

*Arsenic - A historical review**

Arsênio – Uma revisão histórica*

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BACKGROUND

There are few substances like arsenium or arsenic (As) that have such a fantastic history. Its therapeutic use dates back to 400 B.C. and there are reports on it by Hippocrates, Aristotle, Dioscorides and Pliny the Elder. Since then, As has been the object of many studies and imaginary legends and traditions.

It was the poisoning agent of choice in the Middle Ages, and held this distinction until the beginning of the 20th century. Several characteristics contributed much to such popularity: its inoffensive appearance, tastelessness or slightly sweetened taste enable As to be easily mixed to foods; it was easy to obtain; insidious progression of intoxication mimicking diseases; and its presence in embalming fluids - once the victim was embalmed it was not possible to prove poisoning.

The peasants from Steiermark, in Austria, used to feed the horses with As and believed they would become stronger and able to work at higher altitudes. The fur became brighter and the animals seemed to be healthier - a well-known trick in the equine auctions at that time. From then on, it has been speculated that men developed a need to ingest As in order to control their increasingly more potent animals, and started eating large amounts, leading to the famous "arsenic eaters" in the beginning of the 19th century.¹

Arsenic had its heyday as a suicidal agent - hence, it is mentioned in all Forensic Medicine treatises and became the object of exhaustive studies on its toxic action. Its addition to the therapeutic armamentarium occurred in a not very recommendable

manner. Necrosis and erosion resulting from the topical application of arsenicals soon drew attention and raised greed of charlatans who incorporated As in their miraculous "cancer pastes" to destroy accessible tumors.

Its peak as a therapeutic agent took place from the end of the 19th century to mid-20th century. Scientifically supported or not, the arsenical compounds were employed to treat several and diverse dermatoses such as psoriasis, pemphigus, eczemas, herpetiform dermatitis, acne, lichen planus, leishmaniasis, prurigo and syphilis. Moreover, and emphasizing such panacea, they were widely prescribed as tonics and fortifiers, and relievers of undefined symptoms such as "stomach problems", "nervous state" and "fits", or even to treat malaria, chorea, epilepsy and asthma, among other ailments.²

The first observation on As possible carcinogenic action was reported in 1822, when Paris detected that cattle grazing close to foundries developed cutaneous neoplasms in the hips and attributed the cause of these tumors to As-containing expelled gases.^{3*} White, in 1885, described a psoriasis-verruca-epithelioma sequence in two patients who used As to treat skin diseases, but failed to suspect the carcinogenic role of the therapeutic agent.^{4**} In 1888, Hutchinson, in a well-documented and illustrated communication to the London Pathology Society, reported six cases of skin cancer in patients who took As to treat skin conditions. The first patient was a physician from Boston who self-medicated his psoriasis with oral arsenic solutions and witnessed the emergence of malignant verrucous lesions over the

¹ Paris JA. Pharmacologia. London: W Phillips; 1822. *Apud* ³

^{**} White JC. Psoriasis-verruca-epithelioma: a sequence. *Am J Med Sci.* 1885;89:163. *Apud* ⁴

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SULFARSÉNOL

$C_{12} H_{11} AS_2 N_2 CH_2 OSO_2 Na$

O emprego do SULFARSÉNOL está indicado em todos os periodos da Syphilis, onde a sua eficacia é completamente notavel, tanto sobre as manifestações contagiosas, que desaparecem mediante um pequeno numero de injeções, como sobre o resultado negativo da reacção de Wassermann, obtido muitas vezes, em poucas semanas, graças ao emprego de doses accumuladas. Com effeito, a toxidez relativamente fraca do medicamento, permite esta maneira de proceder.

E' util ainda e muitas vezes indispensavel, no tratamento do paludismo, especialmente nas formas, que resistem á quinina, na febre recorrente, na framboesia na filariose, na ulcera tropical, no kala-azar, na angina de Vincent, na varicella, na escarlatina, na doenca do somno, e nas complicações locais ou geraes da blennorrhagia (em particular, orchites, rheumatismos, arthrites, nas peri e parametrites, salpingites: Durœux). Em taes casos, constitue um verdadeiro especifico.

Em pequenas doses, de 2 centigrammas (Empôla D) é utilissimo nas anemias, nas chloroses e estados similares (convalescenças).

Em egualdade de doses, o Sulfarsénol é cinco vezes menos toxico que o 606, e quatro vezes menos que o 914. Em egualdade de doses therapeuticas, a differença de toxidez a favor do Sulfarsénol é ainda mais pronunciada. A julgar pelo seu effeito sobre as lesões visiveis, 12 centigrammas de Sulfarsénol correspondem á 20 centigrammas de 914.

E' o unico sal arsenical que se applica em injeção Subcutanea ou Intramuscular

sem analgesico, dor, endurecimento ou inflamação.

NOTA - Cada caixa leva rotulo de garantia com numero de control, impossibilitando imitação e venda clandestina.

erythematous scaly plaques. Hutchinson, whose study is recognized as the pioneer work in carcinogenic action of As, considered the cases previously described by White similar to his.^{5****} The experimental production of cancer by As dates from 1922, when 1.8% alcoholic solution of potassium arsenite was brushed on rats. The earliest tumor - a squamous cell carcinoma - appeared after 86 days.^{6,****} The main active ingredient of the notorious Fowler's Solution is a 1% aqueous solution of potassium arsenite (KAsO₂). This compound is well-known and used to be prescribed by many of those who are reading this article, including one of the authors (BG).

As yet another chapter in its vast biography, as wound up in the war battlefield in the form of a lethal gas called lewisite (named after W. Lee Lewis, an American chemist), which caused lacrimation and was vesicant and highly respiratory irritant. Fearful of its extensive use in World War II, British investigators created the antidote British anti-Lewisite - BAL, which was also used in metal intoxications, such as gold, mercury, bismuth and antimony.

ARSENIC SOURCES

Arsenic is found in water, soil and vegetables in variable amounts. It may be concentrated by sea organisms and deposited in significant volumes in sedimentary rocks, or be released as the volatile gas arsine (AsH₃) under influence of arsenophilic fungi or agents present in waters containing the substance.

Accidental contamination by As in drinking water has been addressed in many detailed studies. By the end of the 19th century, Geyer reported cases in Reichenstein, Silesia;^{7,****} in 1938, Arguello et al. described endemic regional chronic arsenicism in the Province of Cordoba, Argentina.⁸ Out of 323 cases of epithelioma studied in Argentinean patients during eight years, 39 (12.07%) were in individuals with evidence of arsenic intoxication. Some episodes of hydroarsenicism in Thailand,⁹ Mexico¹⁰ and United States are worth mentioning.¹¹ Today, the major endemic foci are in West Bengal, in India. Based on data from a survey assessing only parts of a region comprising six districts and 30 million inhabitants, it is estimated that at least 800,000 people drink water contaminated by As and 175,000 have skin lesions

*** Hutchinson J. On some examples of arsenic-keratoses of the skin and of arsenic-cancer. Tr Path Soc Lond. 1888;39:352-363. *Apud* ⁵

**** Leitch A, Kennaway EL. Experimental production of cancer by arsenic. Br Med J. 1922;2:1107. *Apud* ⁶

**** Geyer L. Ueber die chronischen Hautveränderungen beim Arsenicismus und Betrachtungen über die Massenerkrankungen in Reichenstein in Schlesien. Arch Dermatol Syphilol. 1898;43:221-80. *Apud* ⁷

Therapeutica Chimica da Syphilis
Tratamento POR VIA BUCCAL

STOVAR SOL

(Acido acetyl-oxyamino phenylarsinico - Composto 190)
O STOVAR SOL tem sido estudado em Paris, no Instituto Pasteur pelos Drs. Levaditi e Navarro-Martin e pelo Sr. Dr. Fournier, do Hospital Cochlin.

Presentação: Les Établissements Poulenc Frères apresentam o STOVAR SOL em vidros de 14 e 28 Comprimidos dosados à 0gr. 25 e em vidros de 20 comprimidos dosados à 0,01 para therapeutica infantil.

Novarsenobenzol Billon

(Dioxydiamidoarsenobenzol methyleno sulfoxylato de sodio)

Emprego de extrema simplicidade
em Injecções intra-venosas ou rectaes.
Innocuidade e Efficacia garantidas
por milhares de Injecções já effectuadas.

No tratamento da Syphilis, do Typho Recorrente, da Angina de Vincent, do Impaludismo, etc...

PREÇOS AO	0.15	0.30	0.45	0.60	0.70	0.90
PUBLICO	3.400	4.200	5.000	5.900	7.300	8.200

NARSENOL

(Novarsenobenzol em comprimidos)

Indicações: As mesmas do que o Novarsenobenzol Billon.

Presentação: Em vidros de 30 Comprimidos de 0gr. 10.

LUATOL

Solução aquosa e suspensão de tartro-bismuthato de sodio e de Potassio (sal solavel) para o tratamento da Syphilis pela via intramuscular.

Presentação: Em caixinhas de 10 amp. de 1 cc. (aquoso) ou 12 amp. de 4 cc. (oleoso) dosadas à 0gr. 10 por cc.

Em todos os casos de Syphilis arseno e mercurio-resistentes.

EPARSENO

(Preparado 132 do Dr. Pomaret)

Solução estavel, estéril de amino arsenophenol para a arsenotherapie da Syphilis pela via intramuscular.

Indicações: Para todos os que não toleram o arsenico pela via venosa.

Presentação: Em caixinhas de 5 ampolas de 1 cc.

Existe o mesmo producto para Therapeutica Infantil:
Em caixinhas de Sampo. de 1 cc. a 0,05

Les Établissements Poulenc Frères
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VENDA ESPECIAL

914 ALLEMÃO

LEGITIMO (NEOSALVARSAN)

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I dose 0,15 - Tubo 4\$500	IV dose 0,60 - Tubo 7\$000
II dose 0,30 - Tubo 5\$000	V dose 0,75 - Tubo 8\$000
III dose 0,45 - Tubo 6\$000	VI dose 1,50 - Tubo 8\$500

Pelo correio - Tubo, mais \$500. Para compras de quantidades, descontos especiais. Aceita pedidos do interior. Rua Gonçalves Dias 54 - Rio

frequently used formulation was 1% aqueous solution of potassium arsenite ($KAsO_2$) (Fowler's solution). Other compounds often prescribed were arsenic trioxide (As_2O_3) in Asian or black pills and 1% Donovan's solution containing arsenious iodide ($AsI_3 + HgI_2$). It sparks one's curiosity to verify that arsenic trioxide, after being abandoned for decades, reemerges in the 21st century as one of the drugs prescribed to treat acute promyelocytic leukemia.¹⁴

Trivalent organic arsenicals – In 1907, after many years of research, Ehrlich and Hata introduced the arsphenamines in the treatment of syphilis through Salvarsan®, also known as preparation 606 since it was the six-hundred-and-sixth product investigated in their studies.^{15,*****} The brand name reflected their hope to save humanity from the plague of syphilis. Later, the arsphenamines lost importance with the development of other arsenicals that were less toxic, such as neoarsphenamine (Neo-Salvarsan® or 914) and oxyphenarsine chlorhydrate (Arsenox®). After the 1940's, with the advent of penicillin, all these compounds were abolished from the anti-syphilitic armamentarium.

Based on his observations, as of 1924, Pupo reported treating three patients with the mucocutaneous form of American tegumentary leishmaniasis with aminoarsenophenol (Eparseno®), and the results were superior to those obtained so far with emetic tartar. This finding was quite auspicious because arsphenamines and neoarsphenamine were considered a complete failure in the therapy of leishmaniasis.¹⁶

Pentavalent organic arsenicals – acting by reduction, their use in luetic patients was restricted to cases of neurological and prenatal syphilis (Stovarsol®). Cacodylates were the compounds better known in this group and widely employed in Dermatology.

It is worth mentioning that As may be present in some current homeopathic products, which are

resulting from arsenicism.¹² The black foot disease, an endemic peripheral vascular disorder leading to gangrene is intrinsically related to exposition to As in well water in Taiwan.¹³

Industries represent another source of As, particularly lead, gold, silver, copper, zinc and cobalt foundries. Arsenic pruritus or smelter's itch triggered by contact with arsenic trioxide (As_2O_3) is a classic symptom. Other exposition sources include glass, enamel, coating, textile and leather manufactures, agricultural products, such as insecticides, pesticides, herbicides and wood preservatives.

The medical source of As was extremely broad and diverse, as it can be seen in the advertisements of the first issue of the *Anais Brasileiros de Dermatologia* herein copied. The main formulations may be broken down as follows:

Trivalent inorganic arsenicals – the most

***** Ehrlich P, Hata S. Die experimentelle Chemoterapie der Spirillosen. Berlin: Julius Springer, 1910. *Apud* ¹⁵

São três comprimidos em dois dedos d'agua!

TREPARSOL

O novo arsenical da SYPHILIS

Tratamento da SYPHILIS em qualquer período
sem injeção
sem dor
sem dieta

Medicamento de acção rápida e poderosa
Cicatrizante imediato
Espirilicida eficaz
Tonicante energético

Cada tubo de TREPARSOL contém 30 comprimidos rigorosamente dosados

considered relatively harmless by their advocates. A recent report described three patients who developed arsenicism after taking homeopathic medication containing As. One of the patients progressed to quadriplegia due to toxic polyneuropathy.¹⁷

CLINICAL SPECTRUM OF ARSENICISM

Patients suffering from arsenicism may present only skin alterations, or isolated systemic manifestations or, like in most cases, associated cutaneous and systemic manifestations.

Gastrointestinal disorders are characteristic of the acute phase and start as incessant vomiting and intense colic. Plasma transudated from capillaries is deposited in the intestinal lumen where it coagulates. As peristalsis increases, abundant diarrhea is observed with typical "rice water stools".

Neurological manifestations are usually observed in massive or repeated intoxications and comprise arsenic motor-sensitive polyneuritis. The initial symptoms are paresthesias, followed by motor disorders in the lower limbs.

Splenic hyperemia was the basis for using As to treat anemia. It used to be prescribed, and has been

presently revived, in cases of leukemia for decreasing the excessive production of leukocytes.

The undeserved reputation of tonic that As held in the past was most probably based on initial toxic vascular actions. The hidden edema caused by capillary lesions was often mistaken for weight gain.

There is a long list of internal malignant neoplasms related to As, comprising tumors in the digestive, genital and urinary tracts, lungs and upper airways.

Arsenic produces its numerous and diverse cutaneous manifestations over an extremely variable period of latency, ranging from a few days to 30 years or even longer. Definitely the most characteristic manifestations are palmar and plantar keratoses, which are usually multiple, symmetric and punctiform, preferably located on the thenar eminence, lateral aspects of palms, base and sides of fingers, soles, heels and plantar aspect of toes.

Arsenical melanoderma may sometimes have an early onset and is manifested in two different forms. Small brownish spots that tend to be confluent, leaving normal skin islets or telangiectasias and achromic atrophic points, correspond to spotted arsenical melanosis. On other occasions, darker color is observed in areas that are normally hyperpigmented (areola, axilla, inguinal region and perineum) or subject to pressure (waist and midthorax in women) - this corresponds to diffuse arsenic hyperchromia. In both cases, the pigment involved is melanin, which is in the upper dermis.

The arsenic epitheliomas have unique features that differ them from skin cancer of other causes. They may manifest as basal cell, squamous cell, mixed or *in situ* (Bowen's) epithelioma and some patients simultaneously present these different types or an association of skin and extracutaneous tumors. They appear in any region, even in areas not commonly affected by these malignancies, such as palms and soles (usually over arsenic keratoses). The most common clinical manifestation of arsenic malignant tumors is basal cell-type superficial multiple epitheliomatosis.^{18,19}

Arsenic is a protoplasmatic poison that exerts its toxicity by inactivating approximately 200 enzymes, especially those involved in the production of cell energy and those related to DNA synthesis and repair.²⁰ However, the pathogenesis of arsenic cancer is still obscure. Despite the fact that recent studies have been able to detect chromosomal aberrations and sister chromatid exchange in individuals exposed to As,²¹ and also highlight the increasingly relevant role played by reactive oxygen species produced by arsenic compounds in inducing skin tumors,²² there is still a long way ahead for the better understanding of this issue. □

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