

Revisiting the Great Imitator: The Origin and History of Syphilis

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Take a look at the passage below. It was written by one of the most famous British authors of the 20th century. Can you guess who the writer is and what disease is being described?

"Something about the man's way of talking struck me and I watched him narrowly. His lip had a trick of quivering, his words slurred themselves together, and so did his handwriting when he had occasion to draw up a small agreement. A closer inspection showed me that one of his pupils was ever so little larger than the other...I did not say anything, for I had not the heart, but I knew that the fellow was as much condemned to death as though he were lying in the cell at Newgate."

"Newgate was a prison in London, which remained in operation for more than 700 years, from 1188 to 1902, and served as one of the main sites for execution."

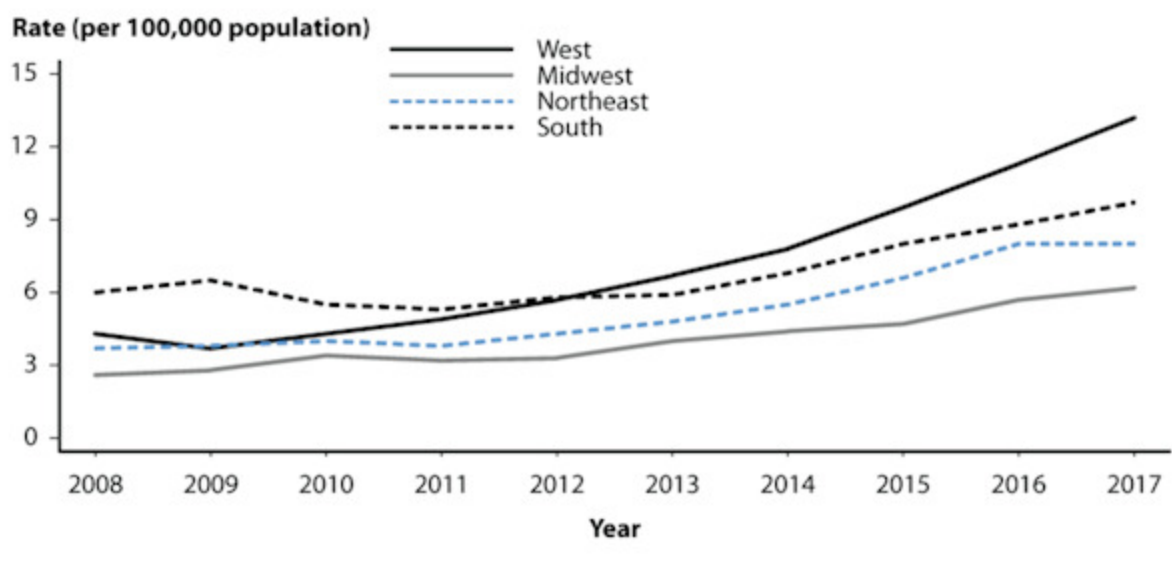
The author of the 1894 short story, "A Medical Document," from which this passage was lifted, is author-physician Arthur Conan Doyle. He is describing here the signs and symptoms of a disease later known as neurosyphilis. Doyle, the author of the Sherlock Holmes mysteries, wrote a [graduation thesis on tabes dorsalis](#), a late manifestation of neurosyphilis, while in medical school. He also wrote "[The Third Generation](#)," a story about a nobleman in London who is revealed to the reader, through description of [Hutchinson's teeth](#) and [interstitial keratitis](#) found during examination by a physician, to have suffered from congenital syphilis. In this story, we learn that the disease has been passed on to him by his father from his grandfather (at the time, the disease was thought to be transmitted paternally during conception). The nobleman is soon to be married, but upon confirmation from the physician that his offspring would be affected, he decides to end his life rather than marry or otherwise avoid the marriage (see [here](#) for a detailed analysis of the piece).

Syphilis and Literature

The association between syphilis and the world of literature is fascinating. [The name of the disease](#) originated from a poem called "Syphilis, Sive Morbus Gallicus" ("Syphilis, or the French Disease"), written by Italian physician-poet Girolamo Fracastoro in 1530. The poem tells the story of a [shepherd named Syphilus](#) who blamed and insulted the Sun-God for the drought that had led to the demise of his flocks and in return received the deific punishment of this horrific disease. During the first 100 years after the first reported syphilis outbreak in the Old World in 1495 (see below where the origin if syphilis is discussed), the disease was much more severe compared to modern venereal syphilis and the agony of the affliction inspired many authors and poets to write about their suffering. During the last few years of the 1400s, Italian poet Antonio Cammelli, while suffering from cutaneous manifestation of the disease, wrote a sonnet that [compares syphilitic lesions that cover his body to a dress](#) as he addresses a woman: "Lady, I am dressed as a French man,...seriously wounded over and under and front and aside/Within the whole flesh of my body,"

Over the next few centuries, the description of signs and symptoms of syphilis in the literature seems to reflect a seemingly attenuated form of the disease that resembles modern venereal syphilis. This includes Shakespeare's play "Troilus and Cressida," written in 1602, where in Act V Scene I, a character mentions a battery of [signs and symptoms presumably of secondary and tertiary syphilis](#) such as "raw eyes" (syphilitic episcleritis, iritis, or uveitis), "bone-ache" (syphilitic periostitis), and "limekilns in the palm" (palmar rash of secondary syphilis). These writings allow us to travel back in time to get a glimpse of how this disease has affected humanity over the past 500 years.

Despite our desperate attempts to fend off syphilis over the past few centuries, the disease keeps rearing its ugly head throughout the world. [Penicillin G](#), aka "[the Silver Bullet](#)," which [was and still is an effective treatment](#) for syphilis (especially for primary, secondary or early latent infections), was discovered about 30 years after the story above was written. The disease should be nothing to worry about by now in the U.S., where healthcare is generally more accessible compared to developing countries. However, for the past decade, the incidence of syphilis in high-income countries, including the U.S., [has been on the rise](#).



Primary and secondary syphilis rates in the United States by region, 2008-2017. (Click to view larger image.)

Source: CDC

The U.S. has experienced a steady increase in syphilis incidence since 2000. To add insult to injury, the Center for Disease Control and Prevention (CDC)'s effort to eliminate syphilis ended in December 2013 due to lack of funding that unfortunately coincided with [a sharp increase in disease incidence](#). In 2017, the rate of reported primary and secondary infections was 9.5 cases per 100,000 population, which is a 72.7% increase compared to the 2013 rate of 5.5 cases per 100,000 population. The increase in primary and secondary infections could be due multiple factors, including an [increase in pre-exposure prophylaxis \(PrEP\) usage](#) and the [effectiveness of antiretroviral therapy](#) among HIV-infected individuals, both of which could lead to increased condomless sex among men who have sex with men (MSM). Reported cases of congenital syphilis in the U.S. have also more than doubled, from 362 in 2013 to 918 in 2017, which is the highest number of cases in 20 years. Despite the recent increase in reported cases of congenital syphilis from all over the U.S., [many physicians today lack awareness of the disease](#), resulting in [missed opportunities to screen and treat](#) infected pregnant women. In light of CDC's [Call to Action to Stem the Tide of Rising Syphilis in the United States](#), This is the perfect time for laboratorians to review the history of the disease, its clinical presentation, and the role of clinical and public health laboratories in preventing syphilis from spreading further in our communities.

Humans have had a long and complicated battle with syphilis, a disease once supposedly described by Sir William Osler as the Great Imitator due to clinical presentations in its late stages simulating "[almost every disease known to man](#)." Before we travel back in time and learn about the origin of syphilis, I'd like to give you a quick review of other closely related human diseases caused by *Treponema* bacteria.



Dark field micrograph of *T. pallidum* from the Centers for Disease Control and Prevention.

Source: CDC

Human treponematoses encompass:

1. Syphilis: caused by *T. pallidum* spp. *pallidum*
2. Endemic treponematoses
 - a. Yaws: caused by *T. pallidum* spp. *pertenue*
 - b. Bejel (endemic syphilis): caused by *T. pallidum* spp. *endemicum*
 - c. Pinta: caused by *T. carateum*

For all human treponematoses, the initial infection usually occurs following an exposure of mucosal surfaces or traumatized skin to bodily fluids containing pathogenic treponemes. After initial invasion between the epithelia or mucosal membrane, the organisms multiply and disseminate hematogenously or via lymphatic systems. Endemicity or geographical distribution of these diseases are quite different. While syphilis is globally distributed, [endemic treponematoses are naturally usually observed in certain regions of the world](#). For example, yaws is endemic in equatorial regions. Although there is overlap in clinical manifestations, each human treponematoses has some distinguishing characteristics. Yaws is mainly a disease of the skin, joints, soft tissue, and bone, transmitted by skin-to-skin contact with no evidence of vertical transmission. Initial papillomatous lesions usually occur in the lower extremities and subsequently develop into ulcers. Late stage central nervous system (CNS) complications are rare, but if left untreated, severe destructive osteitis resulting in permanent deformity may occur. On the other hand, syphilis is sexually transmitted in general, with well-characterized vertical transmission, and when left untreated may result in late stage complications in many organ systems including the CNS.

Debates on the Origins of Syphilis

There is still debate over the origin of syphilis and how it spread to different parts of the world. The most well-supported hypothesis, the Columbian Hypothesis, states that Columbus' seamen, who first [arrived in the Americas in 1492](#), brought the disease back to Europe following exploration of the Americas. The timing of this event correlates with the first reported outbreaks among the French troops in Europe during [the War of Naples in 1495](#). Additionally, there is evidence suggesting that [syphilis was already present in the New World at the time of Columbus' arrival](#). In recent years, a combination of [genetic information](#) about pathogenic human treponemes and [palaeopathological evidence](#) observed through carbon dating and examination of bone pathology have shed some light on how syphilis came into existence and spread worldwide.

Despite the variation in epidemiology and clinical manifestations among human treponematoses, the etiologic agents of these diseases are not that different genomically, morphologically, and serologically. Their genomes are essentially the same sizes at approximately 1.14 Mbp. DNA-DNA hybridization experiments and subsequent whole-genome sequencing suggested that these organisms may have been [clonal in origin](#) with a common ancestor. [A study](#) integrating a worldwide map of palaeopathological evidence with evolutionary models based on genetic analysis of *Treponema* species from all over the world supported the Columbian Hypothesis by suggesting that *T. pallidum* first arose in the Old World as a non-venereal infection, which subsequently spread to the Middle East and Eastern Europe in the form of endemic syphilis, and then to the Americas in the form of New World yaws. A *T. pallidum* strain from the Americas likely underwent genetic mutations and was introduced back into the Old World, giving rise to the progenitor of a modern syphilis-causing *T. pallidum* strain. [A more recent study](#) using whole genome sequencing demonstrated that *T. pallidum* isolates collected from syphilis patients from 13 countries in Europe, the Americas, and Asia all shared a common ancestor that only existed after the 15th century, which would be in concordance with the Columbian Hypothesis.

As mentioned above, there was essentially no solid evidence of the existence of syphilis in the Old World prior to the 1500s. No unequivocal mention of syphilis has been found before then, not [even in ancient Chinese writings](#) where descriptions of many Old World diseases have been identified. The name "[the French Disease](#)" was a result of a blame-game initiated by the Italians. The disease spread throughout Europe like wildfire, resulting in devastating illnesses that have been described by a victim of the disease, German humanist [Joseph Grunpeck](#), as "so cruel, so distressing, so appalling that until now nothing more terrible or disgusting has ever been known on this earth." One of [the first artistic representations](#) of the disease was in woodcuts created by German artist Albrecht Dürer, where he depicted rather grisly chancres on the body of a soldier and suggested that syphilis was a consequence of blasphemy and sins. Syphilis affected individuals from the bottom to the top rung of society, including [priests, cardinals, and even a pope](#). In Europe, the presence of clinical signs of syphilis, including pustules, chancres, and bone destruction or malformation, became a [stigma](#) that was associated with being unclean and led to mistreatment of afflicted individuals that went on for centuries. Soon after the first reported outbreak in 1495, the disease spread into [Asian countries including India, China, and Japan](#). Interestingly, syphilis in its first century in the Old World seemed to progress [more rapidly and resulted in more severe morbidity and mortality](#) compared to the form of the disease that was documented from the 16th century onward. This less-severe, slowly progressing form of syphilis likely became what is now known as one of the most common venereal diseases worldwide.

The First Syphilis Treatments

During the 16th century the 2 most popular treatment regimens were potions made from [guaiacum](#) gum or mercury. The guaiacum potion proved to be ineffective, as opposed to mercury, which had already been used to treat other diseases and had shown some success in curing syphilis. Despite the illness and death caused by mercury poisoning, mercury administration [was used for more than 200 years](#) until the identification of *T. pallidum* as the etiologic agent of syphilis in 1906. This discovery allowed for screening and development of novel therapeutic agents. In 1910, Salvarsan, the first effective treatment for syphilis, was invented.



Salvarsan treatment kit for syphilis used in Germany, 1909-1912.

Source: Wellcome Collection

Salvarsan, or arsphenamine, is an arsenic derivative first synthesized in 1907, but it was not until 1910 that [Paul Ehrlich and his assistant Sahashiro Hata](#) discovered its anti-syphilitic effects. Although adverse effects were reported, [the drug was on the market within a year](#) after its discovery and was quickly adopted as a [mainstay for syphilis treatment](#) until penicillin G was introduced as a safer treatment option in the 1940s. A study in the U.S. called "Tuskegee Study of Untreated Syphilis in the Negro Male," which went on for 40 years despite a complete disregard for [human subject research ethics, violated the rights of its subjects](#) through the lack of informed consent and the decision to withhold treatment of infected subjects even after penicillin became available for treatment of syphilis. After the study, the government took several measures, including the enactment of the [National Research Act in 1974](#), to prevent another grievous error of allowing such unconscionable trials from being carried out.

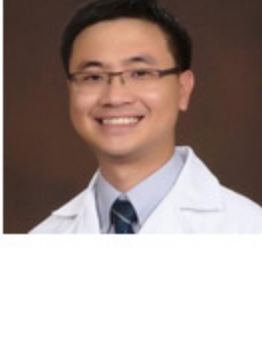
Read the next installment of this series: [A Brief History of Laboratory Diagnostics for Syphilis](#)

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CLINICIAN ARTICLE MEDICAL LAB PROFESSIONAL INFECTIOUS DISEASES DRUG RESISTANCE

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