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Mystery of the Treatment of Syphilis

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Abstract

Syphilis is the commonest sexually transmitted disease (STD) affecting humans globally. On 12.10.1492, Christopher Columbus with his crew landed in Haiti (America) and returned to Spain (Europe) on 15th March 1493. Historians believe that, he and his crew members spread the disease syphilis in Europe, which he and his crew members had contracted in Haiti. The migration of people due to war (soldiers and mercenaries), merchants and slave trade contributed to the rapid spread of the disease and it became a pandemic. Initially, syphilis was highly contagious and virulent, affecting millions of people with very high mortality. Hence, the physicians of that time left no stone unturned for finding a cure. They tried mostly ineffective and harmful methods to treat syphilis. The drugs proved to be more harmful than curative. The fatality due to drugs itself was very significant. Alexander Fleming, a Scottish physician discovered penicillin in 1928 as a crude extract from *Penicillium rubens*. Eagle H and his coworkers in 1940, found that, penicillin at a relatively low dosage used over a prolonged period of four weeks cured syphilis. The discovery of penicillin enabled to transform a disease with high mortality to a manageable disease.

Keywords: Syphilis; Treponema pallidum; Infectious disease

Introduction

Syphilis was defined by Stokes as an infectious disease; due to *Treponema pallidum*; of great chronicity; systemic from onset; capable of involving practically every structure of the body in its course; distinguished by florid manifestations on the one hand and years of completely asymptomatic latency on the other; able to simulate many diseases, transmissible to offspring in man; transmissible to certain laboratory animals; and treatable to the point of presumptive cure.[1]

The King of France, Charles VIII attacked Italy with his army of 50000 mercenaries, 800 camp servants, cooks, medical attendants and prostitutes. His army won the battle in 1495 and indulged in celebrations and debauchery, within few months many soldiers suffered from a terrible disease and today it is called syphilis.[2]

Many soldiers suffered from genital ulcers and slowly progressed to have fever, skin rashes, body aches, and joint

pains and after few weeks to few months, soldiers further suffered from larger ulcers and foul smelling abscesses all over the body. The larger ulcers started invading the skin, soft tissue and bones. The ulcers destroyed the nose, lips, eyes and internal organs. The ulcers were seen in mouth and even the throat got perforated. All organs in the body including central nervous, cardiovascular and gastrointestinal systems were involved. The diseased patients started losing their memory, talking irrelevantly, with grandiose of being rich and strong. The illusions and delusions made their life miserable and most of them died horribly.[3]

The King of Spain, Ferdinand instructed two doctors, Ruy Diaz DL and Fernandez DO, to go to New World Haiti and investigate whether the Haiti people were also affected with this new disease, and if so, what treatment was being prescribed? Both physicians came back from Haiti and informed King Ferdinand about the beneficial effects with *Guaiacum* tree extract (Holy Wood, Wood of Life) for syphilis. This *Guaiacum* tree extract became the first medicine for treatment of syphilis in Europe. Patients were administered frequent enemas to induce diarrhea and were kept in hot and dark room for 40 days to induce profuse sweating. The wounds were covered with *Guaiacum* paste and patients were also given *Guaiacum* drink. Initially physicians claimed good results, and patients also felt symptomatically better. But, soon both the physicians and patients realized that, *Guaiacum* was not having any curative effect.[4,5]

Common man and the members of royal family kept pressuring the physicians, to find a cure for this new disease. Under much duress physicians started practicing mostly ineffective and dangerous methods which were practiced by followers of Hippocrates and Galen such as fasting, inducing vomiting, diarrhea, and bloodletting. None of these methods helped the patients; on the contrary these methods were more harmful to patients.[6]

Physicians prescribed olive oil bath, application of a mixture of herbal medicines in oil and exposure of the skin to sunlight to treat the skin lesions. These treatment modalities failed to help the patients.

Paracelsus in 1527 published an article on syphilis, stating that "Syphilis is acquired by contact with diseased people, cleanliness has to be maintained, and syphilis could be treated by carefully measured doses of mercury". Mercury remained the drug of choice for the treatment of syphilis, for the next 450 years.

In 1936, Georgio Sommariva of Verona successfully used mercury with good results in syphilis cases. He used mercury in all the available forms to treat such as by inunction, applying as plaster, fumigation, and oral solution. In 1839 Thomas James Walker, used mercury as an injection. The effects of mercury proved to be more toxic than its beneficial effects. Many other metals like Tellurium, Vanadium, and Bismuth were tried in the treatment of syphilis with a hope that these metals would be less toxic than mercury. Once a syphilitic patient was put on mercury, the patient continued to be administered mercury till his demise due to natural cause or adverse effects.

Hence, the popular saying that "*A night with Venus and a lifetime with Mercury*" (Dobson M. Disease. London: Quercus, 2007).

"*Two minutes with Venus, Two years with mercury*" (O'Shea JG – mercury as an antisyphilitic).

In 1909, Paul Ehrlich and Sahachiro Hata were working in Robert Koch Institute, and they observed good results when they administered a compound called "dioxy-diamino-arsenobenzol-dihydrochloride" which they named it as drug "606", Salvarsan. This miraculous drug was initially injected experimentally to the rabbits inoculated with *T. pallidum*. In 1912, the same team discovered less toxic arsenic compound called drug "914", Neo-Salvarsan. A Medical officer (LW Harrison), in Royal Army Medical Corps of World War I, used Salvarsan and Neo-Salvarsan on soldiers, infected with syphilis and observed that arsenic preparations were less toxic than mercury and also he opined that, Neo-Salvarsan was better tolerated by soldiers, than Salvarsan.[7]

In 1921, with an objective to reduce the side effects of arsenic, Constantin Levaditi, Robert Sazerac, and Louis Fournier successfully managed syphilis cases with small doses of bismuth and Neo-Salvarsan. The side effects of arsenic compound were less, because a small dose of arsenic was used. Patients' acceptance was also good. The combination of bismuth and arsenic compound became the accepted modality for the treatment of syphilis, till the discovery of wonder drug penicillin in 1943.[8] Austrian physician, Julius Wagner Jauregg, treated neuro-syphilis with pyrotherapy, by injecting a dose of malaria organisms with subsequent treatment of malaria with quinine.

In 1943 John Mahoney, AD Harris, and Richard Arnold cured four patients of syphilis at the US Marine Hospital, Staten Island, they administered intramuscular injection of penicillin for 8 days, and demonstrated cure for syphilis. The introduction of penicillin changed the disease with high mortality to a simple manageable disease.[9] The safety, efficacy and ease of administration was proved overtime. The side effects encountered while using mercury and arsenic were a thing of the past. Hence, physicians all over the world started using penicillin to cure syphilis, the practice being continued even today.

Eagle H and his team observed that, penicillin acted only on metabolically active, dividing *Treponema* and if *Treponema* became metabolically inactive and hid under heavy fibrosis, penicillin was not able to kill the organism. *Treponema* multiplies once in 30 -36 hours. It draws a fibronectin of host called sialic acid and covers itself. Since the sialic acid of the *Treponema* is derived from the host, the IgM and IgG antibodies recognize this as self antigen without

eliciting an effective inflammatory response. The host secretes heavy fibrous tissue around *Treponema* to limit the spread of infection, hence antibiotics will not penetrate the fibrous tissue. If *Treponema* has to survive and multiply by binary fission, it has to become metabolically active and come out of fibrous mesh. *Treponema* will be safe in fibrous mesh for up to 2 – 3 weeks and if does not come out of fibrous mesh, it will die naturally in fibrous mesh. Hence, an ideal antibiotic should have a bactericidal activity for more than 3 weeks, only then will it be able to combat the *Treponema* when it comes out of fibrous mesh and becomes metabolically active and starts to multiply. Eagle H and his team found that, repository preparation of penicillin, Benzathine penicillin G, slowly gets released from the site of injection over four weeks, and will kill *Treponema*, as and when it comes out of safety zone. The half-life of injection Benzathine penicillin G is 336 hours (18 days), but the treponemicidal concentration of 0.02 U/ml will remain in the body for 28 days (Décourt *et al*., 1983). [10]

Today for early syphilis, injection Benzathine penicillin G 2.4 million units, is administered as a single, deep intramuscular dose, after test dose (1.2 million units given in each buttock).

For late syphilis, injection Benzathine penicillin G 2.4 million units is administered as a single dose deep intramuscularly after the test dose. The same dose is repeated for 3 consecutive weeks.

For neurosyphilis and ocular syphilis, intravenous injection of crystalline penicillin 2 to 4 million units every 4 hours is given daily for 10 days. [11]

If patients are allergic to penicillin, then Tetracycline, Doxycycline, Erythromycin, Azithromycin and Ceftriaxone can be given.

Rarely patients receiving penicillin may develop acute anaphylaxis, and Jarisch-Herxheimer Reaction. It is advised to give penicillin after the test dose and under supervision. Till today, treponemal resistance to penicillin has not been reported.

Fig 1. *Treponema pallidum* – Spirochete (black color)

Fig 2. *Treponema pallidum* (black color) covered by fibronectin of host - Sialic acid (pink color)

Antibodies will not elicit an inflammatory response to sialic acid as it is derived from the host tissue. Hence, organism is protected from IgG and IgM antibodies.

Fig 3. TP (black color) covered by sialic acid (pink color), and host derived fibrous covering (yellow color)

The antibiotics do not penetrate the fibrous mesh protecting the organism from antibiotics.

TP remains metabolically inactive for 2 – 3 weeks. If TP does not come out of fibrous mesh, it will have natural death.

Benzathine penicillin G – remains in the body for > 4 weeks. Hence, as and when TP comes out of fibrous mesh in any day of three weeks, Benzathine penicillin G will attack TP and will kill it, hence it is an ideal antibiotic.

References

1) King A, Nicol C, Rodin P. Syphilis and history. In: King AA, editor. Venereal diseases . Great Britain. The White friars Press Ltd. 1980;p. 1–1.
2) Misra RS, Kumar J. Sexually Transmitted Diseases and HIV/AIDS. In: Syphilis: Clinical features and natural course. New Delhi. Viva Books. 2009;p. 262–266.
3) King A, Nicol C, Rodin P. Treatment of syphilis . In: Venereal diseases. London. ELBS. 1980;p. 144–164.
4) Morton RS. Another look at the Morbus Gallicus. Postscript to the meeting of the Medical Society for the Study of Venereal Diseases, Geneva, May 26-28, 1967. *The British Journal of Venereal Diseases* . 1968;44:174–177. Available from: https://sti.bmj.com/content/sextrans/44/2/174.full.pdf.
5) Gaenger S. World Trade in Medicinal Plants from Spanish America, 1717–1815. *Medical History*. 2015;59(1):44–62. Available from: https://doi.org/10.1017/mdh.2014.70.
6) Degeneration of Medicine and the Grisly Art of Slicing Open Arms. 2002.
7) Harrison LW. Ehrlich versus syphilis. *The British Journal of Venereal Diseases*. 1954;30(1):2–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1053920/.
8) Sethuraman G, Sharma VK. Sexually Transmitted Diseases and HIV/AIDS. In: Treatment of syphilis. New Delhi. Viva Books. 2009;p. 318–318.
9) Mahoney JF, Arnold RC, Harris AD. Penicillin Treatment of Early Syphilis - A Preliminary Report. *American Journal of Public Health and the Nation's Health*. 1943;33(12):1387–1391. Available from: https://ajph.aphapublications.org/doi/abs/10.2105/AJPH.33.12.1387.
10) Eagle H, Fleischman R, Musselman AD. The effective concentrations of penicillin in vitro and in vivo for streptococci, pneumococci, and Treponema pallidum. *Journal of Bacteriology*. 1950;59(5):625–643. Available from: https://journals.asm.org/doi/10.1128/jb.59.5.625-643.1950.
11) Syphilis — CDC Recommended Treatment Schedules, 1976. *Morbidity and Mortality Weekly Report*. 1976;25(13):101–107. Available from: https://stacks.cdc.gov/view/cdc/1074.