin of the syphilis pandemic

Syphilis, as the disease is known today, was first documented in soldiers in the campaign of the French king Charles VIII, who invaded Italy in September 1494 and reached Naples in February 1495 with an army of more than 30,000 mercenaries from all over Europe. Naples was defended mainly by Spanish soldiers. After holding the city for a few months, the French army was demobilized, and the mercenaries spread across Europe to their homelands or joined new wars. Many were infected with a previously unrecognized serious disease and carried it through Europe, initially to neighbouring regions, i.e. future Italy, France, Germany, and Switzerland, followed by Holland and Greece, and subsequently to England and Scotland, and later to Hungary and Russia (8).

The origin of syphilis is among the greatest historical and scientific conundrums in the history of medicine. Although the issue has been discussed for

five centuries, there is no indisputable answer (9, 10). The oldest hypothesis suggests that 46 mercenaries, or conquistadors, on their return to Spain in March 1493, 6 months after reaching West Indian soil, brought the infection to Europe. This hypothesis is consistent with depictions of typical external symptoms of syphilis on clay figurines from the 6th century in present-day Mexico (2, 11), and osteological findings of skeletal remains with syphilitic changes in the New World, but not in Europe, prior to Columbus' expedition (9, 12). However, other researchers argue that a milder form of syphilis was present in the Old World long before Columbus' return, which became more aggressive and increased in prevalence in the late 15th century, a time of social turmoil, which promoted epidemics (13). This period was characterized by war, famine and chaos, with armies of mercenaries moving across southern Europe. Support for the pre-Columbian existence of syphilis in Europe is also provided by the fact that the time lag between Columbus' return and the outbreak in early 1495 is too short to explain the magnitude of the outbreak, considering incubation times, and also that, at most, only a few dozen of Columbus' mercenaries were enrolled in the army of King Charles VIII (13). Finally, no connection between Columbus' return and the epidemic was claimed until almost 30 years later, i.e. around 1520. Before that, the epidemic was considered a punishment from God for blasphemy.

The two main hypotheses about the origin of the syphilis pandemic are well-described in recent papers (14, 15). Modern genetic and molecular biological tools have not conclusively solved the issue and have been unable to exclude a pre-Columbian existence of syphilis in Europe (16, 17). Rather, genetic analysis has contributed to an understanding of the complex phylogeny of the causative organism, *Treponema pallidum*, and its status as a "heirloom" organism that spread globally with human development, and, in that context, followed the spread of Asian tribes across the Beringia Land Bridge approximately 15,000 years ago when the Americas were populated (9, 10). Furthermore, as the late 15th century was a time of early and intense colonization, it is not unlikely that trade and travellers might have brought the disease to Europe from other parts of the Old World.

It was soon realized that the new plague, initially called "lues" (Latin for to suffer or expiate; a common name for plague at the time), was sexually transmitted and thus tied to the "act of Venus", which later gave rise to the term "venereal disease". In 1530, when the Italian poet and doctor Girolamo Fracastoro published his allegory about "Syphilus" (a shepherd affected by the disease), this name became widely adopted as a synonym for lues. *Pox major* (German: *Pocker*) was also used to describe the large skin lesions associated with syphilis as opposed to *Pox minor* for smallpox, which had already plagued Europe for several thousands of years.

Manifestations of syphilis

The syphilis that struck Europe in 1495 was a terrible disease (8, 18). The first accurate description was given by a military surgeon during the campaign of Naples, based on his observations of the soldiers. He stated that that the first manifestation of the disease was the appearance of painless skin ulceration on the penis. The infection progressed to what is now known as secondary syphilis, a state with high fever, a generalized skin rash and pruritus, open sores and pustules over the entire body, severe skeletal and joint pain, and neurological symptoms, sometimes leading to death within weeks or months (8).

Since many of the symptoms of syphilis overlapped with other diseases known at the time, false diagnoses of the new plague were legion for many years (examples of likely misdiagnoses are shown in **Table I**).

Early on, syphilis became a stigmatized and shameful disease, and each affected population blamed its neighbours, who were sometimes also antagonists or enemies. This behaviour is well described by Tampa et al. (15):

"So, the inhabitants of today's Italy, Germany, and the United Kingdom named syphilis 'the French disease', the French named it 'the Neapolitan disease', the Russians assigned the name 'Polish disease', the Polish called it 'the German disease', The Danish, the Portuguese and the inhabitants of Northern Africa named it 'the Spanish/Castilian disease' and the Turks coined the term 'Christian disease'. Moreover, in Northern India, the Muslims blamed the Hindus for the outbreak of the affliction. However, the Hindus blamed the Muslims, and in the end, everyone blamed the Europeans."

Documents describing the frightening and violent character of the new disease have been recovered from the first decade after its appearance in 1495, whereas later descriptions show a disease with a clinical course more like that known in modern times (8). This transition in the clinical expression of the disease, which occurred around 1520 to 1540, has not been explained. Some writers suggest that the perceived transition simply reflects what could be called selection bias, and that the victims of the

Table I. Likely misdiagnoses of the skin and mucous signs of syphilis before modern diagnostic tests became available#

Signs and symptoms	Potential misdiagnoses
Genito-urinary ulcers (and discharge)	Gonorrhoea Soft chancre Tumours
Widespread rash (with or without fever)	Smallpox Chicken pox Measles Typhus (spotted fever) Tuberculosis Psoriasis
Nodules and other skin disfigurements	Tuberculoid leprosy Parasitosis Yaws ("endemic syphilis") Prurigo nodularis (eczema) Deep mycoses Tumours

Compiled by one of the authors (AV)

disastrous course in the late 1490s were poor, weakened, malnourished and starving (8, 15). They base this argument on other descriptions, saying that royalties and other wealthy persons were reported as having syphilis at that time, but with a much milder course. Others suggest that the syphilis that spread across Europe around 1495 was due to the emergence of a new mutated virulent strain of a bacterium that was subsequently outcompeted by milder variants that were better adapted to transmission in humans (19).

As mentioned above, the first interpretation of the syphilis epidemic in the early 16th century, judged from available literature, was that it was a punishment from God. Already, by August 1495, the Roman King Maximilian I proclaimed an edict stating that this new disease was a consequence of blasphemy and sins, punishing the sufferers of syphilis for their immoral behaviour (15).

An excerpt from a prayer published in Nuremberg in 1497 reads in translation as follows:

"O most holy father and mighty helper, Denis; Archbishop and praiseworthy martyr. O heavenly teacher, Apostle of France, and mighty ruler of the German lands. Protect me from the terrible disease called the French malady from which you freed a great many Christian people in France when they tasted the water from the living spring which welled up from beneath your sacred body" (18).

This text is the only known background to why the Saint Dionysius (English: St Denis) became the patron saint of syphilis, with the task of protecting his followers from "the French disease" (18).

First appearance of syphilis in art

Several artistic visualizations reflect the impact of syphilis at the end of the 15th century. The most well-known example is the woodcut "Syphilitic Man [*Syphilitischer Mann*]" by Albrecht Dürer, dated 1 June 1496, which shows a mercenary, probably returning home northbound and passing Dürer's hometown of Nuremberg (Fig. 1). The woodcut demonstrates *pox major*-like skin lesions on the man's limbs and face. Metaphysical explanations of the outbreak of this new and terrifying disease surround the mercenary. The zodiac at the top of the woodcut represents planetary conjunctions that occurred in 1484 and to which many intellectuals at the time attributed the outbreak of disease.

FROM EARLY 1500 TO MID-1800

Early spread and early treatments for syphilis

Ever since the horrific appearance of syphilis in the early 16th century, the disease has been highly present in the minds and real lives of people living in Europe. For the first few decennia syphilis was regarded with fear due to



Fig. 1. Albrecht Dürer's painted woodcut "Syphilitic Man [*Der Syphilitischer Mann*]" from 1496 shows *pox major* (plaques or large blisters) of syphilis on the limbs, chest and face. Wellcome Foundation. Downloaded from Wikimedia Commons.

its aggressivity, with severe symptoms and even deaths, during the acute phase of the disease. After that, a milder, more protracted form of the disease was the rule.

The main mode of transmission of the disease was widespread prostitution. Prostitution was largely internalized in societies, although objected to by the church

and at times regulated by the authorities. Syphilis spread rapidly to the higher social classes, who assimilated the disease into fine customs and contemporary fashion. Erasmus of Rotterdam (1466 to 1536), the greatest humanist and scholar of his time, wrote in 1516 that a man who has never had syphilis could be considered "*ignobilis et rusticans*", loosely translated to "*a bit of a country bumpkin*"; quoted in (20). Erasmus himself suffered from the disease. He wrote this at the time when the new syphilis epidemic was destroying Europe, a statement that was in stark contrast to the pious speeches from the church.

An early approach to treatment for syphilis was *Guaiacum officinale* (guaiacol), extracted from a specific tree species (German: *Pockenholz*) first imported from the current West Indies in 1508 (21). In analogy with other ineffective cures, guaiacol was soon abandoned. Instead, mercury, which had been used as a treatment for epidemic diseases since the 14th century, was the preferred treatment for syphilis (22, 23). Paracelsus found it too toxic when used as an elixir (22). Instead, the most common treatment was an ointment (Latin: *unguentum hydrargyri*; blue ointment; Swedish: *gråsalva*) composed of metallic mercury and grease, which was rubbed into the skin once or more times daily for many months. The transcutaneous absorption and inhalation of toxic mercury fumes produced massive salivation and sweating, thought to remove any evil agent from the body. The treatment was given close to a fire, and the sufferer was then left to sweat. The side-effects were terrible and included oral ulcers, excessive salivation, tooth loss, neuropathies, and kidney failure. Many patients died of mercury poisoning rather than from the disease itself. Long-term severe neurotoxicity in the form of what was later defined as "*erethism*" or "*mad hatter's disease*" occurred, especially when treatment was repeated over a period of many years. A common saying then was: "*One night with Venus, a lifetime with Mercury.*"; quoted in (24), or "*For a pleasure, a thousand pains*".

Despite the fearful long-term consequences for a subgroup of persons who contracted the disease, syphilis became an identity marker worth boasting of in "intellectual circles". A self-healing genital ulcer, the primary symptom of syphilis, was at first regarded as a buzzworthy sign of virility among intellectuals and upper-class men. Many of those who were infected continued to have innocuous symptoms of the disease for the rest of their lives. Signs of secondary syphilis, with transient fever and a widespread rash appearing within weeks or months post-infection, were often misinterpreted as measles. In reality, however, it reflects a haematogenous spreading of the bacteria to other organs, potentially leading to the appearance of more sinister symptoms many months or years thereafter, collectively known as tertiary syphilis. Also at this stage, syphilis was among many intellectuals and upper-class people considered an inevitable part of a sinful, yet desirable, lifestyle.

In contrast, in the depths of the population, being infected with syphilis became mostly a warning, combined with disgust and shame, and was regarded as a lack of chastity or fidelity in marriage.

Syphilis spread with trade and shipping and was more common in large cities. As an example, the risk of getting syphilis in London was 25 times greater than in North Wales. By the end of the 18th century, more than 20% of Londoners had syphilis by the age of 35 years (25).

During the 19th century, approximately 15% of the male population of Europe is thought to have been infected with syphilis. Married men who visited prostitutes often became infected but kept this a secret from their families. When their wives became infected, this was perhaps "diagnosed" as "measles".

Role in contemporary culture

Art – in a general sense pictures and models – has been used to reflect and communicate about human life since early humanity. This also applies to the representation of syphilis; works by contemporary artists are invaluable sources in a modern understanding of how the disease has been regarded at different periods (7). While the first years of the syphilis epidemic were viewed as a punishment from God, as exemplified by Albrecht Dürer's woodcut "*Syphilitic Man*" (Fig. 1), later artistic works have a wider thematic description. The contemporary view on syphilis in taverns or public houses in the 18th century is illustrated in the painting "*Tavern Scene*", by the English painter William Hogarth from 1735 (Fig. 2), in which naked legs, a skirt on the floor, and mouches (beauty marks, or patches) hiding syphilitic skin lesions are markers of a sinful life. This painting has a double meaning, a feature that characterizes much of the art depicting syphilis. It is part of a series of paintings by Hogarth, entitled "*A Rake's Progress*", showing the progress of a wealthy young heir who comes to London and lives a life of spending and immorality, ending up in criminality and insanity. A similar and famous series of pictures from the same artist, entitled "*A Harlot's Progress*", described the fate of an uneducated country girl who comes to London, is lured into prostitution, and dies of syphilis, at age 23 years (Fig. 3).

An interesting literary perspective is found in Voltaire's satire *Candide*, which tells the story of a young man, Candide, who is indoctrinated with optimism by his mentor, Professor Pangloss. Pangloss is infected with syphilis, and his health deteriorates over time. He meets his fate with the optimistic statement:

"... if Columbus had not ... this disease, which contaminates the source of generation, and frequently impedes propagation itself, and is evidently opposed to the great end of nature, we should have had neither chocolate nor cochineal." (the latter referring to the carmine dye which became an important export good in the 16th century during the colonial period).



Fig. 2. "The Tavern Scene" by William Hogarth from 1735. Oil on canvas. Sir John Soane's Museum, London.

FROM MID-1800 TO 1920s

Continued pandemic and endemic periods

Syphilis continued to plague large parts of the world's population until penicillin treatment was introduced in the late 1940s. Many persons with acute as well as chronic syphilis needed hospital care, and, during the late 19th century, syphilis was one of the dominant diagnoses in hospitalized patients. At that time, there was also scientific dispute about whether syphilis predisposed to tuberculosis, as both diseases seemed to occur simultaneously in certain populations (26).

There is particularly trustworthy information about the prevalence and spread of syphilis in Sweden, based on a well-conducted study published in 1931 (27). Among other things, this thesis argued that, in the late 19th century, 70% of prostitutes in Stockholm had syphilis. To halt the increasing prevalence of syphilis in Sweden, as in many countries, prostitution was regulated by legal means. Core characteristics of this regulation were the registration of prostitutes and of women suspected of prostitution, regular medical examinations, and isolation at the slightest sign of syphilis or other venereal disease. This regulation was in force until 1918. At that time, many inmates in Swedish mental hospitals had neurosyphilis with accompanying psychosis, dementia, epilepsy, balance disorders, and paralysis.

In sanatoriums, month-long treatments with mercury were given. In general, there were only minor changes in how mercury was delivered over the nearly 500 years it was used to combat syphilis. Over time, slightly lower doses were used, and dosing was adjusted according to the presence of side-effects, such as loosening of teeth, gum pain, and gastrointestinal problems. There were also attempts to use mercury in an organic form in pills and by hypodermal injections (23, 28).

Morbidity and mortality of syphilis in Sweden 1860 to 1920

In the aforementioned thesis "*Der statistische Untersuchung über Syphilis*" (27) the psychiatrist Hjalmar Källmark first reviewed medical records of 8,213 patients diagnosed with syphilis between 1860 and 1900 in 22 Swedish hospitals. Based on these results, he estimated that the total prevalence of hospital-diagnosed syphilis in Sweden was at least twice that number, corresponding to close to 1% of the Swedish population.

The largest number of newly infected patients were noted between 1870 and 1880: 3,048 persons. This number decreased to 1,000 newly infected cases during the last decade of the century. Approximately 60% of the new cases were women, and the age group 15–40 years accounted for 65% of patients. Notably, 19%



Fig. 3. An engraving from "A Harlot's Progress" by William Hogarth from 1732. A young country girl reaches London and is immediately flattered by an elderly brothel keeper who has distinct syphilis marks, and who wants to secure her for prostitution. The picture is full of symbolism well-identified by contemporary spectators. The British Museum.

of patients were less than 1 year old at diagnosis (see more below).

There were approximately 3,000 new cases of syphilis per 3-year period before the First World War, when the numbers rose steeply, to at most 20,000 new cases. Men made up about 75% of these cases. Subsequently, the 3-year incidence rate for syphilis decreased to 5,000 in 1920 (27).

Källmark reported that 75% of cases had responded to the first course of mercury treatment between 1860 to 1900 (27). The remaining cases underwent 2 or more courses over many years. The high number of "cured" cases must be assessed in a context where the frequencies of spontaneous healing and reinfection between treatments are unknown and where the assessment of "cure" is subjective. Indeed, less impressive results were reported in 1,500 prostitutes who came for treatment after being inspected as part of the regulation of prostitution laws, where only 30% "responded" to the first course, and 15% did not respond at all despite more than 5 courses of mercury (a separate study referred to in (27)).

A key aspect of Källmark's study was an evaluation of different expressions of neurosyphilis over time in Sweden. **Fig. 4** shows the accumulated

5-year-incidences of late neurological manifestations recorded between 1870 and 1920, divided by the author into 3 clinical subgroups: tabes dorsalis, general paresis, and lues cerebri, including other neurological symptoms appearing before end-stage disease. There was a steadily increased number of patients reported from hospitals

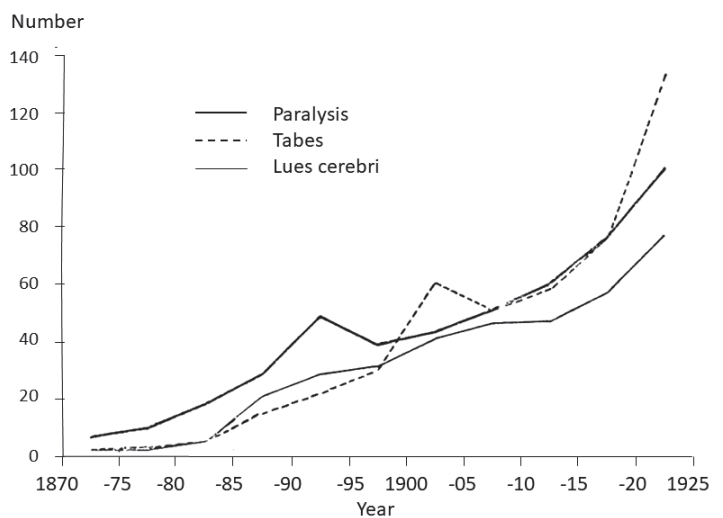


Fig. 4. Numbers of registered cases of the 3 main diagnostic categories of neurosyphilis in the years 1870 to 1925. Tabes: emaciation (of dorsal nerves). Modified from reference (27).

each time. In fact, 7–8% of syphilis-infected patients developed paralysis with a latency period of approximately 10–15 years, and this was more common in men than in women (27).

Källmark also approached the heart of the matter, namely excess mortality linked to syphilis of different durations. He reported that mortality was significantly elevated in all age groups infected with syphilis, especially in men 10–20 years after infection. In this group, the number of deaths was twice as high as expected from age-matched population data.

First study of the natural course of syphilis: from Oslo

As all therapeutics for syphilis were either toxic or had no or little effect on the disease, there was a debate in the late 1800s as to whether treatment was at all meaningful. Some, like Professor Caesar Boeck at the University of Oslo in Norway, even argued that mercury treatment might interfere with the patient's immune defence and thus be counterproductive as treatment of syphilis. Of course, an answer to this controversy required first-hand knowledge about the natural course of the disease.

Consequently, Caesar Boeck practically forbade using mercury in treating syphilitic cases in his wards from 1891 to 1910. During this period, 1,978 patients with syphilis were enlisted in the study conducted at the National Hospital in Oslo. The results, published in 1928 under the title "*The Oslo Study of Untreated Syphilis*", concluded that treatment was justified only when it made sense for a small subset of patients with syphilis (29). Although the study was unique in its design, it was later accused of having a biased patient selection (30). In a noteworthy long-term follow-up study published in 1955, more than 60% of subjects still had no symptoms of their disease, while the rest developed "late syphilis". In just under 11%, the disease had probably resulted in death; cardiovascular syphilis appeared in 10%, and neurosyphilis was diagnosed in 7% of cases (31). There is no published evidence that ethical aspects of withholding treatment for all patients were an issue at the time.

SOCIOECONOMIC AND CULTURAL INFLUENCES

A culture with syphilis

Syphilis has had a profound impact on all societies and social groups, either directly in the form of severely diseased and suffering persons and early deaths, or by the effect of the disease on private lives, sexual behaviour, and economic development. As syphilis was common among artists and intellectuals, it is not too far-fetched to assume that they were more familiar with the effects of syphilis than other people. Several of the most famous 19th-century persons are said to have had syphilis, including several royal individuals, composers, and

writers, such as Gustave Flaubert, Guy de Maupassant, Henri Toulouse-Lautrec, Karen Blixen, Franz Schubert, Gaetano Donizetti, Robert Schumann, and Alphonse Daudet (32, 33). Daudet described his personal experience of late syphilis in his bequeathed notes "*The land of pain*" (French original: *La Dolou*) (32).

Naturally, various facets of syphilis were themes in art produced during this time. The gouache "*Syphilis*" by the British painter Richard Tennant Cooper (1885–1957) represents well the fears of being infected around the *fin de siècle* (Fig. 5).

Many literary works from this time deal with or contain characters infected with syphilis who are living with various consequences. It goes beyond the purpose of this review to cover the contemporary literature in full. Extensive learned reviews are found in references (32, 33). Here, three examples are selected to represent the different faces of syphilis, as depicted in literary characters and their lives.

Syphilis acquired twisted positive connotations within European artistic circles in the late 19th century. The fate of artists such as Friedrich Nietzsche, Gustave Flaubert, Francisco Goya and Oscar Wilde gave rise to a belief that the early phase of late neurosyphilis allowed for increased creativity and inspiration before the illness would finally lead to total mental breakdown. This was thought of as a phase of the disease during which a euphoric spirit and unlimited energy rewarded sufferers. This idea characterizes the first example of literature depicting syphilis, Thomas Mann's "*Doctor Faustus*" from 1947. The novel is about the fictitious eminent composer Adrian Leverkühn, a man with extraordinary intellect and creativity. He deliberately let a prostitute infect him with syphilis, which in the novel is a metaphor for his pact with the devil to increase his talent even further and remain artistically innovative for many years. The novel follows his success and, in parallel, his progressive madness until his death 10 years later.

The second literary example is the play "*Ghosts*" by Henrik Ibsen from 1881, with dark family secrets as its theme. The novel tells of a widow, whose husband had lived a debauched life resulting in syphilis. They have an artist son, Oswald, who the mother discovers also has syphilis, which she believes he had contracted from his father. The family's maid, Regina, who is a secret illegitimate daughter of the husband and a half-sister of Oswald, is attracted to Oswald, whose health is declining with the first signs of neurosyphilis. The play does not end happily.

Finally, a brief description of the social consequences of syphilis in Victorian Britain is found in a short essay by Arthur Conan Doyle from 1894, "*The Third Generation*". At that time, congenital syphilis was thought to be transmitted paternally during conception. The story is about a young noble, a baron, in London with superficial characteristics of having congenital syphilis who visited



Fig. 5. Syphilis. Gouache by Richard Tennant Cooper, 1912. Wellcome Foundation. Downloaded from Wikimedia Commons.

his physician on the eve of his marriage. He was told that his father had given him syphilis, who, in turn, had contracted it from his grandfather. After a long personal consultation, the physician strongly advised cancelling the marriage, which was understood to cause a social scandal amongst the British nobility. The day after, the morning newspapers reported an unexplained fatal traffic accident close to the doctor's office shortly after the baron had left.

It is worth mentioning that very few of the many prostitutes who played principal parts in French novels at the time are described as having syphilis (32).

With the arrival of penicillin, the horror of syphilis, both for the individual and for society, faded away, and syphilis vanished as a theme in literature.

Outcast and despised: the prostitute

Although prostitutes were considered to be the most important source of the spread of syphilis, they remain "elusive historical characters" (34).

Urbanization during the 19th century and world wars during the early 20th century were fertile grounds for both prostitution and for the spread of venereal disease, and syphilis was predominantly spread through prostitution. Sociological factors associated with the incidence of venereal diseases in a population are, in general, linked to the magnitude of prostitution. Such factors are the proportion of young adults, the degree of disparity of the sex

ratio, economic stratification, illiteracy, horizontal social mobility, urbanization, and social disorganization of the population, due to factors such as war (35). Consequently, it is not surprising that the exacerbations in outbreaks of syphilis have been related to the gathering of young men far from home, as in wars and in regions and times with colonists and settlers, i.e. times and places in which prostitution had flourished. This also characterizes the periods of early industrialization and rapid urbanization. During early industrialization, prostitutes had much in common with the mass of urban poor. Temporary moves into and out of prostitution mirrored a fluid social identity among the poor, who made their living from temporary, casual labour and where prostitution was one of several means by which they could endure hard times (34). Contemporary literature describes the poor and uneducated prostitute as a person who dreams of a better and respected life far away from their struggle to survive (34).

The vulnerability and frailty of these prostitutes were strongly augmented during the 19th century, when authorities in most European countries tightened laws relating to their activities, with new regulations intending to reduce the spread of syphilis and other venereal diseases (33). Such regulations included repeated systematic medical examinations and forced genital inspections if venereal disease was suspected. These new regulations gave authorities control over all individuals suspected to be professionally engaged in prostitution. Although these measures were motivated as sanitary, aiming to control

the spread of syphilis and other venereal diseases, they had consequences far beyond the sanitary supervision of prostitutes and increased their role as outcasts. To the extent that prostitutes could be regarded as victims in a harsh and unforgiving world, during and after the Second World War they became an obvious social threat in their key role as a spreader of syphilis and other venereal diseases.

There is a lack of published personal accounts or narratives that can shed light on the prostitutes' world and help to understand their exposed situation. In general, their personal voices are not heard, and virtually all studies of prostitutes suffer obstacles in identifying the precise populations of prostitutes (34). An obvious, but less discussed, consequence of prostitution and syphilis was the birth of many unwanted children with congenital syphilis, who were infected by their mothers during pregnancy.

Congenital syphilis

There is a substantial risk that pregnant women with untreated syphilis will transmit the infection to the child *in utero*. Such placental passage of the infection may have devastating consequences for the child and has been covered by the phrase "curse on two generations" (36). Neonates born with syphilis were recognized as early as 1497 (36). Later during the epidemic, congenital infection of the newborn was common, hideous, and often lethal. In Sweden 1920 to 1926, newly registered cases of congenital syphilis constituted 10% of all new cases of syphilis (27).

The mother can infect the child at any stage of her disease, although the risk decreases over time. The risk, however, increases with advancing gestation (37, 38). An intrauterine infection may result in widely different

clinical presentations, from giving birth to an asymptomatic child to a child with severe disease or, frequently, to stillbirth. It has been estimated that pregnancy in a woman with early syphilis will lead to intrauterine or early postnatal death of the child in close to 40% of cases, a living child with congenital syphilis in another 40%, and an uninfected child in 20% (37). Congenital syphilis can be asymptomatic or "silent" in about 65% of newborns, but usually becomes symptomatic after a few months and leads to stigmata if left untreated. Findings of congenital syphilis include the triad of Hutchinson's teeth, interstitial keratitis, and eighth-nerve deafness, but also neurodevelopmental delays and diverse types of skin lesions (**Fig. 6**). A typical cosmetic feature is a "saddle nose" due to osteitis of the nose bone.

As many mothers with syphilis were unable to care for their children with congenital syphilis, special nursing homes were built. In Paris, a hospice dedicated to neonates with syphilis was opened in 1780 (36). In Sweden, Edvard Welander, professor of Syphilology at Karolinska Institute, pioneered the care of children with syphilis in the late 19th century (39). He took the initiative to a nursing home for children with congenital syphilis in Stockholm. It was opened in December 1900, called "*Lilla Hemmet*" ("*The Little Home*"), with facilities for 12 children (**Fig. 7**; top). Ten years later, thanks to a large fundraising campaign, it was replaced by a newly built 50-bed facility (**Fig. 7**; bottom). The original name ("*The Little Home*") remained until 1953 when the nursing home closed as the newly introduced treatment with penicillin decreased the number of children with congenital syphilis dramatically (39). Prior to the availability of penicillin, between 50 and 100 children per year were born with syphilis in Sweden, which had a population of 5 million at the time. Many of these children died within a

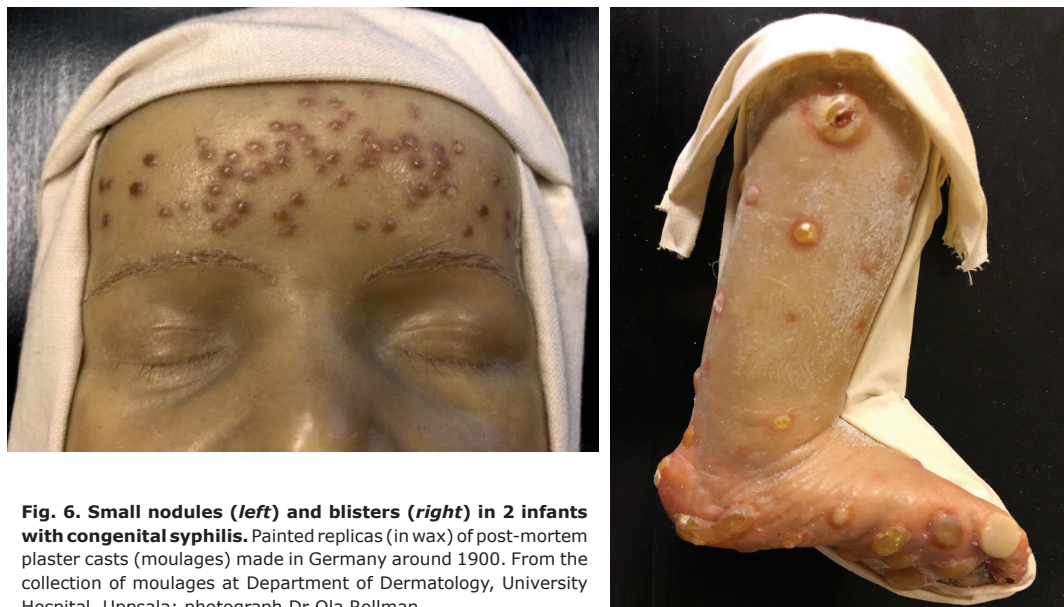


Fig. 6. Small nodules (*left*) and blisters (*right*) in 2 infants with congenital syphilis. Painted replicas (in wax) of post-mortem plaster casts (moulages) made in Germany around 1900. From the collection of moulages at Department of Dermatology, University Hospital, Uppsala; photograph Dr Ola Rollman.



Fig. 7. Caring homes for children with congenital syphilis. *Top:* The old customs house in central Stockholm, which in 1900 was converted into "The Little Home" with room for 12 syphilis-infected children. *Bottom:* The newly built new "Little Home" nearby, with facilities for 50 children and in operation from 1910 to 1953. Public domain.

couple of months. In addition, an unknown number of foetuses were stillborn or aborted.

Artistic preventive campaigns

Around 1920 and onwards, authorities used artists' depictions of syphilis in public campaigns, as leaflets, posters, and pictures in magazines and newspapers. These works reveal much about the view of syphilis at the time and about societal and behavioural perspectives. In France, a poster from the 1920s equated syphilis and tuberculosis in terms of mortality, which far exceeded that caused by cancer (**Fig. 8**). This poster also alludes to a contemporary medical discussion about the common

co-existence of syphilis and tuberculosis in prostitutes. At the same time, it was described as "hereditary" and a "risk for the race".

There is an abundance of posters from the USA, with artistic campaigns for soldiers living separately from family life (or similar) created during the 1930s, warning against the temptations of "occasional sex" and, although unsaid, of "prostitutes"; see, for example, **Fig. 9**. Another type of posters were directed at the public, pointing to the risk of not being diagnosed and having treatment. All these are from the pre-penicillin time when treatment was with mercury and arsenic compounds, both toxic and cumbersome treatment, and with uncertain effects (22).

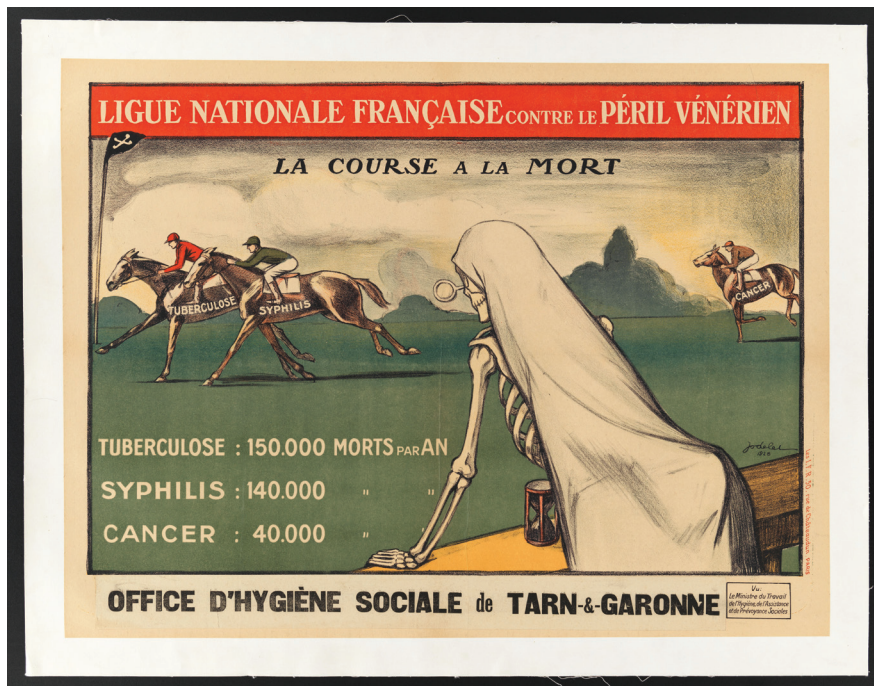


Fig. 8. A warning against sexually transmitted diseases: in a three-horse race watched by Death: "Syphilis" is about to overtake "Tuberculosis", while "Cancer" comes third. Colour lithograph by E.-C. Jodelet, 1926. In copyright. Source: Wellcome Collection.

THE RISE OF MODERN SYPHILIS DIAGNOSTICS AND NEW TREATMENTS BEFORE THE ADVENT OF PENICILLIN

Dawn of modern diagnostics

Until end of the 19th century, a diagnosis of syphilis relied entirely on clinical examination where the identification of typical skin changes was essential also for staging of the disease. Alas, the skin lesions associated with syphilis are notoriously difficult to distinguish from many other dermatologic disorders (Table I), and the situation only gradually improved when histopathologic analysis of skin biopsies became available.

A breakthrough came in 1905 when Fritz Schaudinn and Paul Hoffman identified the syphilis spirochete (*Treponema pallidum*). The motile spirochete could now be detected using dark-field microscopy of "live" smears from wound exudate. This was a time-consuming, although specific, test used in venereology clinics until the 1980s. More common, at least for a first screening, was the diagnostic test developed by Paul von Wasserman in 1906. The test is a so-called "non-Treponema test" as it was not directed to the causative organism but detected host antibodies against lecithin, cholesterol, and cardiolipin, which were released from cell walls during the infection. It exists in different improved variants and with different names. It may trace a syphilis infection in blood samples even when the patient is no longer infectious (39). Up to 30 years ago, the Wasserman reaction was still used for screening hospitalized skin patients in Sweden. Unfortunately, there were false-positive test results for, among other things, rheumatic diseases, a source of error that was overlooked for a long time and

led to unnecessary treatments and tragic accusations of infidelity between spouses. Today, *Treponema*-specific tests that detect immunoglobulin G (IgG) and IgM antibodies against the spirochete are available. Finally, the spirochete can be detected in the active phase with a poly-



Fig. 9. *Booby Trap/Syphilis and Gonorrhoea*. Poster from 1940. University of Minnesota Libraries, Social Welfare History Archives., umedia.lib.umn.edu/item/p16022coll223:204 Accessed 1 December 2023.

merase chain reaction (PCR) on material from tissues and secretions. Current diagnostics are generally based on algorithms with non-Treponema and Treponema-specific tests, used in combinations in screening and treatment follow-up (37).

Arsenic and fever therapy

Treatment of syphilis received a boost in 1910 in the form of *arsphenamine* (also known as *compound 606* or *Salvarsan*), which was an injectable organic arsenic-containing drug, that was less toxic than mercury (40), popularly called the "magic bullet" (22). The final testing of the compound before clinical use was performed at the laboratory of the Nobel Prize-winning immunologist Paul Ehrlich, who also developed the compound further to Neosalvarsan, which was later the predominant drug used in patients. Treatment, however, had many drawbacks, with a complex administration requiring many injections over a long period of time, and with toxic side-effects (22). These two drugs were, for a long time, the most-sold pharmaceuticals worldwide.

Based on early observations that various febrile diseases could suppress psychotic symptoms in patients with neurosyphilis, the Austrian psychiatrist Julius Wagner-Jauregg introduced therapy with an injection of malaria parasites as fever inducers. This discovery was rewarded with the Nobel Prize in 1927 (41). The method was introduced in Swedish hospitals in the 1920s and was used in isolated patients with central nervous system involvement as late as the 1940s. Mortality was, however, high (approximately 10%) and the treatment was quickly abandoned when penicillin became available in the late 1940s.

The groundbreaking discovery of penicillin, the multitude of measures taken to develop its production, and its subsequent use in infectious diseases are well described elsewhere, e.g. (41).

INFAMOUS 20TH CENTURY CLINICAL STUDIES OF SYPHILIS; BACKGROUND, MOTIVES AND CONSEQUENCES

The severe impact of syphilis on societies and the panic-like and thoughtless measures that the authorities felt they were forced to take are exemplified by two infamous clinical studies initiated in the USA after the First and Second World Wars, respectively.

One of those, "The Tuskegee Study of Untreated Syphilis" focuses on the impact of syphilis in high-risk civilian populations, and the other study, "The Guatemala Experiments", focuses on the spread of syphilis in armies and the possibilities of prevention. Both studies were conducted in a highly ethical and morally dubious manner and have since been heavily criticized. The trespassing of ethical borders was ingrained in the studies. Their realization reflects the severity of syphilis as a

social medicine and community medicine problem at the time, and the perceived need to find appropriate measures against its consequences. It is relevant to describe these studies in some detail in this review.

Black communities in the rural Southern United States

In the USA the first half of the 20th century was a period of widespread poverty and social restructuring in the rural South, with local economies in a chaotic state. The abolition of slavery had been an economic blow to the cotton and tobacco farming of the South. At the same time, almost 4 million new free inhabitants needed schooling, employment, and various activities to be fully incorporated into the community. Underlying racism counteracted the incorporation of Black communities in social life, and Black and White people largely lived parallel lives in parallel communities, doing different jobs in society. The time was characterized by segregation and violence linked to that segregation, primitive housing, poor labour conditions, and a maintained social stratification. The healthcare system was also divided; Black people had limited access to the healthcare system of the Whites (42). A separate African American healthcare system developed, with Black healthcare personnel trained in medical schools with Black students and teachers. Black doctors had been excluded from the American Medical Association (AMA), which is why they formed a separate organization, the National Medical Association (NMA).

There was a dramatic increase in the spread of syphilis during the first half of the 20th century. In 1929, 100,000 deaths among adults 25–64 years old in the USA were attributable to syphilis, mainly in the South. The disease was 3–4 times more common in Black people than in Whites. Also, syphilis was the cause of one-third of perinatal deaths (43). At that time syphilis was as important a topic for public health as smoking, cancer, and cardiovascular diseases are today. It caused sincere concern among the medical and public health communities and hindered recruiting industries from investing and thriving in the South (44). In the poorest areas, approximately 30% of the population was seropositive for syphilis. To a limited extent, mercury or arsenic was used for treatment, with doubtful effect, but was nevertheless thought to reduce its contagiousity and spread.

Tuskegee Study of Untreated Syphilis

The prevailing situation demanded more knowledge of the epidemiology, the longitudinal course, and whether it was possible to administer a treatment programme for syphilis in the African American community. A pioneering study was initiated by the Chicago-based philanthropic Julius Rosenwald Foundation in collaboration with the US Public Health Service (USPHS) in 1929 (44); this was the first prospective study of syphilis morbidity in Black US citizens.

The study had 4 objectives: to determine the incidence of syphilis amongst an unselected group of rural Black people; to determine the feasibility of providing field treatment for infected cases; to investigate the effect of syphilis on Black people; and to study the results of treatment (45). Macon County, Alabama, was chosen for the study. It had a large rural Black population (82%) and a well-organized county health department; the Tuskegee Institute, run by the Black community which cooperated in the study. The study began in March 1930 and was run by a Black physician and a Black nurse under the County Health Officer (45). Of 3,606 African Americans tested, 36% were seropositive for syphilis, but only 30 (3%) had had treatment. The study concluded that an actively organized "field service" approach was feasible for mass treatment (45).

The Julius Rosenwald Foundation ended its involvement in 1932 as it did not receive support to strengthen the required infrastructure; see discussion in (45). Instead, the federal government took over the funding and continued a purely observational study based on the recently acquired knowledge. At that time, there was considerable insecurity about who would benefit from the fallible treatment available and what long-term benefits could be expected. This insecurity and lack of knowledge on the meaningfulness of treatment is well portrayed in reference (46).

After screening 1,782 African Americans, 600 men were enrolled in the "The Tuskegee Study of Untreated Syphilis" that started in 1929, 399 with latent syphilis who had passed the infectious stage and 201 seronegative controls (**Fig. 10**). The subjects were not informed that they had syphilis, but that they had "bad blood". The incentives included free medical care, lunches, transportation, and burial stipends. The study was initially intended to be a

6–8-month observational study. However, it was later extended to the time of death and continued between 1932 and 1972, with final closure in 2004 when the last patient died, the 96-year-old control person Ernest Hendon.

Ultimately, 14 peer-reviewed publications were derived from the study (46). Two of those were in journals published by the American Medical Association after 1946, (i.e. references (47, 48)) when the association had adopted far-reaching Principles of Ethics Concerning Experimentation With Human Beings (49), which included provisions for the consent of the human subject, scientific rationale, and scientifically competent investigators. The two articles passed through the peer-review process at the time.

A little more than 10 years after the Tuskegee Study was initiated, penicillin became available worldwide. The first syphilitic patient was treated with penicillin in 1943, and within 12 months, 10,000 patients had been treated. Such treatment was routine in American soldiers from mid-1944. After the publication of three studies in JAMA in January 1947 (50–52), penicillin was considered routine treatment for new cases of syphilis.

Treatment with penicillin was withheld from participants in the Tuskegee Study, as it was argued that introducing treatment or closing the study early would undermine interpretation of its findings. Instead, the study continued for another 25 years, with only a small minority of patients given any curative treatment.

Scandal

When interim partial results of the Tuskegee Study were published after 30 years in a world-leading journal in 1964 (47), no-one reacted, except for a young US intern in internal medicine with 4 years of clinical work after



Fig. 10. Photograph of participants in the Tuskegee Syphilis Study. Records of the Centers for Disease Control and Prevention Series. National Archives Catalog.

his studies, Dr Irwin Schatz. In protest, he wrote to the authors:

"I am utterly amazed that doctors allow patients with a potentially fatal disease to remain untreated when effective therapy is available. I suppose you feel that what can be learned from this untreated group is worth sacrificing them..." [abbreviated].

His letter was filed without reaction and was discovered during a *Wall Street Journal* search of the archives 8 years later when the study had gained public attention (53).

Instead, the death blow to the study was the consequence of whistle-blower activity, which came from a social worker and epidemiologist in San Francisco, 1,600 km west. Peter Buxton, 27 years old, had been hired by the Public Health Service (PHS) to interview patients with sexually transmitted diseases. He heard about the study at his workplace in November 1966, and the information shocked him. He filed an official protest on ethical grounds to the USPHS Division of Venereal Diseases, which was rejected. He filed a second protest in November 1968, arguing that conducting this type of study could be interpreted politically. Again, his concerns were deemed irrelevant.

Four years later, in 1972, Buxton leaked information about the study to a journalist and friend at the Associated Press, where it was handed over to a young journalist colleague, Jean Heller. Heller's story exposing the study was first published in the *Washington Star* on 25 July 1972, became front-page news in *The New York Times* the day after (Fig. 11), and was the start of a public outcry. Senator Edward Kennedy called to Congress hearings, after which the study was terminated (53).

At the time the study was terminated, only 74 of the 600 subjects were still alive; 28 had died of syphilis, 100 of syphilis-related complications, 40 of their wives had been infected, and 19 of their children had been born with congenital syphilis (42).

Aftermath

The Tuskegee Study is a symbol of racism and major contravention of basic human rights in research. It has also, together with an innumerable number of abuses of Black people from antebellum times, been part of an ingrained narrative related to the vulnerability of the Black community in the US. Within African Americans, there is a collective memory of being exploited by the medical establishment. The Tuskegee Syphilis Study confirmed these long-held and deeply rooted beliefs (42, 54).

A thorough historiographic analysis based on contemporary literature has given a good view of the prevailing scientific thought regarding race and heredity in the early 20th century, which must be considered in order to understand the Tuskegee Syphilis Study (55). In the shade of rising social Darwinism,

the prevailing turn-of-the-century idea was that the newly liberated, but still "inferior", African American population would become extinct in the 20th century due to crime, vice, and disease, particularly venereal disease (55). The medical profession shared these contemporary analyses by anthropologists, ethnologists, and biologists. The profession also discounted the socioeconomic explanations for the misery of African Americans. It did not consider that better medical care would alter the evolutionary outcome of the extinction of African Americans (55). The USPHS officers who initiated and continued the Tuskegee Syphilis Study accepted these mainstream assumptions about African Americans and syphilis. The ethical conclusion was, among others, that the USPHS regarded the men in the study as less than human and considered the study a "study of nature" as the men would not be treated anyway. They also thought that, since only a promise of being treated would maintain the men's interest in the study, they participated under the guise of treatment. To accomplish this, the USPHS deceived the men into believing they were receiving treatment. The alternative, of leaving a communicable disease untreated, would risk the entire health of the community. This gave legitimacy to lie to the men.

There were both reason and outrage when the study was made public and discussed in a societal context. The different perspectives are well analysed in references (46) and (56). In general, a more reasoning and intellectual approach dominated, with an attempt to understand the

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER

The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they

IF YOU'RE NOT DRINKING WILLIAM LAWSON'S SCOTCH, DRINK DEWAR'S William Lawson's 86.8 Proof Blended Scotch Whiskies. Imported by Palmer & Lord, Ltd., Syosset, N.Y.—Advt.

have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men.

Continued on Page 8, Column 1

Fig. 11. Article in the *New York Times* revealing the Tuskegee Study, 26 July 1972.

prevailing social context 40 years earlier when the study was designed. A reasoning approach also characterized an editorial in *The Lancet Infectious Diseases* (57), which concluded that uncritically considering the Tuskegee Study as unethical requires an element of "presentism", i.e. judging past actions by today's standards. The editorial commented that the study would have been considered ethical by a hypothetical Institutional Review Board in the 1930s, but not so in the early 1950s when treatment of syphilis with penicillin was widespread. The editorial concluded "Thus, by its 20th anniversary, the Tuskegee Study had become unethical by the standards of the time; patients should have been informed of their diagnosis and given the option of treatment" (57).

Some, however, reacted with fully entitled outrage at the prevailing substandard conditions for the Black community at the time, which was resurrected following emotionally coloured descriptions of the study in the public media. To give an example, Paul & Brooks (56) argued that those who defended the studies relied on an impoverished view of ethics and have "become whitewashers for studies that caused real harms".

In this context, it must be pointed out that leaving both Black and White patients with late latent syphilis untreated was an accepted action at the time (46). The researchers at Stanford University School of Medicine, one of the most respected syphilis departments in the USA, also felt that late latent syphilis was overtreated and that there was no evidence of the efficacy of antisypilitic therapy in late-latent syphilis. Consequently, it was the policy of the Stanford Clinic to withhold treatment for patients with late-latent syphilis. The underlying data were presented as late as 1947 (58).

The Guatemala experiment: actively infecting with syphilis

The First and Second World Wars accentuated the public health problem caused by syphilis, which had always been a major issue for the military. Since the introduction of syphilis in Europe the disease has been common among standing troops and has incapacitated many soldiers. During the Second World War, preventing syphilis and other sexually transmitted diseases was "one of the most pressing problems of military medicine" (59).

An article in *The New York Times* in September 1947 commented on the progress in preventing syphilis using the newly available penicillin and suggested that further progress could be expected in studies where syphilis bacteria were "shot into human bodies". However, such studies would be "ethically impossible" to undertake (60). At that time, however, such studies were already underway in Guatemala under the auspice of the USPHS and after recommendations from the National Institute of Health. Details of those studies have been extensively described elsewhere (59, 61, 62); an overview is presented here.

As earlier studies on US inmates had shown that artificial techniques of inducing venereal diseases were unreliable and could not provide the basis for recommending prophylactic strategies, a study using "normal exposure", i.e. by sexual intercourse, was recommended. Guatemala was seen as the perfect place for this type of study. At that time, it was an underdeveloped country under strong influence from the USA. The study was conducted in Guatemala City Prison, where commercial sex work was legal. Both sex contacts and prisoners were tested, and the outcome was assessed after sex with contagious sex workers. The studies were conducted in 1946 to 1948, with approximately 5,500 persons from Guatemala included (63). A total of 1,300 subjects were intentionally infected, 700 of whom received some treatment. They were not informed about the true aims of the study and to what they were exposed. The study results were never published.

This hidden study was discovered in 2003 by the historian Susan Reverby while searching for documents from the Tuskegee Study. She presented the discovery at a conference in 2010 (63). The discovered documents showed that the study management had done everything to keep the study secret because they knew it was ethically questionable (63). President Barack Obama and Secretary of State Hillary Clinton in 2010 publicly apologized to the people of Guatemala (61).

IMPACT ON ETHICS LEGISLATION AND SOCIETY

The Congress hearings called for by Senator Edward Kennedy in 1973 were the start of a legal and bioethics process. A "National Research Act" was signed in 1974, and the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research" was the first public national body to shape a bioethics policy in the USA. The guidelines produced by this body in 1978 are a guide for protecting research subjects in biomedical and behavioural research and are known as the "Belmont Report" (64). The Belmont Report analysed 4 issues: boundaries between practice and research; respect for persons; beneficence; and justice. It ended with 4 principles: (i) Respect for the individual and protection of their autonomy and worth; (ii) Researchers must be truthful and without intent to deceive; (iii) Goodness with the guiding star "Not harm"; (iv) Fairness meaning reasonable and fair benefits for the subjects. The boundaries between practice and research can be described as "all you do for your current patient is care, and all you do to improve care for forthcoming patients is research". This very straightforward perspective emphasizes that there is no absolute dichotomy between care and research, i.e. that there is no absolute "either this or that", but rather "both this and that": "... research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy."

The Belmont Report has influenced most national and international research ethics regulations, given the USA's dominant position as a research nation. At the same time, it must be pointed out that there are great similarities in the ethics perspectives of the Belmont Report and previous documents. There was, thus, a quite modern text from 1931 in the Weimar Republic (65, 66), which did not survive the Nazis era. There was the previously mentioned Principles of Medical Ethics of the American Medical Association from 1946 (49), the Nuremberg Code (67), and finally, the Declaration of Helsinki (68). The Tuskegee Study went public in the aftermath of the Second World War when the autocracies of Germany and Japan had monopolized the moral degradation of human values. The Tuskegee Study was a wake-up call.

Whistle-blowing researchers noticed the Guatemala Studies long after the Belmont Report. A careful assessment of the results of an investigation required by President Obama (58) strengthens the perspective of moral trespassing, which was even more blatant than in the Tuskegee Study. While the main criticism of the Tuskegee Study is the absence of consent and withholding of penicillin in persons with syphilis, the Guatemala Experiment can be criticized for the absence of consent and for deliberately inflicting disease on healthy men.

CONCLUSION

For over 500 years, syphilis had been a scourge in Europe and much longer than that on the American continent, where depictions of typical symptoms of the disease have been found on even older clay artefacts and skeletal remains. After a brief period when contracting syphilis was considered to reflect a cultivated and urbane lifestyle, the main description of the disease in history books is that of guilt, shame, and divine punishment for an immoral life. Its importance is related to the long-term, even life-long, consequences with destructive effects on most organs and tissues and serious functional sequels. Due to its significant effect on societies and individuals, syphilis also made a strong impression on art and literature of the time. After almost 500 years of inadequate attempts to cure syphilis with mercury and, later, arsenic, the advent of penicillin almost eradicated the disease and its cultural impact.

In the early 20th century, syphilis had a major public impact in some societies, which gave rise to two infamous and ethically questioned clinical studies on exposed groups. These studies were later scandalized, and the first study became the impetus for the development of guidelines for protecting research subjects in biomedical and behavioural research, which have influenced clinical research globally, and the second was carried out secretly but discovered after several decades.

In analogy to tuberculosis, which has also scourged human societies, syphilis may spread "quietly" in the

body, hide from the immune system for a long time in small foci, and many years later give rise to a spectrum of symptoms from other organs, including the skin, not infrequently mimicking other disease states. As syphilis was common prior to the availability of penicillin, and had so many different clinical manifestations, it was a diagnostic challenge well covered by the epithet *The Great Imitator*, or as Sir William Osler once said: "*He who knows Syphilis knows Medicine*".

Before the causative agents were discovered in the early 20th century, diagnosis of both syphilis and tuberculosis was challenging. After that, precise diagnostic tests and more effective treatment were developed. The exceptionally good effect of penicillin treatment on spirochetes ended the syphilis pandemic. However fortunate, the absence of development of antibiotic resistance in syphilis, this is no guarantee for the future. Currently, syphilis among men-who-have-sex-with-men (MSM) is increasing, and, in developing nations, the disease causes several hundred thousand stillbirths and neonatal deaths every year (69). With the possibility of future antibiotic resistance, and in the absence of a vaccine against syphilis, there is a risk that the disease could once again become epidemic. An understanding of collected knowledge about syphilis is, therefore, invaluable.

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