Arsenic – the "Poison of Kings" and the "Saviour of Syphilis"

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Arsenic is a substance that has been well known to both the 'healer' and the 'poisoner' throughout history. It is ubiquitous in our environment and it is a potent neurological and liver toxin as well as a lung, bladder and skin carcinogen.[1] It was used throughout history as a potent poison to kill off kings and emperors and facilitate rich inheritances. Nero used it to murder his stepbrother, Britannicus, so as he might become Emperor of Rome.[2,3] It also has a place in medical history, particularly in the treatment of two great scourges of disease in our time, trypanosomiasis or "sleeping sickness", and syphilis or the "great pox". Paul Ehrlich's and Sahachiro Hata's new therapeutic discovery in 1909 for treating syphilis, Salvarsan, was hailed as "the arsenic that saved".[4,5] In 1918 two organic arsenical compounds, Lewisite and Adamsite, vesicant and respiratory irritant agents, were developed by the US Army as chemical warfare weapons but not in time to be used in the war; both are still listed by the CDC as potential bioterrorism agents.[6,7,8] In the early 19th century arsenicals were also developed to successfully treat trypanosomiasis, and currently arsenic trioxide is approved to treat refractory acute promyelocytic leukaemia.[9]

Arsenic is a metalloid element and is widely distributed in the earth's crust, usually combined with other metals, sulphur or oxygen. Common arsenic ores include arsenopyrite (grey arsenic, FeAsS), realgar or sandarach (red arsenic, AsS), orpiment (yellow arsenic, As2S3), and arsenolite, an oxidation product of arsenic sulphides (white arsenic, As2O3). Inorganic arsenic compounds are more toxic than organic compounds, but organic arsenic compounds are converted to inorganic compounds when absorbed in biological systems.[1,2,4,10]

The word arsenic is derived from the Persian zarnikh and Syriac zarniqa, later incorporated into ancient Greek as arsenikon, which meant "masculine" or "potent" and referred primarily to orpiment, or yellow arsenic. The word became arsenicum in Latin and arsenic in old French, from which the current English term is derived.[4]

The Poison of Kings and the King of Poisons

The toxic properties of arsenic were known by Hippocrates, who in 370 BCE described abdominal colic in a miner of metals, and similar properties were described of mercury and arsenic by Theophrastus of Erebus in the fourth century BCE and by Pliny the Elder in the first century BCE.[10] Pedanius Dioscorides, author of the historical pharmacopeia De Materia Medica and a Greek physician in the court of the Roman Emperor Nero, described arsenic as a poison, which was used by Nero to poison his step-brother Tiberius Britannicus in 55 CE and secure his position as Roman Emperor.[2,3]

The odourless and tasteless properties of inorganic arsenic compounds such as arsenic trioxide (white arsenic) made them an ideal poison. White arsenic was readily made by heating arsenic ore, this produced a white crystalline powder which was soluble in water and virtually undetectable in food or drink, and some said it even improved the taste of wine.[3] Arsenic poisoning was difficult to detect as the symptoms initially mimicked food poisoning, but a single dose could produce severe diarrhoea and vomiting, paralysis, and death. Because of its potency, the ease with which it could be obtained, and the discreteness with which it could be administered, it was a favoured poison of the ruling classes to kill off their rivals and adversaries and so became known as the "Poison of Kings and the King of Poisons".[4]

In Renaissance Europe, the art of poisoning came to its fore and contracts to poison one's noisome neighbour became a social norm. The poisoner made appointments and had set prices, the client named the victim and a contract was made, and the poisoner was paid when the job was done. A family of professional poisoners from the late 15th century were the Borgia family, Pope Alexander IV, his son Cesare, and Cesare's half sister, Lucrezia. A well known poisoner of the mid 17th century was an Italian lady named Giulia Toffana who made cosmetics containing arsenic, Aqua Toffana, and gave the tainted cosmetics with appropriate instructions on how to apply them to the intended victim. Toffana and her daughter, Girolama, were executed in Rome in 1659 for their complicity in the poisoning death of several hundred men.[3,11]

Many others took up this occupation throughout late Renaissance Europe and there was a spate of young, wealthy, married women, suddenly becoming

young, wealthy, eligible widows. In 17th century France, white arsenic became known as poudre de succession, the 'inheritance powder'.[2] From the 18th century the incidence of poisoning waned as methods of post-mortem detection were developed and in 1836 James Marsh, an English chemist, developed a successful chemical test for arsenic poisoning, modified later by Jöns Jacob Berzelius, a Swedish chemist, to be known as the Marsh-Berzelius test.[3,12]

In the 19th century women applied arsenic powder to whiten their faces as well as to their hair and scalp to destroy vermin. It was also thought that arsenic consumption by women gave "beauty and freshness" to the skin, an appearance of pour rajeunisante. Taking Fowler's solution, a potassium arsenite solution developed by Thomas Fowler in 1786 as a treatment for various chronic disorders, was popular with Victorian prostitutes to give them rosy cheeks, an effect due to damage to the capillaries of the skin.[13,14] Arsenic continued to be used in cosmetics well into the early twentieth century and this was a common source of accidental poisoning.

Arsenic as a chemical weapon – Adamsite and Lewisite

During World War I there were over 1.3 million casualties and 90,000 deaths from chemical gas warfare, particularly chlorine, phosgene, "white star" (phosgene and chlorine) and mustard gas.[15] In 1918 the US Army Chemical Warfare Service developed Lewisite and Adamsite to counter the Central Powers' effective use of gas agents against the Allies in the trenches of Western Europe. Lewisite is C2H2AsCl3, dichloro(2-chlorovinyl)arsine, also called "L" and "M-1" agent. The compound was first synthesised in 1904 by Julius Arthur Nieuwland, a Belgium chemist. In 1918, Winford Lee Lewis, a soldier and chemist in the US Army Chemical Warfare Service, perfected the synthesis of the compound and its ability to be delivered as a gas warfare weapon.[6,8]

Lewisite is primarily a vesicant (or blistering agent), but is also a potent respiratory and eye irritant and a systemic poison when absorbed. It has an odour of scented geraniums. Upon contact with skin and mucous membranes it immediately causes large, painful, fluid-filled blisters. When inhaled it causes severe respiratory tract inflammation and necrosis resulting in acute pneumonitis. It can be absorbed through the skin and forms M-1 oxide (chlorovinylarsineoxide or Lewisite oxide) which causes systemic poisoning with diarrhoea, nausea, vomiting, and hypotension ("Lewisite shock"). Lewisite can be dispersed in air as an aerosol or vapour or in water as a liquid. The effects are felt immediately on exposure and death can occur with high or prolonged exposure.[6,15]

Adamsite is C12H9AsClN, diphenylaminechloroarsine, or "DM", and is a respiratory and eye irritant and vomiting agent. It is not as potent as Lewisite and its effects are generally short-lasting, but can be fatal in very high concentrations such as may occur in enclosed spaces.[7] It was developed as a chemical warfare agent by Roger Adams, also a chemist with the US Army Chemical Warfare Service, in 1918. Lewisite and Adamsite were produced too late to be used in World War I but were stockpiled and field tested later in World War II on the western front. However they were found to be not as effective in their delivery as other vesicant and respiratory irritant gas agents and were not used.[8]

In 1997 the Chemicals Weapons Convention (CWC), overseen by the Organisation for the Prohibition of Chemical Weapons, was ratified as an international arms agreement on the prohibition of the development, use and stockpiling of chemical warfare weapons and on the facilitation of the destruction of all current stockpiles.[16] During and after the second world war many countries stockpiled chemical weapons, particularly the US and the former Soviet Union who held the largest stockpiles. Signatories to the CWC continue to destroy their stockpiles, both US and the Russian Federation have destroyed most of their chemical munitions and as at January 2012 seven of nine US chemical weapons destruction sites were closed or under closure. However as time progresses, remaining munitions continue to deteriorate with an increasing risk of explosion or leakage of chemicals, as well as posing a potential serious bioterrorism threat.[17,18] Remaining stockpiles of Lewisite and Adamsite are still of international concern and they are still listed by CDC as potential bioterrorism agents.[6,7]

Arsenic in ancient and Renaissance medicine

Hippocrates used the arsenic sulphides realgar and orpiment to treat ulcers and abscesses, and Dioscorides used orpiment as a depilatory.[1,19] The use of arsenic in traditional Chinese medicines dates back to 200 BCE and was described in the first traditional Chinese medicine book Shen Nong Ban Cao Jing. A common concept in ancient Chinese medicine was to use a poison against a poison. Indian Ayurvedic herbal medicines often contained arsenic, lead and mercury, and it was thought the mineral elixir made from the "essence of five planets" could give perpetual life.[4,20]

Paracelsus was a physician, chemist, and professor of medicine at Padua University, Italy, in the early 16th

century. Paracelsus believed that diseases resulted in a "disharmony of normal functions" and that they came "from without" or the environment, not "from within" or from disturbance of the "humours" as was the prevailing thinking at the time. He criticized the use of unproven remedies passed down through the centuries since Galen's time and advocated the use of chemically prepared tinctures, balsams and essences. He wrote his own pharmacopoeia and introduced the therapeutic effects of elements such as sulphur, arsenic, lead and mercury, particularly the latter for syphilis, the "great pox", which was second only to plague as a scourge of the time.[12,21,22] Paracelsus was the first to document precise directions for the preparation of metallic arsenic as a therapeutic agent and made a balsam from white arsenic which was a favoured method used by the barber surgeons to treat wounds, buboes, carbuncles, anthrax and other similar ulcers.[3,23]

Thomas Fowler's "liquor mineralis"

In 1786 Thomas Fowler, a British physician, published a study on the effectiveness of his solution of 1% potassium arsenite which he called "Liquor mineralis", for "agues, remittent fevers, and periodical headaches". In 1809 "Liquor mineralis", known by that time as "Fowler's solution", was accepted into the London Pharmacopeia and became widely used as an alternative to quinine for "agues" (malaria) and was used for "sleeping sickness" (trypanosomiasis). By the 1880s Fowler's Solution was used for a variety of other ailments including asthma, eczema, psoriasis, anaemia, hypertension, gastric ulcers, heartburn, rheumatism, and tuberculosis, and arsenic paste was used to treat cancers of the skin and breast. Other arsenic preparations at the time included Donovan's solution (arsenic triiodide and mercuric iodide) and de Valagin's solution (arsenic trichloride), both used to treat similar disorders.[2,9,19,24] In 1878 Fowler's solution was discovered to lower the white cell count in chronic myelogenous leukaemia and was used as the main treatment for leukaemia until the advent of radiation and chemotherapy in the 20th century.[1,19]

Fowler's solution remained a treatment for many conditions well into the 20th century and is listed along with arsenic trioxide and sodium arsenate in the 1914 edition of the American Medical Association's Handbook of Useful Drugs as treatment for skin cancer, chronic inflammatory skin disorders, malaria, syphilis and protozoal diseases.[25]

Arsenic in the treatment of leukaemia

In 1878 in Boston City Hospital Fowler's Solution was discovered to lower the white cell count in two normal people with a more significant decrease in a person with chronic myelogenous leukaemia (CML) and subsequently became an accepted treatment for leukaemia.[9,19] In 1931 arsenic trioxide was successfully used to treat CML but it had severe side effects and its use as an antileukaemic agent became superseded by the advent of radiotherapy and cytotoxic chemotherapy. In the 1960's sulphydryl inhibitors were developed which included oxophenarsine but were replaced by other anticancer drugs a decade later.[19]

In the 1990's, several studies from China showed that arsenic trioxide was effective in treating de novo and relapsed acute promyelocytic leukaemia (APL). In 2000 the US FDA approved arsenic trioxide for the treatment of APL.[9,19] In 2001, researchers from the University of Arkansas for Medical Sciences demonstrated the efficacy of arsenic trioxide in the treatment of end-stage high-risk multiple myeloma.[24] Currently arsenic trioxide is approved to treat relapsed or refractory APL and research is continuing to determine its efficacy in other haematological cancers.

The discovery of the cause of syphilis and Paul Ehrlich's "Magic bullet"

In February 1495, King Charles VIII of France, with his army of 50,000 mostly Spanish mercenary soldiers, invaded and took Naples from King Alphonso II. King Charles' aim was to use Naples as a base from which to launch a campaign to the Crusades. While celebrating in the aftermath, an epidemic of a frightening new and terrible disease broke out in the soldiers and the people of Naples – this was syphilis, Grande verole, or the 'Great pox', later becoming known as the 'French pox'. The prevailing hypothesis up to early last century was that Colombus brought the disease with him when he returned to Spain from the New World in 1492 and it had spread to Spanish soldiers and then to the French. In the last several decades paleopathological evidence has indicated that syphilis may have existed in the Old World for some centuries before, however this evidence has been criticised and the question of the origin of syphilis remains unresolved.[26,27]

In 1905, Fritz Richard Schaudinn, a German zoologist, and Erich Hoffmann, a dermatologist, discovered Spirochaeta pallida (the bacteria was spiral shaped, s imilar to animal spirochaetae and pale coloured) as the cause of syphilis.[5,12,28] Later in that year Schaudinn determined that the organism belonged to a different genus to Spirochaeta and renamed it Treponema pallidum.[29,30]

Paul Ehrlich was a German physician who in 1890

joined Robert Koch to work on antitoxins and antitoxin sera, particularly the diphtheria antitoxin, and in histological chemistry and staining of bacteria. In 1897 he moved to Frankfurt au Main, Germany, as Public Health Officer. In 1899 he became director of the Staatliches Institut für Experimentelle Therapie where he became interested in the application of staining dyes and arsenicals as antimicrobial agents. In 1905 he also became director of the Georg-Speyer-Haus Chemotherapeutisches Institut, a research foundation built next door to the Staatliches Institut.[5,31]

Ehrlich developed the hypothesis that therapeutic chemicals could be formulated to target specific microorganisms and destroy them without injuring the host's body tissues, and that such antimicrobial actions were specific to the drug's chemical structure. He applied this theory, along with Kiyoshi Shiga, a Japanese bacteriologist, to experimenting with benzopurpurine dyes against trypanosomiasis. This, along with his work with arsenic compounds, have credited Ehrlich as being the founder of chemical therapeutics based on reasoned theory rather than empirical acceptance.[5,12]

In 1906 Ehrlich read of Schaudinn's and Hoffman's discovery the previous year and Hoffman suggested to Ehrlich that given the similarity between spirochaetes and trypanosomes he try using arsenical compounds against syphilis.[5] Ehrlich and his colleague, Alfred Bertheim, a German organic chemist, had already been experimenting with arsenoxide and arsenobenzene derivatives of aminophenyl arsenic acid, Atoxyl, in treating trypanosomiasis in mice. Ehrlich and Bertheim began experimenting with Atoxyl and its derivatives in treating Spirochaeta infection in rabbits at the Georg-Speyer-Haus Institute. Ehrlich's early experiments were not very successful as most of the earlier arsenicals he experimented with were too toxic.[5,31]

In 1909 Sahachiro Hata, a Japanese bacteriologist who had worked at the Robert Koch Institute in Berlin with Shibasaburo Kitasato studying the plague bacillus, joined Ehrlich at Kitasato's suggestion at Ehrlich's Institute. Ehrlich and Hata finally found success with the 606th compound in their series of experiments, dioxy-diamino-arsenobenzol-dihydrochloride, which they called drug "606" and which is now known as arsphenamine. In 1910 Ehrlich and Hata announced their discovery at the Congress for Internal Medicine at Wiesbaden. This led to its manufacture by a German chemical company, Hoechst, as Salvarsan, "the arsenic that saves lives", and it soon also became popularly known as "the magic bullet".[2,5,12,25,31,32]

Later in 1912 Ehrlich developed neoarsphenamine, Neo-Salvarsan, or drug "914", which was water soluble and easier to administer. Salvarsan and Neo-Salvarsan were listed in the American Medical Association's 1914 Handbook of Useful Drugs as an effective treatment for primary syphilis and spirillar diseases such as relapsing fever and Vincent's angina, and for later stages of syphilis in combination with mercury.[25]

Salvarsan and Neo-Salvarsan were hailed as wonder drugs and a salvation of the time. Ehrlich was named by Victor Robinson, an American pharmacologist and later a physician, as the "saviour of the race" for his "magic bullet":

> ".. as a therapeutic achievement, the production of Salvarsan (606) and Neo-Salvarsan (914) had never been surpassed."[33]

Albert Ludwig Neisser, a German physician specialising in dermatology and venereology, was initially sceptical of arsphenamine's effectiveness in treating syphilis, but within a short time came to accept that Ehrlich's success was true and 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.”[34]

Paul de Kruif, an American microbiologist, wrote in his 1926 book Microbe Hunters :

> "No serum or vaccine of the modern microbe hunters could come near to the beneficent slaughtering of the magic bullet, compound six hundred and six."[35]

Ehrlich and Hata were vilified by some sections of European society for a short period of time. Many believed that syphilis was a divine punishment for sin and immorality and didn't deserve to be cured, but acclaim from the scientific and medical establishment prevailed.[5] In 1908 Ehrlich was awarded the Nobel prize for his work in immunology and the antidiphtheria serum; he shared the prize with Russian biologist Élie Metchnikoff. Ehrlich died in 1915 in Bad Homberg, Germany, from a stroke. Hata returned to Japan to become a renowned laboratory bacteriologist who continued his work in

using arsphenamine against syphilis, rat bite fever and other diseases.

By the 1920's it became apparent that for arsenic to be effective against syphilis, it had to be combined with small doses of either bismuth or mercury. In 1930 it was found that arsphenamine metabolized to oxyphenarsine, also known as mapharside, which was a more stable compound and was marketed for treatment of syphilis under the name Mapharsen. Arsenicals, 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.[5,24,36,37]

Arsenic in trypanosomiasis

In 1901 Paul Ehrlich together with Kiyoshi Shiga had began experimenting with benzopurpurine dyes, Nagana Red and its derivatives Trypan Red and Trypan Blue, in treating trypanosomiasis, or "sleeping sickness". These experiments were largely unsuccessful, but Ehrlich in his search for other antimicrobial compounds turned to Atoxyl, aminophenyl arsenic acid, synthesised by French chemist and biologist Pierre Jacques Antoine Béchamp in 1859, and other organic arsenic derivatives that he and Alfred Bertheim were synthesising in their laboratory in the Georg-Speyer-Haus Institute.[5,38]

By 1905 Atoxyl was being used to treat trypanosomiasis but its effectiveness was outweighed by its neurotoxicity, especially in causing optic nerve atrophy and blindness. Ehrlich and Bertheim began researching less toxic derivatives of Atoxyl. Bertheim's work developed arsenoxides which were effective against trypanosomiasis but were still very toxic, and arsenobenzenes which were not very effective but were less toxic. In 1907 Ehrlich and Bertheim found that drug "418", arsenophenylglycine, was effective, which they had called Spirasyl as it was also effective against spirochaetal infection in mice. It was in this particular series that Ehrlich and Sahachiro Hata later found that diaminodioxyarsenobenzol, drug "606", could cure syphilis infection in rabbits.[5,38]

In 1919 Walter Jacobs, an American chemist, and Michael Heidelberger, an American immunologist, synthesised tryparsamide, a phenylglycinamide arsonate derivative of Atoxyl. Tryparsamide was marketed by May & Baker and remained an effective drug against trypanosomiasis until the 1960's, often used with Suramin, a naphthylamine dye originally synthesised in 1917 as "Bayer 205", or Germanin, later marketed as Suramin.[37,38]

In 1938 Ernest Friedheim, a Swiss microbiologist, synthesised melarsen, a melamine derivative of Atoxyl, and a trivalent analogue, melarsen oxide. Melarsen was effective against trypanosomiasis but was also very toxic, so Friedheim combined the drug with an arsenic antidote, British anti-Lewisite (BAL), developed by Britain to counteract the effects of Lewisite gas, an arsenical chemical warfare agent. This new drug was marketed as Melarsoprol, or Mel B, and was introduced as treatment for trypanosomiasis in 1949. Suramin and Melarsoprol are still used as chemotherapy options for Trypanosoma brucei rhodesiense.[38,39]

Arsenicals were used for some other infectious diseases such as malaria[2,25,40] and May & Baker marketed Stovarsol, sodium acetarsone, for tuberculosis[37], but their application and effectiveness throughout the 20th century were primarily for syphilis and trypanosomiasis.

Arsenic has earned a place in history both as a favoured poison and as a miracle drug. It figured prominently in the development of chemotherapeutic agents by renowned physicians and scientists such as Thomas Fowler, Paul Ehrlich, Sahachiro Hata and Albert Neisser, and became the first antimicrobial agent to be effective against the "great pox", syphilis. Arsenic still has a place in medicine today as a treatment for certain subtypes of leukaemia and trypanosomiasis.

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