Arsenic Curiosa and Humanity

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Abstract: Despite its undoubted toxicity, arsenic is a much-used element, finding applications in agriculture, industry, and medicine. Arsenic as a poison has a prominent role in plays and novels as well as in real life. In medicine, arsenic was so widely used in the 19th century as a cure-all that it has been termed a "therapeutic mule." Some arsenic compounds are still used in the treatment of parasitic disease. Moreover, in a striking development for a material regarded as a carcinogen, arsenous trioxide (brand name, Trisenox) was recently approved for treatment of leukemia. Arsenic has had a profound overall impact on human lives.

Introduction

Arsenic and arsenic compounds have had a long and Janus-type interaction with humanity; on the one hand they have been extensively utilized, but on the other hand their poisonous properties have caused misery and many deaths. While minerals containing arsenic were known from the earliest times, elemental arsenic was not conclusively identified until 1649. The mineral, realgar, As_4S_4, was probably described as early as the 4th century BC by Aristotle. The name derives from an Arabic word meaning "powder of the cave." Similarly, the mineral orpiment, As_2S_3, has a long history, the name being an adaptation of the Latin, *auripigmentum*, meaning "gold pigment." The etymology of arsenic itself is complex but traces to the Greek word, *arsenikon* (*arshenikon*) or *arrhenikon* used for "yellow orpiment," a word tracing back even further to words from Syriac, Middle Persian, and Old Iranian. In addition, the similar Greek word, *arsenikos* (*arshenikos*) or *arrhenikos* meaning "masculine, male" also contributed to its naming.

The highly poisonous nature of arsenic compounds has been known for centuries. The colorless and tasteless compound, arsenious oxide (arsenic(III) oxide, also termed arsenous oxide and often simply white arsenic or arsenic), was at one time employed as a rat poison; because it was easily available; it was also commonly used for criminal purposes, both in real life and in fiction (see later in this article).

Chemistry is so vast a discipline that most students are exposed to little more than the basic chemical facts about arsenic and its compounds; however, arsenic has had a very pervasive influence on humanity in many ways, perhaps more so than most other metals and metalloids. The name, arsenic, is essentially a household word, being synonymous with poison. Arsenic figures prominently in literature as well as in industry, the sciences, in medical practice, and in everyday life. We recount here some of the many curious influences of arsenic on human lives, influences not usually found in chemical textbooks.

Nonmedical Uses for Arsenic and Its Compounds

Over the years, arsenic compounds have found application in the manufacture of cosmetics, foods, glass, insecticides, medications, pigments, pyrotechnics, rodenticides, and wood preservatives, as well as in embalming, metallurgy, tanning, and taxidermy. There have, in consequence, been many cases of poisoning due to industrial uses of arsenic. Although such incidents are declining, the Toxic Exposure Surveillance System reported for the USA in 1998 that there were 956 nonpesticide related arsenic exposures and 339 arsenic-containing pesticide exposures. In the nonpesticide category, there were 4 fatalities [1].

Since about 1991, almost all of the arsenic metal and compounds used in the United States have been imported, mainly from China. In 1997, for the United States, the imported amounts were 1,200 metric tons of arsenic metal, 30,000 tons of arsenic trioxide, and 1 ton of arsenic acid. Of these quantities, 88% of the metal was from China, the remainder being from Japan, Hong Kong, and other countries. For arsenic trioxide, 48% came from China, 20% from Chile, 12% from Mexico, and 20% from elsewhere. Prices for arsenic trioxide in 1997 averaged 26 cents per pound, and for metal from China, 44 cents per pound.

Some old technologies requiring arsenic are clearly declining. For instance, although arsenic was alloyed with lead in the making of shot to harden the metal and to ensure roundness, concerns over environmental toxicity of lead have caused a rapid decline in the use of lead shot and in many places (e.g. the USA) a ban on its use in hunting water fowl. Nevertheless, arsenic is still a component of the lead alloys used in batteries. Embalming with the aid of arsenic (see later) has been discontinued and arsenical pigments are no longer freely available. Moreover, inorganic arsenic trioxide has been replaced as a weed killer by other materials, including some organic compounds of arsenic. The present day use of arsenic and its compounds varies from country to country. In the United States, the major amount is in wood preservation, particularly as chromated copper arsenate (about 16,000 metric tons). Smaller amounts are involved in glass manufacture (900 tons) and for the production of nonferrous alloys (700 tons). This latter category includes one of the new applications for arsenic, in the semiconductor industries where growing crystals (e.g., of germanium, silicon) are "doped" with minute traces of arsenic introduced from the very toxic gas, arsine, AsH_3. Gallium arsenide (GaAs) and indium arsenide (InAs) are

also components of diodes, lasers, and transistors. At this time, about 15 metric tons of high-purity arsenic are used in semiconductor manufacture each year in the United States.

A surprisingly large amount of arsenic, about 5,500 tons, is consumed in the manufacture of herbicides and animal feed additives for agricultural purposes. The materials are sodium salts of dimethylarsinic acid, $(CH_3)_2AsO(OH)$, or monomethylarsinic acid, $CH_3AsO(OH)_2$. The former, also known as cacodylic acid or dimethylarsonic acid, is usually referred to as DMAA and the latter, as the disodium salt, is DSMA and as the monosodium salt, MSMA. A chemical catalog gives the price of pure DMSA as $104.35 for 100 g, but doubtless the price is lower on the DMAA used in agriculture. These derivatives find extensive application in growing cotton and as selective herbicides in facilitating the growth of desired grasses, for example, for golf courses. A variety of organic arsenic compounds, often related to arsanilic acid (phenylarsonic acid, $C_6H_5AsO(OH)_2$), is used in the pig and poultry industries as anthelmintics, and as antirickettsial and antihistomonad agents.

Unfortunately, Lewisite, dichloro(2-chlorovinyl)arsine, Cl-CH=CH-$AsCl_2$, and other arsenic compounds were deployed as poison gases in World War I; they are vesicants and respiratory and systemic poisons. Similar chemical warfare agents were prepared for retaliation in the event that they were used against the allies in World War II; fortunately, this did not happen. Today, sets of vials containing small amounts of sulfur mustard and Lewisite, used by the US army in training for identification of chemical warfare agents from 1928–1969, must be destroyed. However, to do this, a minefield of complicated technical, legal, environmental, and societal issues must be traversed [2]. One part of the difficulty is that these kits are classified as chemical warfare material.

Medical Uses for Arsenic Compounds

Several arsenic compounds have been utilized in medicine. In early times in the East, a mixture of orpiment, slaked lime and water was favored as a depilatory; the action resulted from formation of a hydrosulfide of calcium. Moreover, a paste of realgar was recommended by Hippocrates (460–377 B.C.) for treatment of ulcers. There are many other medical examples of the early applications of arsenic compounds [3]. The 1899 *Materia Medica* prepared by Merck & Co. lists "acid, arsenous" for internal treatment of "malarial fever, skin disease, chorea, neuralgia, gastralgia, uterine disorders, diabetes, bronchitis" and applied externally "to remove warts, cancers, etc." [4]. Arsenic halides are also listed with the bromide indicated for treatment of diabetes. Two arsenic preparations have eponymous names. One was Donovan's solution (a mixture of arsenic and mercuric iodides), which found dermatological use. The most famous was Fowler's solution (potassium arsenite), said to be a most convenient form for administering arsenic; the 1899 *Materia Medica* cautions, however, "Never give it on an empty stomach!." Fowler's solution was apparently a general cure-all in Victorian times. Both Donovan's and Fowler's solutions are still described in the 1996 Merck Index (12th edition).

Fowler's solution has a fascinating history [5]. In the reign of King George III, a patent medicine was claimed as an "infallible remedy for agues and intermitting fevers, even in the most obstinate cases where the bark and every other medicine hath proven ineffectual" (the bark would have been Peruvian Bark, i. e., quinine). This medicine was prepared from "cobalt," probably a pyrite ore containing arsenic. The "patent ague drops" or "tasteless ague and fever drops" were occasionally employed in hospitals. In 1783, Dr Fowler suggested to the apothecary, Mr. Hughes, to duplicate the preparation; Hughes apparently realized the role of arsenic and prepared an alkaline solution of white arsenic that did have therapeutic properties. It became known as Fowler's solution and was first listed officially in the London pharmacopoeia of 1809, perhaps it can be claimed as a very early example of a generic drug. In addition to being a general cure-all, it found application specifically as an antineoplastic (antitumor agent) and for dermatological purposes.

In fact, in the 19th century, arsenic was a major component of the *Materia Medica*, being used both internally and externally, and it has been dubbed the "therapeutic mule" [3]. One physician wrote "If a law were passed compelling physicians to confine themselves to two remedies only in their entire practice, arsenic would be my choice for one, opium for the other. With these two I believe one could do more than any two of the pharmacopoeia" (quoted by Haller) [3]. The popularity of arsenic increased with the knowledge of the Styrian arsenic-eaters (see later).

It has been suggested that the symptoms of Charles Darwin's mysterious malady match those of arsenic poisoning [6]. It is known that he medicated himself with arsenic early in life to treat eczema of the lips and to cure a not clearly specified hand ailment (possibly "a tremor with some degree of dermatitis"). However, there is no real evidence for his regular, long-term consumption of a material such as Fowler's solution. Moreover, as was common in his day, he was frequently treated with another poison, calomel, Hg_2Cl_2.

Early in the 20th century, "arsenious acid" (presumably a solution of arsenious trioxide) was injected into mice infected with parasitic protozoans (trypanosomiasis). Both the trypanosomes and the mice were killed; however, the mice had "died cured" suggesting that arsenic compounds had potential in chemotherapy [7]. In 1905, sodium *p*-aminophenylarsonate $[NH_2C_6H_4AsO(OH)(ONa)]$ was found to have a modest effect on human trypanosomiasis and the material was (optimistically!) named "atoxyl." The current edition of the Merck Index gives no present-day use for atoxyl but includes the warning, "*Poisonous!*." From these beginnings, Ehrlich initiated extensive investigations of the use of organic compounds of arsenic in chemotherapy. One compound with the laboratory number of 606, was arsphenamine (salvarsan, $C_{12}H_{12}N_2O_2As•2HCl•2H_2O$) the famous "magic bullet" for treatment of syphilis. Ehrlich's work with these arsenic compounds inaugurated the era of synthetic chemotherapy. Like atoxyl, arsphenamine was quite toxic and had the reputation of terminating the disease by eliminating the sufferer. The treatments were lengthy and very unpleasant, arsphenamine being injected intravenously over a one-hour period. Courses of the arsenic treatment were alternated with "mercury rubs" or intramuscular mercuric succinamide (mercuric imidosuccinate); hence the aphorism, "two minutes with Venus, 2 years with mercury" (ascribed to J. Earle Moore) [8]. Later, less toxic derivatives were developed, such as 3-amino-4-hydroxyphenylarsinoxide hydrochloride (also known as oxophenarsine hydrochloride and Mapharsen), and the treatment became somewhat more bearable.

In the 1940s, the drug melarsoprol, 2-[4-[(4,6-diamino-1,3,5-triazin-2-yl) amino]phenyl] -1,3,2-dithiarsolane-4-meth-

anol, began to be applied in treatment of African trypanosomiasis. It was used after treatment with pentamidine or suramin because, unlike these materials, it crosses the blood–brain barrier and is effective against trypanosomes in cerebrospinal fluid and the brain. A new drug, difluoromethylornithine, DFMO, finds some application but is not very effective against *Trypanosoma brucei rhodesiense.* Like all the other arsenicals, melarsoprol is quite toxic and causes death in about 5 or 10% of treated patients. Parasitic resistance to melarsoprol is increasing at this time [9].

Despite its nature as a poison, a crude arsenic preparation was a traditional remedy of Chinese practitioners [10], and a purified version of this medication was later developed at the Harbin Medical University for treatment of acute promyelocytic leukemia, APL. Again, despite being recognized as a carcinogen, physicians at Memorial Sloan Kettering Cancer Center began to apply arsenic trioxide (brand name Trisenox) in 1997 as treatment for APL with encouraging results. In September 2001, Trisenox received FDA approval for induction of remission and consolidation in APL patients refractory to or relapsed from retinoid and anthracycline chemotherapy and meeting certain other requirements [11].

The Arsenic Eaters and Cosmetic Use

Very small amounts of arsenic, about 12 to 50 μg day^{-1}, do feature in the diet of humans; the normal laboratory value for excreted arsenic in urine is < 50 μg day^{-1}. In a study of Japanese adults, much larger amounts of arsenic were excreted—mean value of 148 μg day^{-1}. These values probably represent a greater dietary use of fish and shellfish because these foods are known to have relatively high levels of arsenic. There is some evidence that arsenic is actually essential in the diet of some animals but there are no dietary recommendations for humans because its essentiality is questioned, as was that of selenium until the last generation.

The inhabitants of Styria, an Austrian province bordering on Yugoslavia and an important mining district, had a reputation in the 19th century for eating arsenic compounds—a condition termed arsenicophagy or arsenophagy. At that time it was stated that "Arsenic is thus consumed chiefly for two purposes—First, to give plumpness to the figure, cleanness and softness to the skin, and beauty and freshness to the complexion. Secondly, to improve the breathing and give longness of wind, so that steep and continuous heights may be climbed without difficulty and exhaustion of breath. Both these results are described as following almost invariably from the prolonged use of arsenic either by men or animals" [12]. Dr. Von Tschudi had drawn attention to the phenomenon in an 1851 Viennese medical weekly and his paper was discussed in *The Chemistry of Common Life* by J. F. W. Johnston in 1855 [3]. In 1860, Professor H. E. Roscoe (co-author with Schorlemmer of the famous *Treatise on Chemistry*) raised the question of arsenic-eating and possible habituation to arsenic with the Manchester Literary and Philosophical Society [13]. He had received some information from Professor Von Pebal of Lemberg and sought further details from members of that society. In the aforementioned *Treatise on Chemistry*, he and Schorlemmer gave specific instances of arsenic eating in Styria [14].

News of this practice spread quickly among the Victorians, and in addition to prescriptions by physicians (see earlier), they began to self-medicate themselves with arsenic "for everything from venereal disease to tapeworms." Indeed, the Victorians were surrounded with arsenic. It was used for rodent and insect control; sheep dips; grain steeping; and as dyestuffs for clothes, soaps, books, kitchenware, paint, artificial and dried flowers, leaves and fruits, stuffed animals, playing cards, children's toys, candles, paper and packaging, lampshades, wallpaper, and, amazingly, for confectionery, blancmanges, and other foodstuffs (as well as their wrappings) [15]. Earlier still, in the 18th century, arsenic was used as an aphrodisiac.

The Styrian arsenic-eaters began with less than 30 mg doses eaten two or three times a week and increased the dosage to about 130 mg. In some cases, the practice continued for forty years without apparent detriment. In one recorded case, a woodcutter was observed by a physician to eat about 300 mg of pure arsenious oxide; the next day, he "crushed and swallowed" another piece of about 370 mg. On the third day he was still enjoying his usual state of health [14]. Such amounts suggested that these individuals developed a significant tolerance to arsenic; in many cases, 65 mg of As_2O_3 is fatal. The question of habituation to arsenic received much discussion in the 1920s; one lengthy review concluded that it did not occur. Differing observations may have resulted from the fact that samples were of different particle size; experimental work in animals indicated that finely divided preparations are more toxic than coarse [16]. For further information, a recent account of the arsenic-eaters should be consulted [17].

While much of the discussion about arsenic-eating concerns the 19th and early 20th centuries, there is a mid-20th-century report of arsenic-eating by Austrian and Swiss mountaineers. In 1933, H. A. Schroeder, a physician, and two medical students were climbing in the Austrian Tyrol. The native guide took a handful of a blackish-gray crystalline material from an exposed rock, ate a gram or two and saved the rest for future consumption. The material was said to be "arsen," possibly elemental arsenic although no detailed identification was given. Similarly, J. J. Balassa, a Ph. D. candidate when a young man in Switzerland, observed mountaineers spread "arsen" over bread and butter for consumption as a tonic [18].

As just noted, arsenic consumption was believed to give "beauty and freshness" to the complexion and at one time was popular among prostitutes for "producing rosy cheeks" [19]. This cosmetic use is ascribed to arsenic-caused damage to blood vessels in the skin. In the 19th century, "Women not only drank Fowler's solution for their complexions but employed it as a cosmetic wash; others rubbed arsenic into their hair and scalp to destroy vermin, and there were those who actually purchased white arsenic as a hair-powder" [3]. Some physicians accepted moderate arsenic-eating by women so that a healthy appearance (*pour rajeunissante*) was obtained without the use of cosmetics. In a different situation, arsenic use in embalming bleached skin to an acceptable white and left the cadaver more supple (see later). Some face powders contained materials such as arsenic, bismuth carbonate, and white lead, as well as perfumes. In the *Devil's Dictionary* of 1911, Ambrose Bierce defined arsenic as follows with the addition of a verse by Joel Huck:

Arsenic, *n*. A kind of cosmetic greatly affected by the ladies, whom it greatly affects in turn.

"Eat arsenic ? Yes, all you get,"
Consenting, he did speak up;
"Tis better you should eat it, pet,
Than put it in my teacup."

In one recorded case, a violet powder containing 35 % of white arsenic killed a number of children at Loughton, Essex [20]. Powders for wigs contained arsenic as a preservative. Moreover, Fowler's solution used as a general tonic was also believed to be of benefit to the complexion.

Arsenic in Literature and Plays

The Oxford English Dictionary (OED) provides the first record of arsenic in an obscure 1310 publication mentioning orpiment (*de iiij libris de orpiment venditis*). From a more familiar source, arsenic features in Chaucer's *Canterbury Tales* (dated to 1386), specifically in "The Canon's Yeoman's Prologue and Tale," (the original spelling is *Chanouns Yemannes*). Although the Canon is indeed a cleric, he has apparently spent much time on alchemy. His Yeoman assistant does not think well of these activities, especially the many explosions that seem to happen. The Yeoman describes some of the alchemist's materials [21]:

Nat nedeth it for to reherce hem alle,-
Watres rubifying, and boles galle,
Arsenyk, sal armonyak, and brymstoon;
And herbes koude I telle eek many oon,

In David Wright's modern English translation [22], this becomes: "No need to reckon up the lot— rubeficated water, bull's gall, arsenic, sal ammoniac, brimstone; and if I wanted to waste your time, I could recite any number of herbs….." (to rubify means to redden). In addition, the four spirits of the alchemist were named as follows:

The firste spirit quyksilver called is,
The seconde orpyment, the thridde, ywis
Sal armonyak, and the ferthe brymstoon.

Or in translation, "the first spirit is called quicksilver, the second orpiment, the third sal ammoniac, and the fourth brimstone."

The OED also gives a reference to the poisonous nature of the mineral in a poem, *Du Bartas*, written in 1598 by Joshua Sylvester (1561–1618):

"Neither in Golden Platters doth he lick
For sweet ambrosia deadly arsenic"

In Samuel Johnson's *Dictionary of the English Language*, originally published in 1755, "arsenick" was defined simply as "a mineral substance, which is a virulent corrosive poison" [23].

There is a famous arsenic situation in Flaubert's novel, *Madame Bovary* (begun in 1851), where the central character commits suicide [24]. Flaubert, a doctor's son, names the agent as "arsenious acid," probably meaning arsenious trioxide. A little later, in 1864, the very prolific Victorian novelist, Mary Elizabeth Braddon, provided a different situation. In *The Doctor's Wife*, the wife of the title, Isobel Gilbert, contemplates the possible abandonment of her husband for a lover; however, this was "so far beyond her power of comprehension as the possibility that she might steal a handful of arsenic out of one of the earthenware jars in the surgery, and mix it with the sugar that sweetened George Gilbert's matutinal coffee" [25].

Agatha Christie's many 20th-century novels and stories frequently concern poisoning. So much so, in fact, that an entire book is devoted to the topic [26]. Christie's experiences as a hospital pharmacy dispenser during both World Wars probably provided much background material for her. Gerald describes arsenic as "the choice of professionals" and notes that Christie "incorporated arsenic with great regularity throughout her writing career." In fact, almost one quarter of Christie's novels contain some kind of reference to arsenic. One amusing case comes from the novel, *The Mirror Crack'd* (or in the UK edition, *The Mirror Crack'd From Side To Side*). One character, a potential murderer, added a little arsenic to her coffee to deflect suspicion and claimed the beverage tasted bitter so that she did not drink it. The flaw in this proceeding was soon recognized; as another character put it, "Arsenic has no taste."

Beginning in 1941, the play, "Arsenic and Old Lace" became very well known [27]. In this play, Martha Brewster takes no chances. Her infamous elderberry wine, contains per gallon, "one teaspoonful of arsenic, then (add) a half teaspoonful of strychnine and then just a pinch of cyanide." As nephew Mortimer notes, appraisingly, "Should have quite a kick." Perhaps less well known is the play by Dylan Thomas, "Under Milk Wood" [28]. It gives a portrait of a life in a small Welsh town named Llareggub. Although seemingly very Welsh with the double ell beginning, the name is fictional and carries an easily discovered joke perhaps suggesting the backward nature of the village. Among the many colorful characters is a schoolmaster, Mr Pugh, who contemplates the murder of Mrs. Pugh, a "needling stalactite hag and bednag of a pokerbacked nutcracker wife." As he takes her morning tea, Mr Pugh fantasizes:

"Here's your arsenic, dear.
And your weedkiller biscuit.
I've throttled your parakeet.
I've spat in the vases.
I've put cheese in the mouse holes.
Here's your…….[*Door creaks open*]
…….nice tea, dear."

Arsenic Poisoning Through the Ages

One of the earliest recorded examples of poisoning by arsenic was that of Britanicus by Nero in 55 A.D. The literature on this topic is now so vast that only a brief account of a few cases can be given here. For those with more interest, the book, *Poisons and Poisoners* [29] is a truly fascinating compilation.

In view of the common application of arsenic as a poison, there have been attempts to regulate the sale of arsenic compounds. For example, in Siena, in 1365, a statute made it illegal to sell "red arsenic" (*i. e.,* realgar) or corrosive sublimate to individuals under the age of twenty [30]. To purchase these materials, adults had to be well-known to the apothecary. Subsequently, the sale of arsenic compounds has come under some kind of governmental regulation almost everywhere.

Cesare and Lucrezia Borgia (c. 1476–1507 and 1480–1519, respectively) gained reputations as infamous poisoners in Renaissance Italy, particularly from the writings of some historians and novelists. It was alleged that a white powder, *La*

Cantarella, was used and that it contained arsenic. It was supposed to have a sugary and pleasing taste and could be added to food or drink. While, no doubt, there was much killing of political enemies in those days, it appears that some of the activities attributed to the Borgias have been exaggerated [31].

Arsenic was famous as a poison in France and it continued to be popular until the 19th century. It was called, "*poudre de succession*," inheritance powder. A sensational criminal case in France, "The Affair of the Poisons," began in 1679 and implicated individuals in the court of Louis XIV. This affair involved fortune telling, love potions, sorcery, witchcraft, and, of course, arsenic poisonings. The most well-known case is that of Catherine Deshayes Monvoisin, "*La Voisin*," a midwife and fortune-teller. She was convicted of sorcery and poisoning and burned at the stake in 1680. After her death, a special court, *chambre ardente*, was constituted to judge other cases of witchcraft and poisoning and the poison epidemic slowly came to an end [32].

In November of 1871, C.F. Hall, an Arctic explorer, and a diverse crew of Americans, Germans, and Eskimos were wintering the onset of the Arctic's cold, ice and snow at approximately 82 degrees N latitude in a small bay aboard their ship Polaris [33]. Their goal was to discover and/or attain the North Pole. Disagreements and rancor broke out among the crew and upon returning from a scouting trip, the mission's officer in charge, Hall, drank a welcomed cup of hot coffee and immediately fell ill with gastric pain and a violent sickness of his stomach. Symptoms worsened over the next week and included pain, vomiting, a numb and swollen tongue, paralysis, and what appeared to his shipmates as dementia. After a week he improved, grew more clearheaded, and even walked on the deck and updated the ship's logs. On the eleventh day after drinking the coffee, however, he suddenly became comatose and died the next day. He was buried above the permafrost on the nearby shoreline in a well-marked grave. In 1968, a special trip was taken by Hall's biographer, Chauncey Loomis [34], the corpse dug up, and samples taken of Hall's fingernails and hair, both of which can provide a record of heavy metal ingestion. Analysis by neutron activation analysis clearly indicated a large concentration of arsenic and showed an increase in As in the newest tissues of the subject's fingernails suggesting that Hall had been poisoned with arsenic during the last two weeks of his life [34]. As detailed above, 19th-century medical practices included arsenic in various formulations. The medical supplies of the Polaris almost certainly included a version of Fowler's or Donovan's solution and one of Hall's antagonists on the ship was a medical doctor. Loomis suggests that the ship's doctor is the most likely (long-dead) suspect; however, the presence of As-containing medicines on board also meant that Hall could have accidentally poisoned himself in an effort to treat symptoms of his original malady that coincidentally began shortly after drinking the mug of coffee. Two more recent books strongly favor the murder hypothesis [35, 36] but a reviewer finds that they add little if anything to the account by Loomis [37].

Two fascinating books concern some USA murder cases in the 19th and 20th centuries [38, 39]. In New Haven County, Mary Stannard was murdered in 1876. Incorrectly believing herself pregnant, she sought help from her lover, the Reverend H. H. Hayden. Instead of inducing an abortion, he administered arsenic, perhaps as much as one ounce and, as well, he both clubbed her and slit her throat. Arsenic was found in Stannard's body. When Hayden was put on trial, advanced forensic evidence (for that time) showed that crystallographic examination could distinguish arsenic samples from different sources and this evidence implicated Hayden as a liar. Despite this evidence, a Superior Court jury apparently paid more attention to the social status of lay witnesses. They deadlocked with eleven for acquittal and one brave, young farmer for second-degree murder. A retrial could have been held, but was not; essentially, Hayden was acquitted.

In another New Haven case, forensic evidence indicated that between two and four grains of arsenic had been ingested by Jennie Cramer prior to her death. She had been violently raped and was found floating in water; however, medical testimony indicated that she had not drowned. Suspicion fell on two cousins, James Malley and Walter Edmond Malley, who had double dated with Cramer and Blanche Douglass (a prostitute). There was little evidence as to when arsenic had been obtained or administered and there were some suggestions that Cramer might have been an arsenic-eater. The Malleys and Douglass were put on trial, but were found not guilty, the jury requiring less than an hour for their decision.

"The Poison Widow Case" involving the "Great Arsenic Murder Ring" occurred from 1931 to 1938 in a South Philadelphia neighborhood of mostly immigrants with little or no education [39]. There was a strong component of old world magic and witchcraft (*la fattura* and *la fattuchieria*) with potions and pills being freely dispensed. There were twenty murder victims, mostly male and mostly by poison; generally, the poisoners hoped to collect insurance policies held on their spouses— a strong revival of the use of "inheritance powder." With evidence of arsenic in the bodies of victims, some 30 individuals were put on trial for the murders. Three were sentenced to death, two actually being electrocuted; the third had his sentence commuted to life imprisonment by a parole board. Another individual, found guilty of first-degree murder, died in prison before sentencing. Eleven individuals were sentenced to life imprisonment and nine to various jail terms. In most cases, the full term of the sentence was not served. Three defendants were acquitted outright and in three other cases there had been jurisdictional problems. Altogether, 24 defendants were found guilty to some degree of murder; the majority of the cases involved arsenic poisoning.

After the end of World War II, in the spring of 1946, Jews who had escaped from the Jewish Ghetto in Vilna, Lithuania, planned and carried out a revenge act against German Nazis incarcerated by the Allies in a former German prison camp, Stalag 13. As in many other places in Europe, almost all the Jews in the Vilna ghetto had been systematically killed by the Germans except for a few who joined the resistance fighters in the latter part of the war. The German prisoners in Stalag 13, members of the Nazi Elite Guards, were waiting for the results of Allied war trials for war crimes [40]. With arsenic obtained from French chemists and smuggled into Germany, three thousand loaves of bread to be shipped into the camp were painted with a solution containing arsenic, possibly as arsenious trioxide in water. The results were reported a week later in the US press: over 2200 prisoners had taken ill from arsenic poisoning at Stalag 13. The smuggled arsenic containers were later found in the bakery where the bread had been prepared. Although the exact death toll is cloudy, some who have looked at this history suggest that thousands died in the attack [41]. Again, the tasteless and therefore dangerous nature of arsenic oxide came into play.

Poisoning by arsenic continues into the 20th and 21st centuries, again with too many cases to detail all of them. A case report picturesquely titled "An Unhappily Married Man with Thick Soles," describes an individual who was initially diagnosed with Guillain-Barre syndrome in 1995 (this syndrome is characterized by acute peripheral nerve damage possibly caused by viral infection or immunization). Later, hyperkeratosis of his soles and palms, white transverse lines in his fingernails (Mees' lines), and other evidence including assay of samples of hair, nails, and urine, indicated arsenic poisoning. His wife confessed to adding ant killer to his food [42].

A celebrated case of mass poisoning occurred in July 1998 at a "matsuri" (summer festival) in Wakayama, Japan. Curry rice and other dishes were prepared locally by ladies of a neighborhood association. The rice was poisoned; there were four deaths and about seventy other people were sickened. Cyanide poisoning was first suspected but it was quickly found that arsenic had been added to the rice. Suspicion fell on Masumi and Kenji Hayashi, a wealthy couple somewhat aloof from the rest of the community. Masumi sold insurance and Kenji, who was unemployed in 1998, had had a termite extermination business. Masumi was charged with the four curry murders and attempted murder with arsenic of two others—bizarrely, one of the latter was her husband, Kenji. Both Hayashis were also charged with, and pleaded guilty to, fraudulent insurance claims based on exaggeration of injuries received some years earlier. Masumi had been involved in the rice preparation but had not eaten of it. Any motive is obscure. She had a history of temper tantrums and may have sought revenge after a reprimand for an oversight in the food preparation. Despite months of interrogation, she has never admitted the crime. Traces of arsenic were found in her hair and in her house, the latter possibly a relic from the termite extermination business. The trial and appeals will apparently continue well into the 21st century [43].

Judy Buenoano (formerly, Judy Goodyear) found guilty of the murders of her husband, son, and a boyfriend, was electrocuted by the State of Florida on March 30, 1998. Her husband had returned from Vietnam in 1971, but soon sickened and died. Buenoano then moved in with Bobby Joe Morris who likewise sickened and died. She gave "vitamins" to yet another boyfriend who had the good sense to have them analyzed; arsenic was found. She apparently hoped to collect on a large insurance policy. Her son had been paralyzed with arsenic poisoning and, wearing heavy leg and arm braces, was pushed out of a canoe in 1980. She was also suspected of a poisoning murder in Colorado in 1978, but was not charged in view of the Florida death penalty [44].

Arsenic recently made headlines in The New York Times (July 12, 2000) and elsewhere with events concerning a physician, Michael Swango. While working as a paramedic in Quincy, IL, he was convicted of aggravated battery and served two-and-a-half years of a five-year sentence [45]. He had sprinkled nonlethal amounts of an arsenic-based ant killer on doughnuts and in coffee consumed by co-workers. There were mysterious hospital deaths at Ohio State University Hospital and at the VA Medical Affairs Center in Northport, NY, when he worked at those institutions. He went to Zimbabwe in 1993 and was there suspended from his position at a rural hospital when five patients under his care died in suspicious circumstances. By now, it appeared most likely that Swango was, in fact, a dangerous serial killer. When he re-entered the United States in July 1997, apparently to obtain a visa en route to a position in Saudi Arabia, he was arrested and held on some minor charges. In September 2000 he pleaded guilty to killing 3 patients and was sentenced to life in prison without parole.

Arsenic Poisoning of Celebrities

There has been much discussion as to whether Napoleon died from natural causes (stomach cancer) or was the victim of arsenic poisoning. There are two arsenic scenarios: accidental poisoning from wallpaper pigments [46] or a deliberate conspiratorial act of poisoning by an agent of the Bourbons to ensure that Napoleon would never again return to France [47].

In the 19th century, it had been realized that wallpapers decorated with green, arsenic pigments could cause death, especially to the inhabitants of damp rooms containing these papers. Initially, these deaths were attributed to particles of arsenic being stripped from the wallpaper, but in 1893, an Italian physician, Bartolomeo Gosio, demonstrated that certain fungi, growing in the presence of arsenic-containing materials, produced a highly toxic, volatile material. This so-called "Gosio Gas" was produced particularly efficiently by the organism now known as *Scopulariopsis brevicaulis*. It was shown many years later to be trimethylarsine, $(CH_3)_3As$.

One possibility is that Napoleon ingested arsenic from wallpaper by this mechanism during his exile at Longwood House, St Helena. Although an actual wallpaper sample was located and found to contain a toxicologically significant amount of arsenic (0.12 g m^{-2}), it would be expected that other individuals would have been affected. Moreover, the evidence concerning arsenic in samples of Napoleon's hair is contradictory (see below).

The champion of the conspiracy theory, Dr Ben Weider (President of the International Napoleonic Society), argues that Napoleon died from cyanide poisoning following chronic arsenic intoxication. The villain in this scenario was the Comte de Montholon, apparently a scheming and unscrupulous individual. He first initiated a "cosmetic phase," beginning five years before Napoleon's death and possibly even before his exile, in which arsenic was regularly introduced into Napoleon's wine. This was followed by a complex "lethal phase." This two-phase operation beginning with arsenic was to break down Napoleon's health giving the appearance of normal deterioration so that the final act of assassination was not obvious. Tartar emetic was administered, beginning about March, 1821, to induce vomiting; however, over a period of time sufficient corrosion of the mucous lining of the stomach was induced leading to the opposite result, an inability to vomit. Beginning in April, 1821, a drink termed "orgeat" was administered to quench Napoleon's thirst. This fruit-flavored drink was prepared from almonds and so could have contained some mandelonitrile, $C_6H_5CH(OH)CN$, the compound formed from benzaldehyde and HCN. Finally, on May 3, 1821, Napoleon received a relatively large dose of 10 grains of calomel, ostensibly to relieve constipation. Reaction of Hg_2Cl_2 (calomel) and mandelonitrile (or its decomposition product, HCN) may have produced mercury cyanide. Since Napoleon was unable to vomit, this toxic cyanide was retained and led to his death on May 6, 1821. This theory was supported by the fact that a single hair of Napoleon, obtained post-mortem, showed high arsenic levels in certain segments ranging from a low of 2.8 ppm to a high of 51.2 ppm.

The analysis of hair for arsenic is technically difficult. It has been recommended that at least 1 g of hair should be used and that careful washing is necessary to remove external contamination. The use of individual hairs or sections of a single hair is said to be unreliable as an index of toxicity and there are known to be large inter- and intra-hair variations. The analysis is done either by atomic absorption or neutron activation spectrometric analysis. A recent critical review of results on hair samples, claimed to be those of Napoleon, includes 30 measurements with sample dates ranging from 1805 to post-mortem material from 1821 [48]. There is much variation in the results. The highest value during his lifetime was 76.6 ppm (hair from July 14, 1816) and for post-mortem hair, 51.2 ppm. The lowest lifetime value was 4.9 ppm (July 13, 1817) and from post-mortem hair, 1.4 ppm. Clearly many of these arsenic levels are higher than those presently observed in individuals not exposed to arsenic; however, interpretation of the levels of arsenic is complicated by the lack of control samples from Napoleon's entourage and even of control samples from the general population at that time.

There are several possibilities, not involving a conspiracy, to account for the high values—arsenic from the burning of coal, from cosmetics (hair, face, and wig powder, see above), from the use of Fowler's solution, from tartar emetic contaminated with arsenic, from Gosio Gas, and even from the possible addition of arsenic as a preservative for hair samples. It appears to have been overlooked in this controversy that Napoleon has been reported to have become an arsenic-eater "from fear of being poisoned" [3]. A Dr. C. Boner, in 1856, claimed that he was told that "Napoleon was in the habit of taking it, to insure himself against being poisoned," and that such a story was confirmed by others.

Another argument strongly advocated for the conspiracy theory is that many of Napoleon's symptoms can be considered to be those of arsenic poisoning and Weider has challenged the autopsy conclusions that Napoleon died from stomach cancer. Again, there are alternative explanations. Moreover, Napoleon did not have the skin pigmentation and hyperkeratosis of the palms of the hands and soles of the feet or the peripheral neuropathy usually observed in arsenic poisoning. It is possible that Napoleon did die from carcinoma of the stomach complicated by gastric bleeding (probably precipitated by the large dose of calomel) with inadvertent arsenic poisoning exacerbating his medical problems. The controversy remains [48–52]. Ben Weider and the International Napoleonic Society propound conspiracy with religious fervor. The Napoleonic Society of America, with R. Snibbe as President, has been quoted in *Science* as saying that the arsenic conspiracy theory is "complete hogwash" [53].

Almost 3 decades after Napoleon's death, President Zachary Taylor died suddenly in 1850. A lingering suspicion of arsenic poisoning in his case was made very unlikely when his body was exhumed in 1991. Analyses of hair and finger-nail samples were carried out at Oak Ridge National Laboratory, but the arsenic levels were not abnormal [54].

The case of Raphaelle Peale (1774–1825), an important American still-life painter, involves arsenic in the workplace. His father, the more famous Charles Wilson Peale (1741–1827), owned a natural history museum where Raphaelle worked as a taxidermist. Although the father imputed Raphaelle's many medical problems to gout and excessive drink, it is now clear that he was a victim of both arsenic and mercury poisoning. Raphaelle was well aware of the dangers of arsenic and placed numerous signs in the museum reading "Do not touch the birds, they are covered with arsnic [sic] Poison" [55].

Another celebrity, Clare Boothe Luce, was definitely poisoned by arsenic when she was the United States Ambassador to Italy; the illness hastened her resignation in 1956 [56]. Because the poisoning might have been deliberate, a CIA team made investigations in Rome—such a possibility would have influenced the delicate U.S.A.–Italy relationship at that time. It turned out that this was a case of poisoning by particulate arsenic. She slept in a room (not previously used as a bedroom) with a decorative, suspended ceiling containing arsenic-laden materials. On the floor above, a washing machine caused vibrations and particles containing lead arsenate fell as a "gray dust." One biographer has noted a certain irony; she and her husband, Henry, had "long since been dubbed 'Arsenic and Old Luce'" [57].

Arsenic and Drinking Water

Arsenic minerals are widely but sparsely distributed; the earth's crust contains about 5 g per ton. In terms of overall elemental abundance, arsenic ranks twentieth. There is much variation in the arsenic level at any particular locality and, consequently, drinking-water supplies can contain variable amounts of arsenic, ranging from low and presumably harmless levels to high and very dangerous ones, (e.g., 1 ppm). The latter level has led to a major public health crisis in West Bengal and Bangladesh [58]. Until about a decade ago, individuals in those countries collected water for drinking from ponds, streams and rivers. Such sources were subject to microbial contamination resulting in many cases of dysentery, typhoid, cholera and hepatitis. With the laudable intention of providing water free from microbial contamination, many wells were drilled; today there are over 2 million wells both public and private. Beginning in 1992, it was realized that many of these wells yielded water with high levels of arsenic, in some cases, up to 1 mg L^{-1}. Anywhere from 20 to 70 million people may be at risk, and there has already been widespread death and disease as a result of arsenic poisoning. The World Health Organization stated in 1997 that this "major public health issue" should be dealt with on an "emergency basis"; steps to test water supplies and to find alternatives were initiated and the program was further expanded in 1999 [59].

A newly released report from the National Academy of Sciences (NAS) has re-evaluated the risks of arsenic in drinking water [60]. The NAS risk assessment compared two different populations, one As-exposed and another, in a different region, relatively unexposed to As in drinking water. This risk assessment technique differed from the method that has been used by the Environmental Protection Agency (EPA), which compared exposed to unexposed subjects inside the same study population. The NAS cancer risk evaluations were higher than those of the EPA and assessed a 1 in a 1000 increase in the chance of bladder or lung cancer for someone with an arsenic concentration of 3 ppb in their drinking water at a consumption volume of approximately 1 L day^{-1}. At 10 ppb As, the NAS study assessed a 3 in 1000 increased chance of cancer [60]. A maximum permissible As concentration of 10 ppb was the newly promulgated EPA regulation level of arsenic in January 2001 for all U.S. drinking water supplies. This regulation was withdrawn in March 2001, and plans for issuance of a revised arsenic limit were set for February 2002

[61]; however, the original 10 ppb drinking-water standard was promulgated by the EPA in October 2001.

Another unexpected situation has arisen in connection with embalming. Prior to the Civil War, embalming was used rarely; however, the war created a logistical problem in view of the large number of dead and the desire of many families to have their relative's remains returned home from the battlefields for burial. A Dr Thomas Holmes had set up an embalming practice in Washington DC, treating up to three bodies per day at a charge of $100. Eventually, civilian embalmers using his methods set up facilities next to the medical tents on the battlefields. After the war, the practice took hold and spread rapidly [62].

Holmes, regarded as "the father of modern embalming" used arsenic as the preservative. A still well-preserved head and upper torso prepared by him in the 1850s has been shown to contain 28,000 ppm of arsenic (these remains are in the collection of the Armed Forces Institute of Pathology). In general, the embalmers used anywhere from 4 ounces to 12 pounds of arsenic in their work. Arsenic left the cadavers relatively supple, hence easy to pose, and bleached skin to an acceptable white. One forensic disadvantage of the use of arsenic was that it would conceal cases of deliberate poisoning by arsenic. As formaldehyde became more readily available, some embalmers regarded its fumes as more dangerous than the arsenic it eventually replaced. Because both wood and metal coffins degrade over time, arsenic from cemeteries containing many individuals buried from about 1880 to 1910 may be a significant source for contamination of ground-water supplies.

Ground water has also been contaminated with arsenic as a result of industrial operations. In one case, manufacture of organic arsenic compounds as herbicides and fungicides (as well as other materials) caused a severe environmental problem requiring clean up as a "Superfund Site." Beginning in 1966, the New Jersey Department of Health found that the Vineland Chemical Company was discharging untreated waste water, containing up to 67 mg L^{-1}, of arsenic into unlined lagoons. In consequence, there was infiltration of arsenic into ground water. This was not the end of the story because there were extensive problems with storage of waste material and with arsenic leakage from the floors of manufacturing buildings. Various court orders issued in 1977 required containment of waste salts and remedial work was still continuing as late as 1995 [63].

Further Curiosa

Many are the sources of arsenic in materials used by humans. Alcoholic beverages have caused some problems, including a mass poisoning in Manchester in 1901 involving beer containing arsenic. Investigation revealed that the arsenic source was sulfuric acid used to prepare glucose, a component of the fermentation mix. From 1962–1977, 12 documented cases of arsenic poisoning were studied at the Medical College of Georgia (Augusta) Hospital [64]. In five of these cases, moonshine was the source of the poison with samples of illicit whiskey showing arsenic levels of up to 500 μg L^{-1}. The arsenic was possibly derived from solder used in construction of the stills as well as from careless use of rat poison in close proximity to grain and mash stores. Wine has also been shown from time to time to contain arsenic and in most countries arsenic compounds are no longer used in grape cultivation.

Medicinal preparations have also caused problems. In 1975, 74 patients in Singapore were found to have arsenic poisoning. The source was a variety of anti-asthmatic herbal preparations, some containing up to 107,000 ppm of arsenic [65]. Potentially toxic levels of arsenic have also been found in traditional Chinese herbal balls sold in the U.S.A. These preparations are dissolved in water or wine for self-medication, for example, for fever, rheumatism, apoplexy, and cataracts. In the herbal balls examined, arsenic content ranged from 0.1 to 36.6 mg per ball; because the recommended dose was two balls per day, an unsuspecting individual could consume up to 73 mg per day of arsenic [66]. In the United Kingdom, Indian and Pakistani ethnic remedies have also been shown to be possible sources of arsenic. Powders intended to be taken as a single dose included one with arsenic trioxide, 105 mg; mercuric sulfide, 654 mg; and strychnine, 0.7 mg [67, 68]. As Martha Brewster's nephew had remarked, "Should have quite a kick." One man treated in this way for atopic eczema had progressive weakness of hands and legs and other symptoms of arsenic poisoning. After vigorous chelation therapy for five weeks, there was no objective improvement in muscle strength, and two years after the onset of symptoms he was still unable to return to work. The purveyors of these "remedies" need to be reminded of the classic injunction—"First do no harm."

Summary

It may be claimed fairly that in its influence on human lives arsenic is unique among the elements. In industry and agriculture and the raising of livestock it plays many beneficial roles. In medicine it has had a checkered career. In Victorian times arsenic was used as a general cure-all and cosmetic. A more specific application was Ehrlich's development of arsphenamine for the treatment of syphilis in the early 20th century, thus setting the stage for the general development of chemotherapy against various disease states. Although arsphenamine was displaced by penicillin, some organic arsenicals are still of value in the treatment of trypanosomiasis. Interest in the medical potential of arsenic has revived since arsenious trioxide (as Trisenox) was recently approved for the treatment of leukemia. The poisonous properties of arsenic have provided inspiration to many writers of fiction and plays. Unhappily, these properties have accounted for countless acts of murder and in the development of lethal gases for use in warfare. We can think of no other element that, on the one hand, has been of great utility, but on the other, has been so widely exploited both in literature and real life for its poisonous character.

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