

Syphilis - Its Early History and Treatment Until Penicillin, and the Debate on its Origins

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Introduction

“If I were asked which is the most destructive of all diseases I should unhesitatingly reply, it is that which for some years has been raging with impunity ... What contagion does thus invade the whole body, so much resist medical art, becomes inoculated so readily, and so cruelly tortures the patient ?” Desiderius Erasmus, 1520.¹

In 1495 an epidemic of a new and terrible disease broke out among the soldiers of Charles VIII of France when he invaded Naples in the first of the Italian Wars, and its subsequent impact on the peoples of Europe was devastating – this was syphilis, or *grande verole*, the “great pox”. Although it didn’t have the horrendous mortality of the bubonic plague, its symptoms were painful and repulsive – the appearance of genital sores, followed by foul abscesses and ulcers over the rest of the body and severe pains. The remedies were few and hardly efficacious, the mercury inunctions and suffumigations that people endured were painful and many patients died of mercury poisoning.

Sexually transmitted diseases (STD’s) have posed a threat to military service members throughout history. [2, 3] In the US Army during World War I they were the second most common reason for disability and absence from duty, being responsible for nearly 7 million lost person-days and the discharge of more than 10,000 men. Only the Spanish influenza epidemic of 1918-1919 accounted for more loss of duty during that war. During World War II between 1941 and 1945 the annual incidence of STD’s in the US Army was 43 per 1,000 strength. In the Vietnam War during the period 1963 to 1970 the overall average annual incidence of STD’s was 262 per 1,000 strength, compared with, at the time, 30 per 1,000 in continental US-based army personnel. In Vietnam 90% of STD cases were due to gonorrhoea and slightly over 1% were due to syphilis.³ The impact of gonorrhoea and syphilis on military personnel in terms of morbidity and mortality was greatly mitigated after 1943 due to the introduction of penicillin, as

well as other factors such as education, prophylaxis, training of health personnel and adequate and rapid access to treatment.

Up until the early 20th century it was believed that syphilis had been brought from America and the New World to the Old World by Christopher Columbus in 1493. In 1934 a new hypothesis was put forward, that syphilis had previously existed in the Old World before Columbus. In the 1980’s palaeopathological studies found possible evidence that supported this hypothesis and that syphilis was an old treponemal disease which in the late 15th century had suddenly evolved to become different and more virulent. Some recent studies however have indicated that this is not the case and it still may be a new epidemic venereal disease introduced by Columbus from America.

The first epidemic of the ‘Disease of Naples’ or the ‘French disease’ in Naples 1495

In August 1494, King Charles VIII of France led his army of 50,000 soldiers and a large artillery train into northern Italy. The soldiers were mostly mercenaries – Flemish, Gascon, Swiss, Italian, and Spanish – and were accompanied by 800 camp followers including cooks, medical attendants and prostitutes. Charles’ objective was to take over the Kingdom of Naples from Alphonso II so that he could use Naples as a base from which to launch a campaign to the Crusades. The soldiers of Alphonso II were mostly Spanish mercenaries. Charles’ army led by General Louis II de la Tremoille crushed all resistance from intervening Italian cities and in February 1495 took Naples. While occupying Naples the French soldiers indulged in a long bout of celebration and debauchery, and within a short space of time it came apparent that they were afflicted by a terrible disease.^{4,5}

The disease started with genital ulcers, then progressed to a fever, general rash and joint and muscle pains, then weeks or months later were followed by large, painful and foul-smelling abscesses and sores, or pocks, all over the body. Muscles and bones became painful, especially at night. The sores became ulcers that could eat into bones and destroy

the nose, lips and eyes. They often extended into the mouth and throat, and sometimes early death occurred. It appears from descriptions by scholars and from woodcut drawings at the time that the disease was much more severe than the syphilis of today, with a higher and more rapid mortality and was more easily spread, possibly because it was a new disease and the population had no immunity against it.^{5,6,7}

During the Battle of Forova at Emilia in Italy on Charles' retreat back to France, many soldiers were so ill they were unable to fight. On Charles' return to France the army disbanded and the soldiers and their camp followers took the disease with them back to their respective homelands. Voltaire wrote:

'On their flippant way through Italy, the French carelessly picked up Genoa, Naples and syphilis. Then they were thrown out and deprived of Naples and Genoa. But they did not lose everything - syphilis went with them.'

By the end of 1495 the epidemic had spread throughout France, Switzerland and Germany, and reached England and Scotland in 1497. In August 1495 the Holy Roman Emperor Maximilian I proclaimed that nothing like this disease had been seen before and that it was punishment from God for blasphemy. By 1500 syphilis had reached the Scandinavian countries, Britain, Hungary, Greece, Poland and Russia. It was a time of world exploration and Europeans took the disease to Calcutta in 1498, and by 1520 it had reached Africa, the near East, China, Japan and Oceania.⁵

Syphilis had a variety of names, usually people naming it after an enemy or a country they thought responsible for it. The French called it the 'Neapolitan disease', the 'disease of Naples' or the 'Spanish disease', and later *grande verole* or *grosse verole*, the 'great pox', the English and Italians called it the 'French disease', the 'Gallic disease', the 'morbus Gallicus', or the 'French pox', the Germans called it the 'French evil', the Scottish called it the 'grandgore', the Russians called it the 'Polish disease', the Polish and the Persians called it the 'Turkish disease', the Turkish called it the 'Christian disease', the Tahitians called it the 'British disease', in India it was called the 'Portuguese disease', in Japan it was called the 'Chinese pox', and there are some references to it being called the 'Persian fire'.^{5,8,9}

Early descriptions of the disease

In 1496 Sebastian Brandt, best known for his work *Der Narrenschiff*, 'The Ship of Fools', wrote a poem entitled *De pestilentiali Scorra sive mala de Franzos*

relating how the disease had spread all over Europe and how the doctors had no remedy for it.¹

Johannis (Giovanni) de Vigo, an Italian surgeon who was appointed as surgeon to Pope Julius II, wrote about the contagiousness of the disease, its origin from sexual intercourse with an infected person and its rapid dissemination throughout the body in *De Morbo Gallicus*, 1514, the fifth book of his work *Practica in arte chirurgica copiosa*. He accurately described the primary chancre, the secondary eruption of rash, ulcers and pustules, the terrible night bone pains and the late "tumours of scirrhus hardness". De Vigo expressed the view that this was a new disease.¹⁰

"The contagion which gives rise to it comes particularly from coitus: that is, sexual commerce of a healthy man with a sick woman or to the contrary. ... The first symptoms of this malady appear almost invariably upon the genital organs, that is, upon the penis or the vulva. They consist of small ulcerated pimples of a colour especially brownish and livid, sometimes black, sometimes slightly pale. These pimples are circumscribed by a ridge of callous like hardness... Then there appear a series of new ulcerations on the genitalia... Then the skin becomes covered with scabby pimples or with elevated papules resembling warts... A month and a half, about, after the appearance of the first symptoms, the patients are afflicted with pains sufficiently to draw from them cries of anguish... Still very much later (a year or even longer after the above complication) there appear certain tumours of scirrhus hardness, which provoke terrible suffering."¹⁰

Ulrich von Hutten, a German scholar who suffered from the 'great pox,' described its effects and its treatment with guaiacum, or holy wood, in his work *De Morbo Gallico* of 1519, dying from the disease himself four years later on the island of Ufenau on Lake Zurich. Von Hutten wrote of the terrible abscesses and sores, the nocturnal bone pains, *dolores osteocopi nocturne*, and the diseases of the internal organs, ulcers in the bladder and muscle disease.⁷

In 1527, Jacques de Bethencourt in his work *New Litany of Penitence*, introduced the term *Morbus veneris*, or 'venereal disease'. Bethencourt rejected the term *morbus gallicus*, and suggested that "since the disease arises from illicit love it should be called the malady of Venus or venereal disease". He also considered it was a new disease not known to the ancients and not appearing in Europe until the end of the 15th century.¹⁰

In 1530, Girolamo Fracastoro in his poem *Syphilis sive morbus gallicus* described in detail the symptoms

of syphilis and its treatment with guaiacum, the holy wood, a herb made from the bark of trees from the guaiacum family which was brought back from the Caribbean and South America in the New World, and the treatment with mercury. Fracastoro coined the term 'gumma' (L. 'gumma' meaning gum or resin), referring to the 'pus that escapes from the body and hardens into scabs like resin' that were the late scirrhous skin lesions.⁷

The origin of the term 'syphilis'

The name for the disease, 'syphilis', originates from an epic Latin poem *Syphilis, sive morbus gallicus*, 'Syphilis, or the French disease', published in 1530 by Girolamo Fracastoro (L. Hieronymus Fracastorius). Fracastoro was a poet, mathematician and physician from Verona in the Republic of Venice, who in his work *De contagione et contagiosis morbis* first described typhus and wrote on contagion, contagious particles that could multiply in the human body and be passed from person to person or through the mediation of fomes, and which were the cause of many epidemic diseases.^{4,11,12}

Fracastoro blended the writings of the historian Gonzalo Hernandez de Oviedo y Valdez with a fable *Metamorphoses* from the ancient Roman poet Ovid. In his poem *Syphilis, sive morbus gallicus*, Fracastoro tells of a mythical shepherd named Syphilus who kept the flocks of King Alcithous. When a drought affected Syphilus' people, he insulted the Sun-God by blaspheming against him and blaming the god for the drought, and as punishment the Sun-God struck Syphilus and his people down with a disgusting and odorous new disease.^{5,6,14,15}

Sir William Osler in his biographical essay *Fracastorius* from his 1909 work *An Alabama Student and Other Biographical Essays* wrote of Syphilus:

"He kept the flocks of King Alcithous, and one year the drought was so extreme that the cattle perished for want of water. So incensed was Syphilus that he blasphemed the Sun-God in good set terms and decided from henceforth to offer no sacrifices to him, but to worship King Alcithous. The shepherd won all the people to his way, and the king was overjoyed and proclaimed himself 'in Earth's low sphere to be the only and sufficient deity'. But the Sun-God, enraged, darted forth infection on air, earth, and streams, and Syphilus became the first victim of the new disease."¹⁴

Verses from the poem where Fracastoro refers to naming the disease after Syphilus are:

"A shepherd once (distrust not ancient fame)

Possest these downs, and Syphilus his name."

"He first wore Buboes dreadful to the sight.

First felt strange pains, and sleepless passed the night.

From him the malady received its name.

The neighbouring shepherds catch'd the spreading Flame"^{14,15}

When Desiderius Erasmus (1466-1536) used the term 'syphilis' in his essays, many other scholars followed suit⁶, see p. 193. Daniel Turner (1667-1741) was the first English medical author to use the term syphilis, as well as writing on the use of the 'condum' to prevent its transmission.¹⁶ However the name syphilis was not in general use to describe the disease until the early nineteenth century. Up until that time the disease was usually known as the French disease or French pox, the Spanish pox, or just simply, "the pox".^{6,7}

Syphilis in the 16th century and its social ramifications

Fifty to a hundred years after its appearance in Naples the disease became less virulent and less lethal. The disease had several distinct phases. The first began with genital sores, or "pocks", later called chancres. After these had healed and several weeks following, there appeared a generalised rash, often accompanied by fevers, aches and the night bone pains, *dolores osteocopi nocturne*, described by Von Hutton and De Vigo.^{7,8,10} As well, a rash of verrucous papules often broke out in the genital area. When these healed, a long latent period occurred, lasting months initially and as history passed, several years, in which there were few symptoms. The last phase consisted of the appearance of abscesses and ulcers, and the gumma referred to by Girolamo Fracastoro, often ending with severe debility, madness or death.⁷ It was this phase of the disease for which syphilis was greatly feared, because of the disfigurement it caused and the social ostracism that ensued. It was viewed by ordinary people as a sign of sin, for which they were shunned and punished.⁹

During the 1520's it became clear to historians and physicians of the time that the disease was contracted and spread by sexual intercourse. In Europe the authorities had become so concerned with the rise

in venereal diseases that they attempted to control prostitution and sexual encounters outside marriage. Henry VIII of England (reigned 1509 – 1547) tried to close down the 'stews', or brothels, and communal bathhouses of London. In many other places strict regulations were issued for brothels and bathhouses, forcing prostitutes who had disease or infections out of employment, and mixed bathing was prohibited.^{7,8}

16th and 17th century writers and physicians were divided on the moral aspects of syphilis. Some thought it was a divine punishment for sin, and as such only harsh treatments would cure it, or that people with syphilis shouldn't be treated at all. In 1673, Thomas Sydenham, a British physician, wrote an opposing view that the moral aspect of syphilis was not the province of the physician, who should treat all people without judgement.⁹

Syphilis and medicine in the 18th and 19th centuries

During the 18th century medical thinking on the disease began to advance. In 1736 Jean Astruc, a French royal physician and professor of medicine at Montpellier and Paris, wrote one of the first great medical works on syphilis and venereal disease, *De Morbus Veneris*. In 1761 the Italian anatomist and pathologist Giovanni Battista Morgagni published *De Sedibus et Causis Morborum per Anatomen Indagatis* in which he wrote that the symptoms of syphilis and gonorrhoea arose from separate conditions.⁹

Up until the 19th century, there was still much confusion as to whether syphilis and gonorrhoea were manifestations of the same disease. In 1838 Philippe Ricord, a physician and surgeon who worked under Guillaume Dupuytren, a French anatomist and military surgeon, firmly established that syphilis and gonorrhoea were separate diseases and differentiated the three stages of syphilis, and the primary lesion of syphilis was given the name of Ricord's chancre.⁴ In 1861 Jonathan Hutchinson, surgeon to the London Hospital, described the features of congenital syphilis.¹¹ In 1893 Jean-Alfred Fournier, a French dermatologist who worked as an understudy to Ricord, published a work on the treatment of the disease but cautioned there was no cure. He described the association of late stage syphilis with a wasting and paralysis disorder known as *tabes dorsalis*.⁴ In 1913 Joseph Waldron Moore and Hideyo Noguchi isolated the syphilis spirochaete *Spirochaeta pallida*, which had previously been discovered in 1905 by Fritz Schaudinn, from the brains of people who had died from a condition called "general paralysis of the insane", establishing syphilis as the cause of this condition.¹²

Sir William Osler (1849-1919), a founder of the John Hopkins School of Medicine and pioneer of modern medical and clinical education and later Regius Professor of Medicine at Oxford, described the history of the sudden appearance of this new and terrible disease in 16th century Europe :

"A mysterious epidemic, hitherto unknown, which struck terror into all hearts by the rapidity of its spread, the ravages it made, and the apparent helplessness of the physicians to cure it."¹³

By the early 18th century syphilis had ceased to be a virulent epidemic disease and became more of the episodic disease it is today. From about the middle of the 19th century to the middle of the 20th century the incidence of syphilis in developed countries declined, except in times of war. During each of the World Wars, the Korean war and the Vietnam War, the incidence of syphilis, and STD's in general, rose sharply but only briefly. After 1943 and with the advent of penicillin and institution of public health measures, its incidence declined again, although in past decades it has slowly increased.⁹

The early treatments of syphilis

In the early 16th century, the main treatments for syphilis were guaiacum, or holy wood, and mercury skin inunctions or ointments, and treatment was by and large the province of barber and wound surgeons. Sweat baths were also used as it was thought induced salivation and sweating eliminated the syphilitic poisons.

In his 1530 poem *Syphilis, sive morbus gallicus*, Fracastoro described the use of guaiacum:

".. in external use for dressing ulcers, abscesses and pustules. For internal use drink the first potion by the beaker twice a day: in the morning at sunrise and by the light of the evening star. The treatment lasts until the moon completes its orbit and after the space of a month conjoins again with the sun. The patient must remain in a room protected from wind and cold, so that frost and smoke do not diminish the effect of the remedy."⁷

Guaiacum was not effective as a cure and the alternative was mercury. Mercury had been used as a treatment for epidemic diseases since Guy de Chauliac, (personal physician to the Pope in Avignon), advocated its use in his work *La Grande Chirurgie* in 1363, and this became the accepted treatment for syphilis.⁷

Paracelsus (1493-1541) derided the use of guaiacum as useless and expensive and instead promoted mercury, metals being one of Paracelsus' favoured medicinal treatments for disease. After a time however he did recognise its toxicity when administered as an elixir and resorted to using it either as an inunction, an ointment made from metallic mercury and rubbed into the skin, or as a suffumigation, the inhalation of and bathing of the body in fumes, or indeed both at the same time. Many physicians doubted the efficacy of mercury, especially as it had terrible side effects and many patients died of mercury poisoning. Beck (1997) describes a typical mercury treatment :

"A patient undergoing the treatment was secluded in a hot, stuffy room, and rubbed vigorously with the mercury ointment several times a day. The massaging was done near a hot fire, which the sufferer was then left next to in order to sweat. This process went on for a week to a month or more, and would later be repeated if the disease persisted. Other toxic substances, such as vitriol and arsenic, were also employed, but their curative effects were equally in doubt."⁹

Mercury had terrible side effects causing neuropathies, kidney failure, and severe mouth ulcers and loss of teeth, and many patients died of mercurial poisoning rather than from the disease itself. Treatment would typically go on for years and gave rise to the saying,

"A night with Venus, and a lifetime with mercury"⁸

Gerhard van Swieten (1700-1772), an Austrian army surgeon, introduced the internal use of corrosive sublimate, mercuric chloride, or liquor Swietenii, which stayed in use as treatment for syphilis for many years, and Guido Bacelli in 1894 developed it as an injection.¹¹ In the late 19th century, calomel, mercurous chloride, a purgative and laxative, was used as an inunction and in tablet form and later as an injection. Ammoniated and salicylated mercury ointments were developed and the pharmaceutical formulae for unguentum hydrargyri ammoniate and unguentum hydrargyri salicilate were still in the Australian Pharmaceutical Formulary in 1955. Mercury stayed in favour as treatment for syphilis until 1910 when Ehrlich discovered the anti-syphilitic effects of arsenic and developed Salvarsan, popularly called the "magic bullet".^{11,12}

New discoveries of the syphilis organism and its treatment

When it was realised by physicians that the toxic effects of mercury often outweighed any benefits it might have had, they looked for alternatives. The Polish surgeon-general Friedrich Zittman (1671-1757) mixed a drug consisting of the root of sarsaparilla with traces of mercury and called his elixir Decoctum Zittmani. The English surgeon William Wallace (1791-1837) introduced iodine therapy, potassium iodide with small doses of mercury. In the late 19th century various other metals such as tellurium, vanadium, platinum and gold were tried but were not effective.⁷

In 1905, Fritz Richard Schaudinn, a German zoologist, and Erich Hoffmann, a dermatologist, discovered *Spirochaeta pallida* (the bacteria was spiral shaped and white under dark ground illumination, now called *Treponema pallidum*) to be the causative organism of syphilis. In 1906, August Paul von Wassermann, a German bacteriologist and an assistant of Robert Koch, developed a complement fixation serum antibody test for syphilis – the "Wasserman reaction".^{7,11,12}

In 1906 Paul Ehrlich, a German histological chemist at the Robert Koch Institute who later in his life founded the sciences of chemotherapy and immunology, read of Fritz Schaudinn's discovery. He had been experimenting for some years with the use of arsenic compounds in treating trypanosomiasis. Ehrlich then began experimenting with arsenic compounds in treating syphilis in rabbits. His experiments were not very successful as most of the earlier arsenicals he experimented with were too toxic, but in 1909 he and his assistant Sahachiro Hata, a Japanese bacteriologist, finally found success with the compound dioxy-diamino-arsenobenzol-dihydrochloride which they called drug "606". This led in 1910 to the manufacture of arsphenamine, which subsequently became known as Salvarsan, or the "magic bullet", and later in 1912, neoarsphenamine, Neo-salvarsan, or drug "914". In 1908 Ehrlich was awarded the Nobel Prize for his discovery.^{7,11,12}

Albert Ludwig Neisser, a German physician specialising in dermatology and venereology and who had been using some of Ehrlich's earlier arsenicals to treat syphilis, described Ehrlich's new drug :

“Arsenobenzol, designated “606,” whatever the future may bring to justify the present enthusiasm, is now actually a more or less incredible advance in the treatment of syphilis and in many ways is superior to the old mercury - as valuable as this will continue to be - because of its eminently powerful and eminently rapid spirochaeticidal property.”¹⁷

LW Harrison, a medical officer in the Royal Army Medical Corps during World War I, described the effectiveness of Salvarsan and Neosalvarsan on soldiers who contracted syphilis during the war.¹⁸ Arsenic however, while being able to cure syphilis whereas mercury wasn't, had many drawbacks - administration of treatment was complex requiring many injections over a long period of time, and it also produced toxic side effects. In 1916, A. Robert and Benjamin Sauton discovered the trypanocidal properties of bismuth, and in 1921, Robert Sazerac, Constantin Levaditi and Louis Fournier successfully treated syphilis with bismuth.¹⁹ It then became apparent that for arsenic to be effective, it had to be combined with small doses of either bismuth or mercury. Arsenic, mainly arsphenamine, neoarsphenamine, acetarsone and mapharside, in combination with bismuth or mercury, then became the mainstay of treatment for syphilis until the advent of penicillin in 1943.^{20,21}

In 1917 Julius Wagner-Jauregg, an Austrian physician, introduced the treatment of neurosyphilis with fever therapy by infecting the patient with malaria, then treating the malaria with quinine. The observation had been made that after a febrile illness the symptoms of neurosyphilis diminished, and the rationale was that it was easier to treat malaria with quinine than the syphilis with mercury or arsenic. Fred A. Kisligh and Walter M. Simpson, two American physicians, introduced in 1936 the treatment of electropyraxia, using a short-wave apparatus to induce pyrexia in a patient to treat syphilis and gonorrhoea.^{7,20}

In 1943 penicillin was introduced as a treatment for syphilis by John Mahoney, Richard Arnold and AD Harris.²² Mahoney and his colleagues at the US Marine Hospital, Staten Island, treated four patients with primary syphilis chancres with intramuscular injections of penicillin four-hourly for eight days for a total of 1,200,000 units by which time the syphilis had been cured. This became a turning point in the treatment for syphilis as penicillin was shown to be highly effective when administered during either its primary or secondary stages, and it had few side effects of any significance when compared

to mercury or arsenic. Arnold wrote in 1986 of his early work with penicillin and syphilis:

“Syphilis was once a dreaded and dreadful disease involving millions of US citizens. Before the introduction of penicillin, the heavy-metal cure often caused thousands of deaths each year. The morbidity and mortality of the disease itself was horrendous, involving all ages from the fetus to the elderly.”²³

Was syphilis introduced from the New World into the Old World by Christopher Columbus in 1493 ?

Over the past five centuries, and particularly in the last century, the origins of syphilis have caused great controversy amongst historians, physicians, anthropologists and palaeontologists. Up until the early 20th century the most popular theory on the origin of syphilis was that it was a new disease, contracted by Columbus' men in the New World and introduced to the Old World after their return to Spain on 15th March of 1493. An alternative theory was put forward in 1934 by Richmond Cranston Holcomb that syphilis had already existed in the Old World before Columbus' time, and in the latter part of last century palaeopathologists found possible evidence that this may have been so. A recent analysis of the evidence however by Kristin N. Harper, George J. Armelagos and other US anthropologists in 2011 has swung back to the “Columbian hypothesis” of the origin of syphilis.²⁴

There have been three main hypotheses on the origin of syphilis - the Columbian hypothesis that Columbus brought syphilis from the New World, the pre-Columbian theory that syphilis had already existed in the Old World and had evolved into a more virulent form around the time of Columbus, and the Unitarian theory that all treponematoses are a single disease with syphilis being an environmentally determined variant where social and environmental conditions in the late 15th century favoured its transmission by sexual intercourse.²⁴

Because the Naples syphilis epidemic appeared two years after Columbus returned in 1493 from Hispaniola, the belief that Columbus' crew had contacted the disease in the New World arose in the scholarly and medical literature by the early 16th century.²⁴ When Charles VIII invaded and seized Naples in 1495, Naples was populated by Spanish immigrants and was defended largely by Spanish mercenaries who had probably already contracted the disease in Spain and who then passed the disease onto Charles' soldiers and followers when they invaded Naples.^{7,11,15,25} Schreiber and Mathys (1987) describe that the disease had first appeared

in Barcelona in 1493 and had spread throughout Spain that year.⁷

Castiglioni (1946)²⁶, Wills (1996) [6] and Harper et al (2011)²⁴ state that the Columbian hypothesis is supported by descriptions by several 15th and 16th century scholars such as Fernandez de Oviedo y Valdes in 1526, Bartolome de las Casas in 1530, Ruy Diaz de Isla in 1539, the latter a Barcelona physician who claimed to have treated Columbus' men for the disease, and Gabriele Fallopius (1523-1562), all of whom stated that Columbus' crew had a new disease and that a similar disease had been present on the island of Hispaniola for many centuries before Columbus.

The Columbian hypothesis that syphilis was brought to Europe from America in 1492 was reaffirmed in the 1950s and 1960s by a number of historians and physicians such as Harrison (1959), Dennie (1962), Goff (1967), and Crosby (1969).²⁷ Crosby (1969) and Harrison (1959) state that the two most important historians of the time, Fernandez de Oviedo y Valdes and Bartolome de las Casas, were eyewitness to conditions in Hispaniola when Columbus was there and both considered that Columbus brought the disease back from the New World to Europe.^{28,29} Crosby states that both Ulrich von Hutton and Ruy Diaz de Isla identified 1493 as the year the disease first appeared in Europe. Crosby quotes Ulrich von Hutton as saying, "In the yere of Chryst 1493 or there aboute this most foule and most grievous disease beganne to sprede amonge the people." Crosby's view was that treponematoses was originally a single disease which evolved into several related but distinct diseases and that venereal syphilis is the variant that developed in America, from which it probably was introduced to Europe with the return of Columbus.²⁸

A third important scholar of the time who believed in the Columbian origin of syphilis was Ruiz Diaz de Isla, a Barcelona physician, who published in a book in 1539 that Columbus' men contracted the disease in Hispaniola in 1492 and that he had observed its rapid spread through Barcelona after Columbus' return. De Isla wrote that he had treated the men for the disease but hadn't realised it was the same disease that had been ravaging Europe until many years later. He called it *Morbo serpentine*, 'the hideous, dangerous, terrible disease'.²⁸

The pre-Columbian theory arose in the early 20th century. Garrison¹¹ refers to a 1912 publication by Karl Sudhoff, a German medical historian from the University of Leipzig, who stated that the Naples epidemic was typhoid or paratyphoid fever. That syphilis was present in Europe before Columbus'

return from Hispaniola was supported by the facts that many literary works and religious edicts referred to syphilis before the Naples siege of 1495, and also that mercury treatment had been used since the 12th century for a diversity of infectious disorders that were probably syphilis. Garrison himself says "That sporadic syphilis existed in antiquity and even in prehistoric times is quite within the range of probability."¹¹

An editorial article in JAMA in 1935²⁵ cited Capper (1926) as stating that many historical descriptions of leprosy were in fact syphilis, and that syphilis among the Romans was described by Celsus, Aretaeus and Aetius. The article also cited Butler (1933) as stating that historical evidence of aortic aneurysm being treated by Antyllus, a contemporary of Galen in Roman times, was evidence of the existence at that time of syphilis, and that Celsus accurately described a genital syphilitic chancre. Richard Holcomb's argument in 1935 that syphilis was of pre-Columbian origin was based on a description by Michael Angelus Blondus, a 16th century Italian surgeon, who identified it with a disease described by Aurelius Cornelius Celsus, a 2nd century Greek philosopher, and Paul of Aegina, a 7th century Greek physician.²⁵ In 1974, two anthropologists, John Loddell and Douglas Owsley, stated "syphilis can probably not be "blamed", as it often is, on any geographical area or specific race. The evidence suggests that the disease existed in both hemispheres of the world from prehistoric times. It is probably only coincidental with the Columbus expeditions that the syphilis previously thought of as "lepra" in Europe flared into virulence at the end of the fifteenth century."³⁰

Several medical historians over the last century have postulated other reasons for syphilis being a pre-Columbian Old World disease – a greater lay and medical recognition of syphilis developed in recent eras, and that syphilis had evolved from other treponemal diseases into a more virulent form due to a combination of social, cultural and environmental changes around the time of Columbus. In the last several decades development of palaeopathology has enabled close evaluation of Old World skeletons and many studies have published their findings of evidence for syphilitic bone disease.^{24,27}

The Unitarian hypothesis, proposed by EH Hudson in 1928¹⁰, that treponematoses are environmentally determined expressions of the same disease of which syphilis is one variant, with syphilis being hindered from skin to skin transmission because of development of hygiene and changing to become a sexually transmitted disease, has been refuted by genetic studies which show the different treponem

subspecies are genetically distinct and evolved along different paths.²⁴

Critics of recent palaeopathological studies have pointed out the difficulties in distinguishing syphilis from other diseases that had similar symptoms and left similar bone scars such as leprosy, osteomyelitis, hypertrophic osteoarthropathy, and histiocytosis^{31,32}. In 2005 Bruce M. Rothschild published a review of the historical and palaeopathological record of syphilis. Rothschild found that the pathological osseotype features of syphilis were absent in human specimens from re-Columbian Europe, Africa and Asia. However specimens with evidence of treponal disease were identified from North America dating back some 8,000 years. Bruce Rothschild as co-author with Christine Rothschild in their review study in 2000 found that somewhere between 2000 and 1800 years ago the first identified osseotype evidence of syphilis occurred in North America and it appeared that syphilis had transmuted from yaws.³³ Rothschild (2005) states that it is clear syphilis was present in the New World at the time of Columbus' arrival, perhaps in a milder or a non-venereal form, and there is evidence it existed in the same area of the Dominican Republic at which he landed. Rothschild also states that all evidence for treponal disease existing in re-Columbian Europe represents isolated cases for which alternative diagnoses are more likely.³²

A review of palaeopathological studies of treponal disease in the New and Old World by Baker and Armelagos in 1988 documented an abundance of pre-Columbian New World finds, but an absence of Old World finds, a finding that was reaffirmed by Powell and Cook and by Rothschild in 2005.^{24,27,32} Baker and Armelagos (1988) concluded that pre-Columbian American skeletal analyses reflect a treponematosis that spread to the Old World through non-venereal contact, and that European social and environmental conditions at the time favoured the development of venereal transmission. They also stated that the rapid spread of syphilis throughout Europe around 1500 reflected the introduction of a virulent disease into a population that had not been previously exposed and had no immunity to it.²⁷ In 2008 Harper et al published a comprehensive phylogenetic analysis of 26 geographically disparate strains of pathogenic *Treponema*, which found that the venereal syphilis strains originated recently and were more closely related to yaws strains from

South America than to other non-venereal strains, further supporting the hypothesis that syphilis, or a progenitor of the bacteria, came from the New World.³⁴

In 2011 Harper et al evaluated all published reports of pre-Columbian Old World treponal disease, using a systematic approach involving diagnostic criteria, certainty of diagnosis, and the accuracy and reliability of palaeopathological dating and radiocarbon dating. The authors concluded that among the 54 reports they evaluated using their criteria they did not find a single case of Old World treponal disease that had both a certain diagnosis and a secure pre-Columbian date. They came to the overall conclusion that evidence for an Old World origin for syphilis remains absent, and that this further supported the hypothesis that syphilis, or its progenitor, came from the New World.²⁴

Syphilis was a terrible disease because of its propensity to mimic many medical disorders, and its importance to medicine was emphasised by Sir William Osler who in an address given to the New York Academy of Medicine in 1897 titled *Internal Medicine as a Vocation* said :

"I often tell my students that it is the only disease which they require to know thoroughly. Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you."³⁵

From its beginning, syphilis was greatly feared by society – because of the repulsiveness of its symptoms, the pain and disfigurement that was endured, the severe after effects of the mercury treatment, but most of all, because it was transmitted and spread by an inescapable facet of human behaviour, sexual intercourse. The origin of syphilis is still a topic of debate and research, believed by physicians and scholars up until early last century to have been brought to the Old World from America by Christopher Columbus. In recent times, archaeologists and palaeontologists had found possible evidence it existed in the Old World before Columbus. This has been disputed by other researchers however and it seems that it is still possible that Columbus did bring syphilis, or its progenitor, to the New World.

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