

Hallmarks in history of syphilis therapeutics

***I rimedi che hanno caratterizzato la storia
della terapia della sifilide***

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It is quite interesting to consider for a moment how many different drugs and therapeutic schedules have been employed at one time or another for the treatment of syphilis.

Syphilis appeared in Europe in the late 15th century and rapidly reached epidemic proportions. The first drug that was administered was the plant *Guaiacum officinalis* (guaiac) imported in 1508 from the Dominican Republic and its use became widespread by 1517. Guaiac's miraculous effects, though sporadic, were much discussed by physicians and by a prominent humanist, victim of syphilis, Ulrich von Hutten (1488-1523), who was persuaded to undergo a guaiac cure [1] (Figure 1).

Guaiac treatment requirements were diarrhea induced by enemas and profuse sweating by resting 40 days in a dark and hot room following a strict *cura famis*. Guaiac was administered externally in ointments and internally in potions. Hygienic and dietetic measures exhausted the patients [2]. However, from 1550 onward, treatment with mercury returns to scene and guaiac becomes an adjuvant drug for syphilis. Since the earliest history mercury was used in the treatment of skin diseases and it seemed quite natural its introduction in the treatment of syphilis under various forms: pills, suppositories, inhalations, fumigations, ointments, sachets and injections (Figure 2). However, mercuriotherapy was accompanied by painful and fatal complications [3].

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Figure 1 - Preparation of a guaiac decoction. Gravure of Jean Stradan, 1570, Paris.

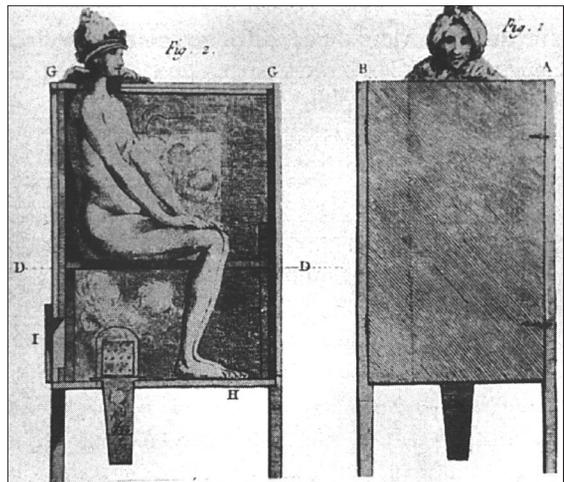


Figure 2 - Box for mercury fumigations.

The salivation, a sign of mercurial poisoning, was misinterpreted as a positive therapeutic sign of response to treatment by the elimination of harmful humours. Nevertheless syphilis' recurrence questioned the therapeutic efficacy of mercury [3].

However, in the 18th century, mercury divided the medical community in pro and contra mercurialists. The former group was by far more numerous and potent despite some trials of the later group members that reported a lack of efficacy. Medical controversies of the time were reflected by the continuous treatment extension up to life long and increasing doses. The opinion of eminent syphilologists as Professor Alfred Fournier (1832-1914) established the administration of mercury as first-line treatment of syphilis. At that period, potassium iodide was used in the treatment of neurosyphilis by the English dermatologist William Wallace (1791-1837) [3].

In the 19th century, the supporters of serotherapy and mainly the French physician Joseph-Alexandre Auzias Turenne (1812-1870) experimented on inoculations to cure syphilis with disappointing results since the disease does not leave immunity [4].

At the middle of the 19th century, arsenic compounds were introduced in the treatment of syphilis and remained in use until 1940's as monotherapy or in combination with other antisyphilitic drugs [5].

In 1909, arsenobenzol (*Salvarsan* or 606), an arsenic compound, was discovered by the distinguished German physician Paul Ehrlich (1854-1915). *Salvarsan* was given intramuscularly or intravenously in scaling doses and seemed to be microbiologically effective, having some action on *Treponema pallidum*. Concerning the clinical effectiveness of arsenobenzol, in primary syphilis it was seen persistence of lymphadenopathy and in secondary syphilis pro-

longation of symptoms. The drug was liable to decomposition in the presence of air making it poisonous. However most of the reported deaths were attributed to *Herxheimer reaction* rather than to drug decomposition. *Salvarsan's* therapeutic results were superior to mercury and physicians used to administrate the drugs simultaneously adding in their schedules potassium iodine for the prevention or treatment of neurosyphilis [5].

Ignoring that syphilis is a systemic disease from its onset, syphilologists also used topical cytotoxic treatments for the rash.

In 1921, Constantin Levaditi (1874-1953) and Robert Sazérac introduced bismuth which was proved to be more effective and less toxic than all previous drugs. During bismuth therapy the clinical manifestations of syphilis were disappearing and *Wassermann reaction* was turned negative. Bismuth was distributed in salt form for intramuscular administration in a treatment schedule of 20 injections [5].

The absence of treponemal serum tests and the erroneous attribution of the positive *Wassermann reaction* exclusively to *T. pallidum* infection resulted in prolonged and non proven effective treatments. It is worth mentioning that *Wassermann reaction* may become positive in tissue damage that can be provoked not only by syphilis but also from the cytotoxic action of the heavy metal treatment [3].

Although, the discovery of penicillin by Alexander Fleming (1881-1905), its development for therapeutic use by Florey and Chain, and the first clinical trial in 1943 by John Mahoney (1899-1957) revolutionized the treatment of syphilis giving the final solution [6].

Keywords: Syphilis, mercury, arsenobenzol, bismuth, penicillin.

Conflict of interest: none

SUMMARY

At the end of the 15th century syphilis appeared in Europe as a devastating epidemic. For nearly four centuries mercury was regarded as a remedy of first-rate importance along with guaiac and potassium iodide.

In the early 20th century, two new substances were added to syphilis therapeutics, namely arsenoben-

zol and bismuth. The absence of treponemal serum tests and the erroneous attribution of the positive Wassermann reaction exclusively to *Treponema pallidum* infection resulted in prolonged and non-proven effective treatments. In 1943 John Mahoney introduced penicillin, revolutionizing the treatment of syphilis.

RIASSUNTO

Verso la fine del XV secolo, la sifilide fa la sua comparsa in Europa con un'epidemia di vaste proporzioni. Per circa quattro secoli, si ritiene che il migliore rimedio per la cura della malattia consista nel trattamento a base di mercurio, guaiaco e ioduro di potassio.

A tali rimedi vanno ad aggiungersi, all'inizio del XX secolo, due nuove sostanze ovvero l'arsenobenzolo e il bismuto. L'assenza di test sierologici mirati alla rilevazio-

ne del *Treponema*, e l'errata attribuzione della positività della reazione di Wasserman esclusivamente all'infezione da *Treponema pallidum*, determina il protrarsi, per lungo tempo, di trattamenti dall'efficacia non comprovata.

Il primo studio clinico con penicillina, condotto da John Mahoney nel 1943, rivoluziona radicalmente il trattamento della sifilide.

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