

WHY IS KNOWING THE HISTORY OF SYPHILIS IS CRITICAL, EVEN DURING THE COVID-19 PANDEMIC?

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Amid the greatest world health medical challenge, enforced by the COVID-19 pandemic, the Calendar of the History of Syphilis comes to light, supported by numerous governmental, academic, and civil society organizations and led by the *factotum* from the study of sexually transmitted diseases in Brazil, our friend Professor Mauro Romero Leal Passos.

This Calendar exposes, in an elegant and illustrated way, a detailed historiographical description of the saga of syphilis throughout its relation with humanity, presented in a ludic way, in a yearbook that daily reinforces the importance of this timeless disease: it is as old as it is current. However, given the medical-social drama laid out by COVID-19, an unsuspecting event, inopportunistly and decontextualized, is the emergence of this launch amidst the on-going pandemic.

The present editorial aims to highlight the importance of initiatives in the field of medical history for the full understanding of syphilis, whose teachings can transcend the pathology and clarify the entire understanding of the health-disease process, fundamental at a time in which medicine has the greatest challenge of the last century, perhaps of the entire existence.

SYPHILIS: GENERALITIES

Syphilis is determined by bacterial infection of the *Treponema pallidum*, a sexually transmitted spirochete. Despite having well established treatment since the 1940s, thanks to the studies of Sir. Alexander Fleming (1881-1955) and the uses of penicillin⁽¹⁾, roughly 45 million people are estimated to be infected by this disease in the world, with an incidence of six million new cases/year, causing the death of approximately 100,000 people annually⁽²⁻⁵⁾. This scenario becomes more dramatic when we compare more than 200,000 fetal deaths from untreated congenital syphilis in the world, which accounts for about 25 to 40% of fetal deaths index^(6,7). Understanding the reasons involved in the high prevalence and incidence of a preventable, curable, and eradicable disease may provide strategies for public health action to deal with other infectious conditions, including COVID-19.

THE ORIGIN OF SYPHILIS

The origin of syphilis is still under debate. Paleopathological studies contain records of syphilis still in antiquity (3000 BC), speculating that Hippocrates of Kos (460 BC-370 BC) described

neurosyphilis, and archaeological evidence points to bone lesions in the tooth of children born with congenital syphilis in Pompeii as well⁽⁸⁾. Not only the Ebers Papyrus but also Assyrian and Babylonian cuneiform inscriptions already reported circumscribed genital disease, which would arise after sexual exposure and culminate in widespread skin rashes⁽⁹⁾.

Three are the most accepted theories to describe the origin of this condition: the pre-Columbian hypothesis, the Columbian one, and the unitary theory^(10,11). Although we do not deepen these considerations, it is undeniable that syphilis has spread throughout the world, evolving from a mild disease to a disease of great virulence due to mutations suffered by the pathogen at the end of the 15th century⁽¹²⁾. Regardless of being autochthonous from the Old World, syphilis spread as an epidemic after the Great navigations. Both the arrival of African slaves and the return of the 44 crew members of Christopher Columbus (1451-1506) and the 10 indigenous people brought to Europe coincided with the large treponemes spread of the 15th century^(13,14).

Without being precise on the geographical focus of the disease, the inhabitants of what are today Italy, Germany, and the United Kingdom called syphilis “the French disease”, at a time when all the great powers of Europe (in particular France, but also Spain, the Holy Roman Empire, and the Papal States) wanted to conquer the Italian Peninsula. Syphilis was diagnosed by Italian doctors in French soldiers and may have contributed to the defeat of the French army in the Northern Apennines campaign, acting as a biological weapon. The return of the defeated was even more bitter, as the French soldiers took the syphilitic evil with them, which in turn was called the “Neapolitan disease”; memories of the war interspersed with a history of rape and prostitution, contributing to the strong spread of syphilis throughout Europe. Jean Molinet (1435-1507), official historian of the House of Burgundy, reported the arrival of syphilis in France:

Finally, Jean was afflicted by smallpox, a violent, heinous, and abominable disease by which he was troubled; and many of those who returned to France (after the military campaign at Naples) were most painfully afflicted by it as well; and, since no one had heard of this terrible plague before his return, it was called the Neapolitan disease⁽¹⁵⁾.

Likewise, the publication of the Edict of Expulsion, signed in 1492 by Ferdinand of Aragon (1475-1504) and Isabella of Castile (1451-1504), also contributed to its dissemination, leading to a diaspora: 200,000 unconverted Jews migrated from the Iberian Peninsula to northern Africa and Southern Europe. Among the refugees, there was an outbreak of syphilis with 30,000 deaths, affecting citizens of Rome⁽⁸⁾ in the so-called “sickness of the Jews”, in spite of the

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barriers imposed for the entry of the exiles into the eternal city. Upon arrival in Russia, syphilis received the name “Polish disease”, the Poles blamed the Germans for the Germanic epidemic; in northern India, Muslims blamed Hindus for the affection, while Hindus blamed Muslims. And in the end, everyone blamed the Europeans for the evil that afflicted them⁽⁸⁾. Syphilis was thus consolidated as an “evil of the other”; it would be better if it characterized as the “evil of all” or, ideally, as the “evil to be fought”.

PHILOLOGY OF THE SYPHILIS VERNACULAR

The term “syphilis” was coined by a Veronese poet and physician, Girolamo Fracastoro (1478-1553), in his celebrated epic poem depicted in three books called “Syphilis sive morbus gallicus”, published in 1530 (the complete seminal translation of which is one of the extraordinary achievements of Professor Mauro Romero). In this work, clearly inspired by Virgil’s *Georgics* (70 BC-19 BC), Fracastoro presents *Syphilus*, a shepherd who led the herd of King Alcionus, a character of Greek mythology. In his tale, Syphilus, furious with Apollo for drying the trees and consuming the fountains that fed the herds, swore to no longer worship the son of Delos. Apollo, offended, cursed people with a disease called syphilis, named after the unfaithful shepherd⁽⁹⁾.

A great scholar of infectious diseases, Fracastoro, credited his Genesis to the presence of transferable particles, called spores, admitting the indirect and non-sexual transmission of syphilis, through fomites, described exquisitely as follows: “I call fomites [from Latin, fomes-material used to start fire] such things as clothes, sheets, etc., which despite not being corrupted by themselves, can, however, shed the essential seeds of contagion and thus cause infection”⁽¹⁶⁾. The disease-causing seeds, he called “*seminaria morbis*”, establishing that they could be transmitted by direct contact, by vehicle (the aforementioned fomites), or by air, thus anticipating the microbial theory of the disease, which would be carried out by Louis Pasteur (1822-1895), only in the 19th century.

ETIOLOGY OF SYPHILIS

Although today *Treponema* is, incontestably, the cause of syphilis, perspective cannot be lost as to its great outbreak, because Europe lived the transition from the Middle Ages to the Renaissance, in which medical practices were still guided by patristic-monastic philosophy. The decree of the Holy Roman Emperor Maximilian I (1459-1519) illustrates this assertiveness, published in 1495, which treats syphilis as the “smallpox of evil”, inflicted by God on blasphemous humanity⁽¹⁷⁾. Thus, one of the main medieval theories for the cause of syphilis was divine cholera, in the face of sins perpetrated in a society fraught by lust and depravity. Therefore, healing practices that associated prayers and confessions aimed at pleasing God and receiving the blessing of healing were common.

There was also a miasma theory that associated the occurrence of two solar eclipses and the confluence of Saturn and Mars determining a greater rainfall regime, contaminating the earth with water and generating a poisonous rot of the air, which would cause sores in the human body, rotting its flesh and corrupting its health⁽¹⁸⁾.

In 1496, Sebastian Brandt (1458-1521), best known for his work *Der Narrenschiff* (“The ship of fools”, wrote a poem entitled “*Of pestilentiali Scorra Sive mala of Franzos*”, reporting how the disease spread throughout Europe and how doctors had no medicine for it⁽¹⁹⁾. Paracelsus (1493-1541) described the origin of syphilis emerging from carnal corruption between a prostitute infected with gonorrhea, or with a uterine abscess, and a French leper⁽⁸⁾. This perception gains strength and causes syphilis to be grouped with all other sexually transmitted infections known at the time, including as being a specter of a single disease, whose sexual transmission transmuted its condition to venereal disease, in allusion to the Roman goddess Venus (equivalent to Aphrodite in Greek mythology), Regent of love, pleasure and sex.

It fit Giovanni da Vigo (1450-1525), Italian surgeon, in the fifth book of his work *Practica in arte chirurgica copiosa*, named *Of Morbo Gallicus*, published in 1514, to describe primary cancer, the secondary rash of skin lesions, with its ulcers and pustules⁽²⁰⁾. In the 16th century, Jean François Fernel (1497-1558), a Parisian physician and professor, coined the term “*lues venera*” (venereal plague) in his treatise dedicated to the disease⁽⁷⁾.

In truth, until the 19th century, many believed that the origin of syphilis was due to contact with period blood during sexual intercourse, with a blatant predisposition to poorly groomed women and with disgusting behaviors⁽²¹⁾.

DIAGNOSIS OF SYPHILIS

It was only at the beginning of the last century that the German zoologist Fritz Schaudinn (1871-1906) and the German-based Polish dermatologist Erich Hoffman (1868-1959) discovered, in 1905, the etiological agent of syphilis, named *Spirochaeta pallida*, proving its existence in fresh and colored specimens by the technique of the German chemist and bacteriologist Gustav Giemsa (1867-1948). It fell to the responsibility of the same researchers to modify the name of the spirochete to *Treponema pallidum*⁽²²⁾. Karl Landsteiner (1868-1943), Austrian physician and biologist based in the United States, revolutionized the diagnosis of this infection by introducing, in 1906, the use of the method of dark field microscopy for the detection of this bacterium. The German bacteriologist August Wasserman (1866-1925) developed, in 1910, the first serological test for syphilis, eliminating the major obstacles to the accurate diagnosis of this condition.

TREATMENT OF SYPHILIS

In addition to the isolation in leprosy, which during antiquity and the Middle Ages housed all sorts of ailments, from early signs of scleroderma anticipating leprosy to cases of psoriasis, elephantiasis, pustules, impetigo, Formica, to syphilis, the most rudimentary organized treatment of treponemes infection was only systematized after the 15th century.

In the Middle Ages, the suffering imposed on those infected was excruciating, because syphilis was treated with bleeding, passing through inserting penile tourniquets to prevent the disease from advancing, reaching cauterization with hot iron in the genital ulcer⁽²³⁾.

In venturing the hypothesis that syphilis had come to the spoils of the New World, with the soldiers of Columbus, the belief that herbal medicines from overseas was said to be equally effective in

the treatment of this disease. The most popular of these was guaiac, whose purging action promoted sweating, diarrhea, and polyuria, causing the purification of contaminated blood⁽²²⁾.

From Arabic medicine, mercury came to be adopted in Europe for the treatment of syphilis, under the blessings of Paracelsus. Taking advantage of its diuretic property and ability to promote hypersalivation, mercury would be prodigious to eliminate the pathogen through bodily secretions. Its administration was varied: from topical use (causing ulceration), through the oral route through the Barbarossa pill, containing a mixture of mercury and perfume essence and fruit flavors, to the therapeutic fumigation of the metallic form of mercury. The side effects were diverse and, in addition to not promoting cure, there were still cases of death among the treated patients, possibly due to hydrargyris. Indeed, the jocular dialogue between Fracastoro and his assistant, who questioned him for how long he recommended the use of mercurial ointment, to which Fracastoro replied: “As long as the disease does not disappear. It could be for life, who knows? This is the price you pay. A night with Venus, a lifetime with Mercury”.⁽²⁴⁾

This moral judgment has accompanied the medical treatment of syphilis over the centuries. Filthy disease rots the flesh of the unchaste who gave in to lasciviousness. Thus, the treatment of syphilis should be painful enough to punish perversion (hence the bleeds, purges, and mercurial frictions). This assertive is illustrated by the description of the French philosopher Michel Foucault (1926-1984), that venereal from 1679 could only be admitted to the General Hospital of Paris “with the condition that they submit to correction, first of all, and be whipped”⁽²¹⁾.

It was, however, unusual the discovery of the German bacteriologist Paul Ehrlich (1854-1915), who identified, in 1911, a compound that accidentally acted as an antibiotic, called arsphenamine (Salvarsan — from Latin *salvare* ‘save’ and arsenic - *arsan*). Enduring, its discovery became also known as “compound 606”, since it was discovered after 606 failed experiments. By developing a drug capable of specifically binding to a bacterium and fighting it, without affecting human cells, to what Ehrlich called the “magic bullet”, he came to be considered the father of chemotherapy⁽⁷⁾. His treatment for syphilis, considering Salvarsan and its superior generation, Neosalvarsan, was also associated with a formulation based on bismuth subsalicylate, introduced in the treatment of syphilis by Robert Sazerac (1875 -?) and by the Romanian physician Constantin Levaditi (1874-1953), both linked to the Pasteur Institute of Paris⁽²⁵⁾, in 1921, adding bactericidal effect to arsenic.

These treatments, isolated or combined, were only replaced in the 1940s, when the identification of penicillin was made (1928) and its production (from 1943) by Fleming, awarded the Nobel Prize in Physiology or Medicine, in 1945, for his discovery and generosity, since he immediately donated the patent of this drug to humanity.

In a salutary way, these formulations were received with the same enthusiasm as penicillin, since the cure of syphilis would be established for good. It is known as the “epitaph” predicted by Júlio Afrânio Peixoto (1876-1947), Professor of Legal Medicine at the Faculty of Medicine of Rio de Janeiro and Immortal of the House of Machado de Assis, in 1913, when anticipating the future of syphilis after Salvarsan: “away from the quackery of interest, which still hinders the application of treatment to all syphilitics, syphilis will disappear and end with the last syphilitic. In fifty years, the redemption of humanity will be from yet another scourge”⁽²⁶⁾. Nothing else could be misleading: after a century

of arsenic salt and bismuth formulation, so many other decades after penicillin, syphilis continues to graze for humanity.

UNETHICAL CLINICAL CONDUCT IN THE TREATMENT OF SYPHILIS

Although the cure of syphilis has been established incontestably with Fleming’s penicillin, numerous empirical treatments have been described throughout the history of Medicine, aiming to control the disease. However, the recommended therapeutic formulations, especially in the last 400 years, were notably ineffective, in a context in which the cure was not possible.

An episode related to the treatment of syphilis draws attention to the impoverished city of Tuskegee, in the United States state with the lowest quality of life — Alabama. In this scenario, the infamous experience perpetrated by the public health service of the United States occurred, between 1932 and 1972. To evaluate the natural history of syphilis, a cohort of 600 black and poor patients was established, of which 399 were diagnosed with “bad blood” (euphemism to refer to syphilis, whose diagnosis had not been revealed to them) and whose outcomes were compared to other 201 healthy individuals (control group). For undertaking, patients in the study group, with “bad blood”, should not receive any treatment for their disease. Even though penicillin was not available in 1932, the “magic bullet” containing arsenic, in its original version (Salvarsan) or improved (Neosalvarsan), or even bismuth, were already in common use and promoted some control of the disease, which was no longer considered devoid of treatment.

Even though they never gave their consent to participate in a scientific investigation, or have never even renounced the available treatment, these individuals received free medical treatment, transportation to the clinic, free meals, coverage of the expenses of their funeral, but no medication. Apart from this unacceptable ethical deviation, what has been seen next is staggering. Once the effective cure of syphilis with penicillin administration was established, the study should have been discontinued in the 1940s as soon as the drug was available in the United States. Behold, to the shame of humankind, the study lasted until 1972, about 30 years after the commercialization of penicillin.

At the end of this ignominy, recorded under the epithet of the study of untreated cases of Tuskegee syphilis, only 74 patients were still alive; of which 25 had died from syphilis and 100 died from disease complications. Another aspect is that 40 wives of the 399 participants with “bad blood”, who ignored their condition, were infected and gave birth to 19 stillbirths with congenital syphilis⁽²⁷⁾.

The epigraph case only became public when the press released its vexatious content to Americans, and the government of the United States took another 25 years to acknowledge its guilt and formally apologize to the eight still-living participants of the study.

(UNLEARNED) LESSONS FROM THE HISTORY OF SYPHILIS AND THE COVID-19 PANDEMIC

In January 2020, a new epidemic was first recognized in Wuhan province, China. Caused by a new type of coronavirus (SARS-CoV-2), the

disease came to be known as COVID-19; it produces symptoms similar to the flu, however more intense and often lethal, spreading rapidly throughout the world. Declared an international emergency due to its spread to other countries in January 2020⁽²⁸⁾, the World Health Organization (WHO) raised the condition of a pandemic on March 11, 2020⁽²⁹⁾.

Although all the viral genome of this disease was sequenced within a few days after the outbreak in Wuhan – which contrasts with the hundreds of years required to identify the *Treponema* – countless unlearned lessons from other epidemics, in particular syphilis, have contributed to thousands of lives being lost in today's pandemic.

Even though being a disease that has spread throughout the world through travelers (air transport in comparison to the Great Maritime navigations of the 14th and 15th centuries), the illusion of the Romans in 1492 has been repeated, when they opted for closing the borders of the city to the Jews expelled from the Iberian Peninsula, they presumed that it would prevent the spread of the disease – which was a derision. Attention to the persecutory and warlike rage of humanity in insisting on these events as a biological war. Although sanitary control at the borders is important, the pandemic only exists because it does not respect the territorial boundaries of nations. Elements of importance in addition to closing the borders, the establishment of screening, strict quarantine for travelers, hygienic guidance for the population, and preparation of the health system to cope with the pandemic are the preparatory strategies at the beginning of a pandemic.

Currently, the epicenter of the disease is of minimal concern. Attempts to blame the ethnic origin of the outbreak (French evil, Neapolitan disease, plague of the Jews, Polish affection, Muslim plague, Hindu disease, European disease) in addition to reinforcing xenophobic stigmas, bring unreasonable prejudices to explain its cause (carnal corruption between a prostitute infected with gonorrhea, or with a uterine abscess, and a French leper). COVID-19 exposed the disrespectful way the Chinese people were treated, some even expelled from commercial establishments, or ridiculed for traditions, as the exotic eating of bats, as they could be eating goat stomachs or sturgeon roe.

More than five centuries since the end of the Middle Ages, in which religion controlled the conception of the health-disease process and presented syphilis as a consequence of sin, the COVID-19 pandemic brought the consecration of holy oils and miraculous foods that would protect the faithful (especially those generous to the Church) against this modern plague.

Naturally, in a new disease, with no treatment well-established, therapeutic attempts are carried out by doctors. Committed to the patient, syphilis experienced centuries of an alchemical Pharmacopoeia, mostly inexhaustible, and frequently imposed suffering and damage on its carriers. In COVID-19, we have also seen numerous well-intentioned prescriptions to prevent the disease or even lessen its complications, which have become the stage of political quarrel (partisan and medical, which in these days have been of an atrocious nature). Under the argument of Medical Ethics, in different prisms, we saw Hippocrates fighting himself for the dispute of the correct narrative. Note that in the case of untreated syphilis, in Tuskegee, medical ethics were far from considered. But in the COVID-19 pandemic, the simple evocation of medical ethics was not enough to prevent inappropriate medical conduct from being practiced, showing that bioethics needs to be based on the best scientific evidence to be at the service of the patient.

To conclude the present Editorial, which is already long, it should be said that COVID-19 has brought a bitter final lesson. Although the concept of a pandemic was recorded by the Hellenic philosopher Plato of Athens (427/428 BC-348/347 BC) to characterize an affection that affects the entire population of a nation, in this on-going pandemic, experiences were crowned with cruelty. Even if COVID-19 does not distinguish social class, the outcomes among those affected are extremely different when considering the social conditions and the quality of hospital care the victims receive. Since the syphilis pandemic did not differ in terms of social stratum or therapeutic effectiveness, the –COVID-19 pandemic could be viewed as a syndemic, a concept created by the American anthropologist Merrill Singer⁽³⁰⁾ to particularize pandemics whose ominous outcomes arise not specifically because of the dominant generating fact (COVID-19 infection, for example), but is aggravated by social and economic vulnerabilities (about 38% of COVID-19 deaths in Brazil occurred in patients outside intensive care units in 2021, due to depletion of ICU beds, especially in the Public Health Network of states and municipalities).⁽³¹⁾ Thus, to insist on the concept of COVID-19 as a pandemic is to ignore the deep inequalities caused by this syndemic condition.

Finally, in addition to celebrating the launch of the Calendar of the History of Syphilis and making a simple sketch for its saga over the centuries, we urge readers of this simplicity: do not forget the aphorism of the polymath and famous writer Johann Wolfgang von Goethe (1749-1832): “Anyone who does not know their history knows nothing of its Art”. Knowing the history of Medicine allows doctors to recognize the mistakes of the past and glimpse a more adventurous future for The Art of Kos. Abel de Lima Salazar (1889-1946), a Portuguese physician, already predicted that “the doctor who only knows Medicine, not even Medicine knows”, reinforcing the need for this competence, within the dimension of humanities, as a fundamental element to the construction of the medical *ethos*. The Irish philosopher Edmund Burke (1729-1797) generalizes this conception as if predicting society by claiming that “those who do not learn history are doomed to repeat it”. Hopefully, favorable winds can gust us, dispelling, beyond the miasmas, all the ignorance and ignominy that contribute to the true scourge of contemporaneity: the lack of love between the *sapiens* who inhabit the Earth.

Participation of each author

Antonio Braga: publication theme, bibliographic review, writing of the text, review for sending the paper.

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