'Two minutes with venus, two years with mercury' - mercury as an antisyphilitic chemotherapeutic agent

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A European pandemic

In the late 15th century Europe was swept by an epidemic caused by a deadly and an apparently novel disease which began in Spain soon after Columbus' expedition to the Americas. It next reached France, and by 1494 after the invasion of Naples by the French King Charles VIII, almost all of Italy was beset with the disease[1]. From the invading French army the disease acquired its first popular eponym, the 'morbo gallico' (French disease). It was not until 1530 that the disease acquired its modern designation - syphilis. The disease derives its name from a shepherd who is beset with a loathsome and repugnant disease for an act of religious impiety in Gerolamo Fracastoro's 'Syphilis or the French Disease'[2]. Fracastoro's poem was so popular that it overshadowed his more important medical writings - most notably the *Treatise on contagion* (1546)[3].

Is it possible to definitively equate the rapidly spreading epidemic with the disease we now know as 'syphilis'? Close reading of contemporary literature provides definitive proof that it was actually syphilis that caused the epidemic. De Vigo[4] provides a strikingly accurate picture of the disease. He notes that it arises from an indurated ulcer on the genital organs, that it is not only contagious but that it is sexually transmitted. He notes the appearance of a pleomorphic rash after the genital lesion and finally that much later schirrous, tumour-like lesions occur commonly involving the skeleton and the skin. These lesions, gummata, are pathognomic of late benign syphilis. Fracastoro and Von Hutten confirm the essentials of de Vigo's description of the disease. De Vigo's description of a chancre prefigures Hunter's by 251 years[5].

One can see several parallels with the ancient epidemic and the modern AIDS epidemic. Both provided the impetus for a great deal of medical thought and writing. Fracastoro's *Treatise on contagion* was the apotheosis of clinical medicine in the first half of the 16th century. Fracastoro comes close to expressing the modern conception of bacterial infection and describes contagion as caused by particles not perceived by the naked eye and he recognizes the contagiousness of syphilis, tuberculosis, rabies and measles[3]. In this he is prefigured by Von Hutten and Di Vigo who also recognizes the contagiousness of the 'morbo gallico'. Coincidentally, the island of Haiti is mentioned as being of key epidemiological significance in both AIDS and syphilis. The transatlantic origin of syphilis is still controversial as there is evidence of endemic syphilis (Bejel) in Asia Minor before 1492[6]. The 15th century was an age of great global exploration and it is indeed possible that a more virulent form of *Treponema pallidum* arrived in Europe by another, more circuitous, route.

The ability of syphilis to cause epidemics has been well documented - serious outbreaks of the disease occurred in 18th century Polynesia. The great epidemic is probably explained by several factors. It is likely that the strain of *Treponema pallidum* was more virulent than is now encountered. It is often observed that a disease is at its most virulent during the exponential phase of an epidemic. Secondly, there was probably no 'herd immunity' to syphilis. Thirdly, the epidemic is probably also explained by 'disease synergy'. The Oslo study showed that syphilis produced an excess of mortality not directly attributable to the disease itself[7]. Malnutrition and intercurrent illness probably exacerbated syphilis. Ancient armies usually lost many more men to disease than battle and poorly provisioned 15th century armies were probably at special risk of disease and also an important vector for the pancontinental spread of syphilis. In summary, then, the story of epidemic syphilis in Europe begins at the end of the 15th century. The disease provided the impetus for important new theories concerning the transmission of disease in general. We shall now consider the efforts of the medical profession to treat and confine the illness - with special reference to mercury chemotherapy.

Early proponents of mercury for syphilis

Phillipus Von Hohenheim (1493-1541), called Paracelsus, was amongst the earliest proponents of mercurial chemotherapy for syphilis. His extensive writings on the use of mercury were summarized by Johann Karl Proksch in 1882[8].

In the subsequent controversy about the relative efficacy of mercury and guiac wood Paracelsus entered the lists in favour of mercury whilst Von Hutten favoured the wood and became the most influential of the 'anti-mercurialists'.

The attraction of mercury was based on two premises. The first was the theory of contagion that syphilis was caused by invisible particles transmitted from one host to another. The second was based on the pharmacological properties of mercury salts. Mercury is a potent diuretic and in toxic doses it induces salivation. It was thought by inducing diuresis and salivation that the syphilitic 'virus' would be excreted, aborting the illness.

The second premise is a fallacious one and resulted in grievous clinical errors. Modern chemotherapy aims to bring about the in vivo destruction of *Treponema pallidum*, the causative spirochaete. Diuresis is merely an unpleasant side effect of medication; salivation indicates toxicity. The grave

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difference between the modern philosophy of antiluetic chemotherapy has not been appreciated. Contemporaries of Paracelsus actually recommended that for chemotherapy to be effective three pints of saliva needed to be produced[6]. At this dose poisoning was no doubt occurring.

Moreover, for the Paracelsians mercury had a special significance. Attempts at curing syphilis were based on a humoral concept of disease; mercury and sulphur were elements with magical and astrological qualities[9]. The diuretic properties of mercury partly explain why it held its ground against bismuth when the latter was introduced in 1884. Even after Fritz Schaudinn's discovery that syphilis was caused by *Treponema pallidum* (1905) many textbooks still give 'excretion of *Treponema pallidum*' as the mode of action of mercury (rather than killing of the bacteria)[10].

Giacomo Carpi, Konrad Schellig (1448-1508), Joseph Grunpeck (1470-1531) and Pedro Pintor (1423-1503) were eminent contemporaries of Paracelsus and early proponents of mercury.

Administration of mercury

Metallic mercury is poorly absorbed from the bowel. Physicians administered mercury as inorganic salts or by fumigations of mercury vapour.

Mercury sublimate is the bichloride ($HgCl_2$). It was produced by reaction of metallic mercury, copper sulphate and sodium chloride. The compound was known as 'corrosive sublimate' because of its actions of biological tissues. It was mixed with fat to produce an unction which when administered caused local ulceration.

Calomel, mercurous chloride ($HgCl_3$), was known as mercurius dulcis - 'sweet mercury'. It was a brilliant white salt and was far more widely used than was the sublimate. It is poorly soluble and was administered as a diuretic, an anti-syphilitic and a cathartic.

The oral absorption of calomel increases with prolonged use because of local effects on the bowel[11]. In the 18th century opium was concurrently administered with calomel. This was for two reasons: the first, because opium was also believed to have antiluetic properties and, secondly, because opium decreases the motility of the bowel and enhances absorption[12,13]. Calomel was also administered by injection, and by ointments and inunctions[13-15].

A method of administering metallic mercury was by therapeutic fumigation. Fumigations were used in the first decade of the 16th century and were still being used as late as 1928. Englebreth found that few patients undergoing fumigation treatment found it unpleasant and there were few side effects[16]. He also noted urinary excretion of metallic mercury in high concentrations. Systemic mercury poisoning and pneumonitis can follow inhalation of mercury vapour and it is indeed possible that poisoning did occur with this treatment in earlier centuries when it was less well controlled.

Medicinal mercury was also occasionally administered as bromides, nitrates and sulphides. These compounds are less toxic than the chloride salts[13,16].

The dose of calomel was reduced as it was gradually realized that it was not necessary to induce drastic side effects to obtain therapeutic results.

It was common to administer calomel in quantities of 5 grains ($\cong$ 325 mg). There was no standard regimen for the administration of this toxic drug and physicians titrated it to the individual requirements of their patients[13,14,17,18]. Textbooks of the 20th century stressed the avoidance of stomatitis and proteinuria which were rightly regarded as early manifestations of toxicity[17,19,20].

There was also considerable variation in the duration of therapy. English physicians of the 19th century often advised their patients to refrain from intercourse for two years and to take calomel daily[17,18]. Continental physicians advised longer and heavier courses. Rene Laennec, Sir James Clark and John Hunter were all famous proponents of mercury who advised very cautious and judicious use of the metal. James 'Calomel' Curry, Phillipe Ricord, Sira Borda, Abraham Colles and many of the Edinburgh school of physicians and surgeons of the late 18th and early 19th century were notably less restrained in their use of calomel!

Thus, examination of contemporary textbooks shows that the regimens used to administer mercury varied a great deal. Two trends are observed over 450 years: (i) towards decreased doses and (ii) to avoid toxic side effects. The 'humoral' theory of mercurial action was directly responsible for the enormous doses used by 16th century physicians.

The 'antimercurialists'

It must be stressed that at no time did the entire medical profession advocate the use of mercury to treat syphilis. Ulrich Von Hutten was amongst the earliest and most influential critics of mercury. Von Hutten was born near Fulda in 1488 and became a monk in the Benedictine house there. He had a penchant for literature and he left the monastery to the chagrin of his conservative father. His literary gifts won him the favour of the Archbishop of Brandenberg and he became poet to his ecclesiastical court. However, he did not remain in this secure post for long because he contracted syphilis. Not only was he the victim of a loathsome and feared disease but he was also a strong advocate of Lutheranism, and he was summarily dismissed by the Archbishop! Pope Leo X ordered his arrest and he fled to numerous courts before finding refuge on the island of Ufanau in the lake of Zurich. He died there at the age of 35.

Von Hutten suffered greatly under mercury chemotherapy - he lost his teeth. Hutten's protest against mercury was published in 'De Morbo Gallico' of 1519 and it was very influential in the therapeutic history of syphilis and was the fountainhead of a steady stream of antimercurial literature, as Johann Proksch wrote:

> 'The vociferous protest against the eleven courses of inunctions to which the unlucky knight submitted for nine years and his enthusiastic praise of guaiac by which he believed he was promptly healed could not be brushed aside and coming from such a man was also believed.'[13]

As well as providing a very detailed early account of syphilis Von Hutten provides a similarly detailed account of the symptoms of mercury poisoning. In chapter 4 of his book he describes, inter alia, stomatitis, dental loss, gastroenteritis, salivation, 'Hatters Shakes', oliguria and pneumonitis[21].

Sebastian Brandt (1458-1521) was another influential 'antimercurialist'. Proksch notes that 10 other metals and 22 materials of plant origin were used against syphilis in an effort to find a less toxic chemotherapeutic agent[13].

Johann Karl Proksch (1840-1923), who was both a noted medical historian and a critic of mercury, wrote five books on chemotherapy for syphilis. His largest compilation was published in 1895[13]. His first work dealt with Paracelsus' writings on mercury. It was published in Vienna in 1822[8]. Proksch's writings have a special significance because they immediately prefigure the works of Schaudinn, Wassermann and Boek who collectively would corroborate his findings and would make syphilology a far less empirical science.

Proksch found 65 entries dealing with syphilis in the 17th century and 43 of these concerned mercury. In the 18th century he found 517 articles on antiluetic therapy and of these 382 dealt with mercury. Published accounts of the adverse effects rose from two in the 17th century to 21 in the 18th century. In the 19th century there were some 3000 articles on the treatment of syphilis: one-third of these dealt with mercury and there are about 400 reports of mercury intoxication[16]. The more subtle of the protean manifestations of mercury poisoning were not described until late in this century[22]. Polson and Tattershall also provide a detailed chronology of the discovery of the adverse effects of mercury[11].

The 19th century British writers, C R Drysdale[23], S O Habershow[14], J Hamilton[18] and A Mathias[14], also wrote extensive treatises on the over use and adverse effects of mercury.

The emerging sciences of microbiology, serology and biomedical statistics would confirm scientifically the empirical observations of these men with regard to the relative hazards and benefits of mercury.

Impact of 20th century science on mercury chemotherapy

Advances in the diagnosis and prognostication of syphilis

The discovery of *Treponema pallidum* in 1905 by Fritz Schaudinn and Paul Hoffman was a major advance in the study of syphilis. Dark field microscopy is still the most definitive mode of the diagnosis of this disease[25].

August Wasserman and Albert Neisser developed a complement fixation test for *T. pallidum* in 1907. The test is still the basis for today's non-specific cardiolipin-based serological tests and directly lead to semi-specific serological testing[25,29]. Although non-specific and specific serology has several drawbacks and its use in the Oslo Study has lead to criticism of that study[3], it is a tool of immeasurable diagnostic importance.

The Oslo Study of untreated syphilis, which was undertaken by C P M Boek (1845-1917) until 1910 and thereafter by eminent successors until 1951, became the model for the American studies of untreated syphilis. T Gjestland noted the high incidence of spontaneous resolution of primary and secondary syphilitic lesions. He noted that some cases were free of the outward manifestations of syphilis within a month and others took up to a year, the average being 3-6 months[7].

Spontaneous resolution of syphilitic lesions had been noted by 19th century practitioners. William Ferguson observed apparent resolution of untreated syphilis in 1812[26]. The Oslo Study confirmed the view that many of the 'cures' attributed to mercury could be more justly attributed to the fluctuating nature of cutaneous luetic infection.

Moreover, Gjestland observed that up to 70% of those with early syphilis could live their lives with minimal discomfort. (However, this is still controversial and his findings are not reflected by the American studies of untreated syphilis.)

New chemotherapeutic agents

Mercury was overshadowed by more effective medication, bismuth was introduced in 1884. It is less toxic and more spirilocidal than mercury. Surprisingly bismuth was not widely used until after the First World War. It then replaced mercury as the principal agent of heavy metal chemotherapy[6]. (Bismuth is still being used medicinally. Bismuth preparations are said to be more efficacious than H_2 antagonists in ulcer disease. The postulated reason is its antimicrobial action. It is toxic to campylobacter pyloridis which is found in gastric ulcer craters.)

Paul Erlich won the Nobel Prize in 1908 for his work on the synthetic arsenicals salvarsan and neosalvarsan. These were highly effective and remained the mainstay of chemotherapy until the use of penicillin by John Mahoney of New York (1940). This antibiotic remains the drug of choice for syphilis[6,27].

Slow decline of mercury

Although new medication supplanted mercury it was still being used sporadically for syphilis until the 1950s. (These cited 20th century textbooks recommended its use, particularly when there are reactions to salvarsan[17,19,20].) The overwhelming efficacy of modern antibiotics made mercury an anachronism.

Efficacy of mercury

Leonard Goldwater writes of mercury chemotherapy: 'The use of mercury in the treatment of syphilis may have been the most colossal hoax ever perpetrated in a profession which has never been free of hoaxes'[16]. Is this a fair appraisal?

Mercury was undoubtedly strongly spirilocidal. It was noted to induce a Herxheimer reaction[27] and to clear cutaneous lesions of spirochaetes[17,19,20,27]. The problem was its toxicity; stated in the simplest pharmacological terms, it had a very disadvantageous therapeutic ratio.

Mercury was undoubtedly ineffective in curing secondary syphilis where there are large numbers of active spirochaetes. In primary infections where there are fewer spirochaetes topical and systemic mercury may have occasionally aborted the infection.

There are no in vitro studies of the effectiveness of mercury. This is because it was, and remains, almost impossible to culture *T. pallidum*. (It grows only in sophisticated cell culture preparations.)

However, mercury and heavy metal chemotherapy were undoubtedly of use in the treatment of the cutaneous lesions of late, benign syphilis. Here there are relatively few spirochaetes, there is chronic inflammation, fibrosis and attempted healing. Topical and systemic mercury could reduce gummas[27,28]. Mercury is a powerful antimitotic and anti-inflammatory agent and locally applied mercury probably aided healing.

Therapy for syphilis was highly empirical before the discovery of *T. pallidum*. However, it is likely that many of the observed effects of mercury on syphilis were not purely artefactual.

In summary, mercury was the mainstay of antiluetic chemotherapy for nearly 500 years and it remained in use until the advent of penicillin in 1940. The use of mercurial salts for medicinal purposes is one of the more interesting chapters in the history of chemotherapy.

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