FROM "BLUE PILLS" TO THE MINAMATA CONVENTION: MERCURY, A SINGULAR METAL

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Abstract

Mercury is a singular element, which was employed in the past as both a medicine and a medium to carry out the death penalty. These purposes are apparently contradictory, but they rely on a single property: its high toxicity. Mercury toxicity was already known when its compounds were used as medicine in past centuries for the treatment of various diseases, mainly bacterial infections. The most common knowledge related to mercury toxicity is the Minamata disease and the "mad hatter syndrome." However, throughout history, whether through accidental or intentional poisoning, mercury has made countless victims from murders, unsuccessful medical treatments, occupational diseases, accidents and environmental crimes. Instead of discussing the most famous and popular cases involving mercury contamination, we seek to report and discuss different uses of mercury compounds in the treatment of diseases, as well as peculiar and little-known cases of mercury poisoning over the 19th and 20th centuries. To conclude, it will be shown that even today there are cases of deaths due to mercury poisoning in mining, homes and even schools. Thus, there is currently a global effort, represented by the Minamata Convention, to minimize the damage caused by mercury to the environment and human health.

Introduction

The singular properties and famous toxicity of mercury make it a unique element: it is the single metal that is liquid at normal pressure and room temperature; it is a highly toxic heavy metal with the ability of bioaccumulation and biomagnification in the environment; and also, it is considered a global pollutant. This element, which has aroused scientists' curiosity for centuries, is connected to relevant events in history and is part of popular knowledge. Minamata disease, the expression "mad as a hatter," the antiseptic brand names Mercurochrome and Merthiolate: all these mercury-related terms may be and have been found in the present or recent past.

Mercury was employed in the past both as a medicine and in carrying out the death penalty. These purposes are apparently contradictory, but they rely on a single property: its high toxicity. Mercury made countless victims throughout history through both accidental and intentional actions: murder, unsuccessful medical treatments, occupational diseases, environmental crimes and accidents.

Famous scientists such as Sir Isaac Newton, Blaise Pascal and Michael Faraday, who suffered intensely from their pathologies, may have been victims of mercury poisoning because of their scientific work (1). Furthermore, when speaking about occupational poisoning in science, the tragic death of renowned American researcher Karen Wetterhahn in the late 20th century has shaken the scientific community.

Here, we present a review of some issues that make the study of mercury so fascinating, starting with its unique properties, and some aspects about the chemistry of mercury culminating with its toxicity. We present different uses of mercury compounds in disease treatments, as well as peculiar and little-known cases of mercury poisoning illustrated through medical reports from the 19th and 20th centuries. To conclude, lest the reader think that mercury poisoning and contamination are problems of past centuries, it will be shown that even today there are cases of deaths due to mercury poisoning in mining, homes and even schools (including children). Thus, there is currently a global effort, represented by the Minamata Convention, to minimize damages caused by mercury to the environment and human health.

Mercury: Sources and Properties

Mercury is released by a variety of natural sources, such as volcanoes and other geothermal phenomena (as fumaroles and hot springs (2)); biomass burning and weathering of rocks and soils; anthropogenic processes, such as burning of fossil fuels; ore processing; chlorine; soda industry; incineration of temperature and pressure measuring devices, and electrical and electronic materials (3). Methylmercury compounds were used in the United States and Europe as fungicides, because they were economical and highly efficient (4). But in other places in the world, mercury is still currently used in pesticides and fungicides (5). Almost 50% of mercury anthropogenic release into the atmosphere comes from Asian sources. Nowadays, artisanal and small-scale gold mining (ASGM) and coal burning are the main anthropogenic sources of mercury emissions (5).

Once emitted into the atmosphere, elemental mercury is retained for long periods. Consequently, this element can be transported over large distances and is therefore characterized as a global pollutant. Atmospheric transport is particularly important for mercury. The same is not true for other metals, for which the aqueous medium is the main means of transport (5, 6).

In nature, mercury occurs mainly in the form of cinnabar, a mineral of mercury (II) sulfide, HgS, due to the strong interaction between mercury and sulfur, soft acid and base, respectively. HgS was used in China a thousand years before Christ, as a red pigment, and in the Greco-Roman world for the same purpose, when Hippocrates and Galen recognized their toxicity (7).

Metallic mercury has a melting point of –38.83 °C (8). It is the only metal that appears in the liquid state under normal pressure and room temperature. This characteristic has been explored in important applications throughout history, such as its use in thermometers and amalgam formation for the extraction of precious metals. The ability of mercury to form amalgams with other metals has been known for a long time. In about 500 BC, in the Mediterranean region, amalgamation of noble metals and subsequent heating was already employed to extract these metals (9).

The characteristic of presenting itself in liquid state at room temperature was also responsible for the naming and representation of the chemical element. The symbol ☿ used by alchemists in the 17th and 18th centuries is a reference to the god Mercury's caduceus. The modern symbol (Hg), introduced by Swedish chemist Berzelius, comes from the Latin word *hydrargyrum*, which means "liquid silver." The earliest written reference to mercury was made by Aristotle, who referred to the metal as "silver fluid" (10). Why is mercury the only metal that appears in the liquid state at normal pressure and room temperature?

Mercury also shows other singular properties. It has the highest density of all liquids under normal conditions, 13.546 g cm^{-3}, at 20 °C (8). It has low electrical and thermal conductivities, and it is the only metal that does not form a diatomic molecule in the gaseous state (9, 11). Compared with gold, for example, its neighbor in the periodic table, mercury shows very different properties (Table 1).

Table 1. Some physical properties of mercury and gold under normal conditions (9)

Property	Mercury	Gold
Melting Point (°C)	–38.83	1064
Density (g cm^{-3})	13.53	19.32
Enthalpy of fusion (kJ mol^{-1})*	2.30	12.8
Conductivity (kS m^{-1})	10.4	426

*Fusion entropies, on the other hand, are very similar, 9.81 and 9.29 J K^{-1} mol^{-1}, for mercury and gold, respectively.

Since the 1970s, the anomalous behavior of mercury has been explained by strong relativistic effects (9). However, only in 2013 the hypothesis was demonstrated by a group of researchers from Massey University of New Zealand. Employing quantum models, Calvo and collaborators (11) showed that, ignoring the relativistic effects, mercury's melting point would be 82 °C. On the other hand, including relativistic effects, the calculated melting point of mercury was very close to tabulated values. This hypothesis has just been demonstrated because, until then, computers could not complete the complex calculations performed by the group (11). According to the authors, their study shows that relativistic effects on chemical bonding drastically change the thermodynamic state of mercury (11).

To sum up, a few factors contribute to mercury being liquid: the 6s orbital is relativistically contracted and filled. In mercury, the two 6s electrons do not contribute significantly to the metal bond; the Hg–Hg bond is predominantly van der Waals, and, therefore, weak. This also explains the low electrical conductivity of mercury compared to that of gold: in mercury, the two 6s electrons are more localized and thus do not contribute to electrical conduction. For further details, the works by Norrby (9) and Calvo *et al*. (11) are recommended.

Mercury as a Medicine: Cases of Illness Treatments

In this section, we will show several medical cases from the 19th and early 20th centuries that report the use of mercury as a medicine. Note that some terms used in past centuries to designate chemical substances or units of measurement are not so usual today. For example, for mercuric chloride (Hg_2Cl_2), the term "perchloridum hydrargyri" (12) or "perchloride of mercury" (13) was used, as well as "corrosive sublimate" or "mercury bichloride." As for mercurous chloride, it was referred to as "protochloridum hydragyri" (12), "calomel" or "blue pill." About measurement units, for example, Dudgeon (13), reports "I then gave him 1/16 grain (gr.) of perchloride of mercury in 10 c.cm. of normal saline." Grain (gr) is an old unit of mass, which is equivalent to 64.799 mg and "c.cm" is short for cm^3.

In the 19th century and early 20th century, the lack of specific treatment for many acute infections resulted in the preparation of different formulations. Different mercury compounds had already been used in the treatment of a wide range of diseases, such as cases of anuria (failure to pass urine), eye diseases (e.g., conjunctival lesions and corneal opacity), and erysipelas (a skin inflammation), as reported by Hall (14). In fact, mercury had an important role in medicine, in the words of Professor William Brande at a chemistry lecture (12):

> The next metal on our list is mercury, which is an important metal in many respects, but especially on account of its extensive use as a medicine. [p 168]

It is likely that one of the most important uses of mercury in medicine has been in the treatment of syphilis. After the Black Death, which decimated about a third of the European population in the 14th century, Galen's medicine was discredited, and medical novelties were desired. A century and a half later, when syphilis became epidemic in Europe, mercury was adopted as the standard drug for treating the disease, although Galen had already recognized its toxicity (15).

Paracelsus was one of the first to propose the use of mercury for treating syphilis; based on the diuretic properties of mercury salts: at the time, it was believed that by promoting diuresis and salivation, the causative agent of syphilis could be eliminated from the body (16).

Sarsaparilla, introduced by the French physician Nicholas Monarde in the 16th century, became popular in Europe because of the belief that syphilis had been brought from Asia by Columbus's sailors and that any native disease of a country could be cured by a native plant (15). Although sarsaparilla was most beneficial, mercury had been the major antiluetic for about 500 years and continued to be used until the development of penicillin in 1940 (16). The popularity of sarsaparilla probably decreased, because the treatment had to be done concomitantly with a month of confinement in a hot room over forty days of abstinence from sex and wine (15).

Treatment of diseases such as syphilis and gonorrhea were performed by administering pills and intravenous or intramuscular injections of mercury salts. To illustrate the use of mercurous chloride for the treatment of syphilis, referred to as "blue pills" by Abernethy, in a lecture at St. Bartholomew's Hospital (17):

> I believe that mercury, to a certain extent, will counteract the progress of the specific malady, and as some sores are doubtful, as you cannot exactly decide whether they are specific or not, I should advise you to give mercury. Tell them to take the blue pill, but take it mildly. If the sore be syphilitic, it will heal under the administration of mercury, and if it be not syphilitic it will do no harm, but frequently promote the healing of the sore. [p 165]

According to Dudgeon (13), intravenous injections of mercuric chloride in the treatment of syphilis and gonorrhoeic rheumatism were employed, for example, by Baccelli in 1907.

> The first case of septicemia which I treated with perchloride of mercury occurred in 1918 in the Balkans. The patient, a soldier, was suffering from an acute illness which was diagnosed on clinical evidence as malignant malaria. … I then gave him 1/16 grain (gr.) of perchloride of mercury in 10 c.cm. of normal saline [(18)], intravenously, which was repeated about 12 hours later as no improvement had occurred. After the second injection the temperature fell rapidly

from 105 °F; to 100 °F; and then to normal, and the patient made a complete and rapid recovery. The only ill effects were a sharp attack of diarrhea and mercurial stomatitis, both of which responded to treatment. [p 170)]

Vecki (19–21) employed intravenous and intramuscular injections of calomel, sublimate, and mercury salicylate. He advocated the use of mercury in the treatment of syphilis, including another medicine, salvarsan, an arsenic compound introduced in 1910 by Paul Ehrlich:

> It is very hard to judge of the relative value between salvarsan and mercury. Salvarsan surely has its charms and allurements. But, plainly speaking: if I had to abandon one of the two remedies it surely would not be mercury. [(21), p 372]

> We know now that intramuscular injections of insoluble mercurial salts can be given with absolute safety, that when the proper preparation is used in the right way, the patient is never in any danger, that even calomel, the most powerful of all mercurial compounds, can be injected, the disadvantage of causing abscesses avoided and the ensuing pain reduced to a tolerable minimum. [(20), p 359]

In 1919, Young, White and Swartz introduced a new drug for the treatment of bacterial infections, particularly for treatment of genital-urinary tract infections: Mercurochrome 220. According to the authors (22):

> In synthesizing a drug for local use as a urinary antiseptic, it was sought to combine the following properties: 1) ready penetration of the tissues in which the infection exists; 2) lack of irritation of the drug to tissues; 3) high germicidal activity; 4) ready solubility in water and stability of the solution; 5) freedom from precipitation in urine, and 6) sufficiently low toxicity to avoid systemic effects from the small amount of the drug that may be absorbed.

Dudgeon (13) reports the use of perchloride of mercury or Mercurochrome (Figure 1) (23) (Mercurochrome 220) or both in numerous cases of acute bacterial infection. The author reports that 330 patients underwent treatment with these drugs. Mercury perchloride was the treatment for 200 cases of acute bacterial infection, including puerperal fever (24), infections caused by Staphylococcus aureus, hemolytic and non-hemolytic streptococci and Bacillus coli. (13)

> Chemically it is the di-sodium salt of dibromoxymercury fluorescin. It is readily soluble in water and normal saline and is unaffected by moderate heat or exposure to air. It contains about 26 per cent of mercury, and even 1 per cent of this preparation does not form a precipitate with hydrocele fluid. The wide range of application of the drug in urinary and many other septic processes is fully recognized, but it is only the intravenous use of this preparation which is now under consideration. [p 170]

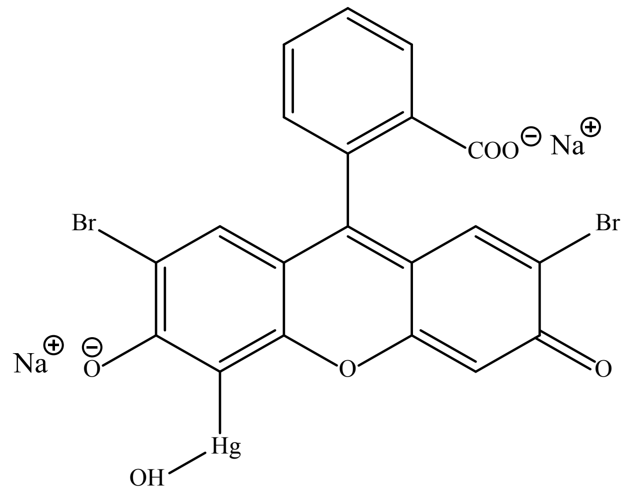

Figure 1. *Chemical structure depiction of Mercurochrome, a trade name of merbromin, more descriptively known as dibromohydroxymercurifluorescein disodium salt* ($C_{20}H_8Br_2HgNa_2O_6$) *(23).*

The use of mercury for treating syphilis was widely publicized and advocated, and some physicians extended its use to other diseases. This practice was not unanimous among physicians, since the toxicity of mercury compounds had been known for centuries. The following text, taken from a lecture by Dr. Astley Cooper from Guy's Hospital, on mercury treatment of venereal diseases, illustrates his indignation at the practice for gonorrhea patients (25).

> At the present time, however, a surgeon must be either grossly ignorant, or shamefully negligent of the duty which he owes to the character of his profession, and to the common dictates of humanity, if he persists in giving mercury for this disease. Let those persons who suppose that gonorrhea can be cured by mercury, go round our wards and see whether mercury has any effect on that disease. Look, gentlemen, at 100 patients in our foul wards, many of whom come into the hospital with syphilis and gonorrhea; and many, I am sorry to say, who have only gonorrhea, but who are invariably carried to those wards. What is the miserable treatment of these patients? You are aware, gentlemen, that I scarcely ever enter the foul wards of St. Thomas's Hospital. When a particular case demands my attention, I have the patient removed to the clean ward. I will tell you why I do not enter those wards, gentlemen. I abstain from entering them, because patients under gonorrhea are compelled to undergo so infamous a system of treatment that I cannot bear to witness it. To compel an unfortunate patient to undergo a course of mercury, for a disease which does not require it, is a proceeding which

> reflects disgrace and dishonour on the character of a medical institution. [p 464]

According to *The Lancet* (1836) (26), later discussing Cooper's words, his "denouncement of the odious system was honest, bold, and unflinching."

Another acclaimed mercury medicine is "Merthiolate," the trade name of thiomersal or thimerosal, whose IUPAC name is ethyl(2-mercaptobenzoato-(2–)-O,S) mercurate(1–) sodium ($C_9H_9HgNaO_2S$), Figure 2 (27). A patent (US1672615) (28) was applied for in 1927 by organic chemist Morris Selig Kharasch from College Park, Maryland Later, the pharmaceutical giant Eli Lilly and Company marketed thiomersal under the trade name Merthiolate (29).

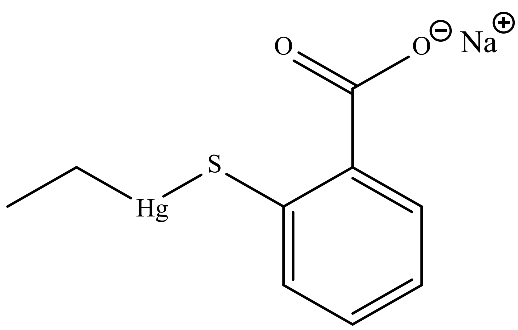

Figure 2. *Chemical structure depiction of thiomersal or thimerosal, whose IUPAC name is ethyl(2-mercaptobenzoato-(2–)-O,S) mercurate(1–) sodium ($C_9H_9HgNaO_2S$) (27).*

It is possible to find several records in medical literature of the 19th and 20th centuries that advocate the use of mercurial compounds in the treatment of diseases with numerous examples of successful cases, as well as records that abhor it, describing diseases developed by mercury poisoning after treatment with such medicines. This controversy dragged on nearly to the present day, and now the use of medicines containing mercurial compounds is prohibited in several countries. In Brazil, the prohibition was enforced in 2001 by the National Health Surveillance Agency (ANVISA).

Mercury as a Poison: Cases of Acute Poisoning

The use of poisons in murder or suicide is an old and successful practice. As recently as the early 19th century there were few tools to detect toxic substances in corpses. Sometimes investigators deduced the poison's identity based on symptoms that preceded death or built a case by feeding animals with the victim's last meal (30). Of course, few cases were resolved that way. Thus, chemistry had a fundamental role in the solution of crimes from the beginning of the 19th century with isolation and identification of chemical elements and the creation of the periodic table. To do so, the knowledge of chemical reactions and methods of separation were essential for developing methods of analyses.

Specifically, for mercury, Mathieu Orfila (1787-1853), professor of chemistry in Paris, published in 1832 a systematic procedure for identification of mercury compounds in *mixtures* (31):

> For some years past the various scientific journals have contained instances of poisoning occasioned by mixtures of arsenic and laudanum, proto-nitrate of mercury, and verdigris; but as far as I am aware, no particular attention has been paid to the chemical questions involved in these discussions. I have deemed it my duty to study this subject with the greater care, inasmuch as it offered to my consideration many remarkable and unexpected phenomena. [p 614]

To illustrate this topic, seven cases of poisoning by inorganic mercury compounds, published in the early 19th century will be reported below in their chronological order.

The first case presented here was reported by Alisson (32). In 1829, a girl with suicidal intent, out of jealousy, ingested a quantity of a poison, a "red mercury powder." According to this report, the woman was first given grains of ipecacuanha and zinc sulfate. Afterwards, gastric lavage was performed, and castor oil and laudanum were administered for a few days. The girl gradually recovered her health. Although it was not reported in the account, the powder mentioned is probably mercuric oxide.

The second case, a more serious one, reported by Herapath (33), did not have a happy ending: the evolution of the patient's clinical condition led to her death nine days after poison ingestion. On October 12, 1845, a 27-year-old female patient with epilepsy, who had already suffered various seizures as a result of her disease, swallowed the contents of a bottle containing mercuric chloride dissolved in hydrochloric acid. The following section reports the first steps taken:

> Upon our arrival, we learnt that vomiting had occurred within two minutes after the poison was swallowed, and it was encouraged by the frequent administration of copious draughts of warm water by her friends. Purging had also commenced in the first quarter of an hour, and the patient had remained upon the night commode ever since, as it was impossible to remove her. We arrived within an hour after the

> accident; the patient was cold and clammy, almost pulseless, having an anxious countenance, swollen, and almost livid, vomiting occasionally. Warm water was injected by the stomach pump, and several eggs were beaten up and administered by the same means, which the stomach retained. … Milk and eggs to be administered frequently at short intervals. [p 699]

The third case, also lethal, involving two brothers, is very impressive. Hall (34) reports the case of two men who rubbed a mixture of mercuric chloride and lard on their bodies in order to cure an itch. One of them, 24, was found after an hour feeling intolerable thirst and excruciating pain. He said he felt as if he was being burned alive. After suffering from vomiting with blood, he died eleven days after intoxication. His brother, 19, used the same amount of the mixture and had the same symptoms, dying four days after his brother.

The fourth case, also involving mercuric chloride poisoning, and also fatal, was reported by Skegg (35). On October 27, 1861, a 54-year-old man ingested about seven grams of mercury chloride solution for suicide. He was treated with egg white and induced vomiting. Milk was given *ad libitum* and, in intervals, brandy and water. However, the patient died three hours after taking the dose. In both cases reported by Herapath (33) and Skegg, the patients presented symptoms of pale skin, covered by cold and sticky perspiration, weak pulse and white tongue.

The fifth case, reported by Meeres and Fox (36), is a tragic instance of a medical treatment gone wrong. In 1871, the physician Edward E. Meeres was accused of poisoning a child after a very concentrated application of mercuric chloride on the head and neck of the victim for local treatment of a mycosis—tinea tonsurans, a cutaneous fungal infection of the scalp caused by the dermatophyte *Trichophyton tonsurans (*37*)*. The practice was common at the time, as supported by physician Tilbury Fox (36):

> When I published the first edition of my work on "Parasitic Diseases of the Skin," in 1861, I had already used the remedy a long time, and it was on the strength of my experience that I then approved it … I contend that my very large acquaintance with the remedy proves that in Dr. Meeres' case there must have been some very exceptional circumstance operating, and that I feel sure was idiosyncrasy; and, as far as I can see, no foresight on his part could have appreciated this. [p 414]

The sixth case is a non-lethal mercuric oxide intoxication reported by Ord (38). In July 1887, a 51-year-old tailor was admitted to St. Thomas's Hospital, unconscious, vomiting, and presenting pupils of average size, equal, and inactive toward light, cold sweaty face and hands, and a weak pulse. There were traces of a reddish powder on the patient that was later identified as mercury oxide. The patient was submitted to gastric lavage and treated with milk, lime water and beaten eggs. He gradually improved and left the hospital well twelve days later.

The seventh case, also reported by Ord (38), is about a non-fatal intoxication by mercuric chloride. In August 1887, a surgical instrument maker aged forty-nine, swallowed a small portion of mercuric chloride. The patient vomited a bloodless greenish mucous fluid and complained of burning throat and stomach. He had moist skin, his tongue lightly coated with white material, and congested throat fundus. It was initially treated with zinc sulfate, egg white and milk, in addition to other substances. After a week in the hospital, the patient was released.

Among these seven reported cases, five involved mercuric chloride intoxication and four of them were fatal. The poisoning symptomatology depends on the dose and the exposure rate. Furthermore, biological behavior, pharmacokinetics and clinical significance vary with the chemical species (39).

For example, the lethal dose (oral intake) for mercuric chloride is 0.5 g, while for metallic mercury it is 100 g (7). In the case of the two inorganic compounds, mercuric chloride ($HgCl_2$) and mercuric oxide (HgO), the difference in toxicity is due to the difference in solubility and their consequent bioavailabilities. Mercuric chloride solubility is 7.31 g/100 g of water (at 25 °C) (8), whereas mercuric oxide is practically insoluble in water (40).

Mercury as a Poison: Cases of Occupational Diseases

In the 17th century, mercury was introduced, first in France, in the process of manufacturing hats. Mercuric nitrate was used in felting for making the outer stiff hairs on the pelt soft, limp, twisted and roughened so that they packed together more easily (41).

In 1902, Porter (42) described in detail this process: through a process called "carroting," hatters produced felt treating the skin of small mammals such as rabbit, hare, beaver and muskrat with mercuric nitrate solution. The hatter removed the skin from this mercury nitrate solution with his hands and subsequently entered the drying chambers to put and remove skins and thus came into contact with mercury vapors.

At that time, many hatters developed neurological disorders whose symptomatology gave rise to the popular expression "mad as a hatter." For this reason, it is widely reported that Lewis Carroll drew on this phenomenon to create his character "Mad Hatter" from Alice in Wonderland. However, this does not seem to be the case.

According to Wedeen (43), the first description of mercurialism in hatters was published in 1860 by J.A. Freeman in "Transactions of the Medical Society of New Jersey," only five years before Carroll published his work. Nevertheless, it would be unlikely that Carroll was aware of this report. For Waldron (41), the belief that Carroll's Mad Hatter was the victim of mercurialism is an example of the Bellman's fallacy (44). The author suggests that Carroll was inspired by his acquaintance, Theophilus Carter, an eccentric furniture dealer and inventor, known for wearing a high top hat. Victims of mercurialism exhibit excessive shyness and introspection, qualities that would not be present in Carroll's character (41).

According to Hunter and collaborators (45), organic mercury compounds were first used in chemical research in 1863 by Frankland and Duppa at St. Bartholomew's Hospital. They used dimethylmercury to determine the valence of metals and metallic compounds and two laboratory technicians engaged in this work died after developing symptoms of mercury poisoning. One of them, aged 30 years, had been exposed to dimethylmercury for three months. He manifested hand numbness, deafness, poor vision and gum pain, in addition to slow and dull behavior, unsteadiness in gait and inability to stand. The symptoms quickly worsened, and he died two weeks after the onset of symptoms (45). The second technician, aged 23 years, had worked with dimethylmercury for only two weeks. One month after exposure, he began to show pain in his gums; numbness of feet, hands and tongue; deafness and decreased vision. The speech was confused, and he answered questions slowly. Three weeks after the onset of symptoms, he had difficulty swallowing, inability to speak, urinary and fecal incontinence, and became restless and violent. He remained in a confused state and died of pneumonia twelve months after the first symptoms (45).

Despite these two cases, it was only in the 1940s that contamination by mercury organic compounds was better studied by doctors Donald Hunter and Dorothy S. Russell. Even so, methylmercury poisoning, then known as Hunter-Russell syndrome, gained further attention after the Minamata disaster, which revealed to the world the true toxic potential of mercury. The Minamata disease will be discussed later in this text.

In 1940, Hunter and collaborators (45) reported a full account about a clinical and experimental study with a group of four patients, before the Second World War, suffering from profound neurological disturbances as a result of industrial exposure to methylmercury compounds. Years later, in 1954, Hunter and Russell (46) reported a study about the necropsy of one of them. The man, aged 23 when he first came under observation, had been exposed to dust of methyl mercury phosphate and nitrate for four months, beginning five months before admission to hospital. The first symptoms appeared in 1937. The patient's neurological deterioration worsened as years passed by, and he died in 1952, after a pneumonia (46).

Cases of occupational diseases caused by mercury compounds occur worldwide and most commonly among workers in industrial plants and mining. In the early 20th century, mercury was used in numerous industries. Neal (47) presents an extensive listing of mercury applications in industry (chemical, electrical, hat manufacturing, dentistry, pharmaceutical, explosives, pesticides, photography and others) as well as mining cinnabar, gold and silver. In most cases, contamination occurs by exposure to elemental mercury vapors. However, contamination by organic forms is also possible, as in the pesticide manufacturing industry.

Agate and Buckell (48) report a study about mercury poisoning from fingerprint photography, an occupational hazard of policemen. At that time, the powder most commonly used in British and United States police forces was "hydrargyrum cum creta B.P." that is mercury-with-chalk or grey powder prepared by triturating one part by weight of metallic mercury with two parts of chalk in a mortar. Out of 32 men engaged regularly on such work, seven were found to have evidence of chronic mercurialism (48).

In the 1970s, two dentists in Utah, USA, experienced mercury poisoning and even after correcting working conditions took almost two years for disappearance of their symptoms (49). Studies have suggested that, at that time, one in seven dentists was contaminated with significant amounts of mercury vapor (50). A study conducted in the same period with 284 dentistry workers showed that dental assistants who prepared dental cavity filling amalgam showed the greatest risk of exposure to mercury vapor (51).

In the 1990s, Italian researchers reported color vision loss in workers exposed to elemental mercury vapor, from factories engaged in the production of precision instruments as thermometers, thermostats and barometers (52, 53). These symptoms were also observed in São Paulo, Brazil, in workers from fluorescent lamp companies (54).

In the scientific community, the most famous case of occupational poisoning by mercury involved the renowned American professor and researcher Karen Wetterhahn in 1997 at Dartmouth College, a victim of dimethylmercury (DMM) contamination. In 1996, professor Wetterhahn spilled a few drops of DMM on her gloved hand while preparing an experiment. The substance passed through the glove and was absorbed by her skin. At that time, it was not known that latex gloves were permeable to DMM. Six months later, she slipped into a coma and died from acute mercury poisoning. Dartmouth has established several memorials in honor of professor Wetterhahn (55).

Mercury as a Poison: the Case of Minamata

From the 1920s to 1960s, the chemical factory Chisso Ltd. (56), located in Kumamoto, Japan, synthesized acetaldehyde and vinyl chloride using mercury(II) sulfate and mercury(II) chloride, respectively, as catalysts. Methylmercury, a by-product of the syntheses, was dumped into Minamata bay by Chisso, contaminating marine biota and water (57, 58).

In the 1950s, a mysterious neurological disease began to affect the population of villages near Minamata Bay. At first, dead fish began to appear in the bay. In addition to the death of fish and crows, some domestic animals, such as dogs and pigs, but mainly cats started to show neurological disorders. As described below by McAlpine and Araki (59), cats had symptoms that led to this disease becoming known as "dancing cat disease."

> In the 40 affected families there were 61 cats and 50 died between 1953 and 1956, sometimes in as little as 2 days. Unsteadiness, frequent falls, circling movements, and convulsions were observed; forced running appears to have caused some of them to enter the sea and be drowned. … The brains of 10 cats were examined; the changes were similar to those observed in the human material, the granular layer of the cerebellum being especially affected. The disease could be readily produced experimentally in cats by feeding them for 2 to 4 weeks with fish from Minamata Bay. [p 630]

In 1956, the mysterious nervous illness had assumed epidemic proportions. Fishermen and their families were mainly affected, and evidence suggests that the illness was caused by eating fish from Minamata Bay (59). In 1959, it was proved that methylmercury was the cause of Minamata disease and in 1960s Chisso was pressured to modify its waste disposal methods. Nevertheless, Chisso and other chemical industries continued to discard inorganic mercury, although not methylmercury, into Minamata Bay until 1968 (60). In the 1960s and 1970s, various health problems were noted in the children of mothers exposed to contaminated fish: neurological disorders (mental retardation, chronic brain damage, developmental disturbances), hypertension, liver disease, and poor metabolism (59, 60).

According to the Minamata Disease Museum (58), by 1997 more than 17,000 people in Kumamoto and Kagoshima prefectures had applied for certification as Minamata disease victims. At the end of May 2013, the number of certified patients was 2,977 (1,784 in Kumamoto Prefecture, 491 in Kagoshima Prefecture, and 702 in Niigata Prefecture), of which 646 (330 in Kumamoto Prefecture, 130 in Kagoshima Prefecture, and 186 in Niigata Prefecture) are still alive (61).

More than a decade passed since the first cases of Minamata disease to government's acknowledgment of Chisso factory's responsibility. Thousands of people were officially recognized as patients with Minamata disease, but how have victims been compensated?

Akio Mishima shows, in the book *Bitter Sea: The Human Cost of Minamata Disease* (60) how nefarious this event is. The preface, written by Lester R. Brown, founder of the Worldwatch Institute, highlights this sentiment:

> *Bitter Sea* is an in-depth case study painfully chronicling the struggle between the victims of Minamata disease (mercury poisoning) and the corporation that discharged the mercury into Minamata Bay. It is gripping account of how the victims and their friends and sympathizers organized to seek justice. It is discouraging to see that the government is sometimes less interested in protecting the victims than those who are responsible for their pain. … At times, in reading this book, one has the feeling of reading a novel, so dramatic is the account. Unfortunately, it is not fiction. It is a real-life story of how callous corporate greed can cause enormous human suffering. [p 7]

According to Mishima (60), Dr. Hajime Hosokawa, director of the hospital attached to Chisso's Minamata plant, suspected the factory may have been the cause of the mysterious illness. Therefore, he began conducting experiments in which cats were fed with food contaminated with factory effluents. Some time later, one cat had symptoms similar to those exhibited by human victims and its brain tissue was examined. Results revealed degeneration of the cerebellum, characteristic of Minamata disease. When, Hosokawa reported his findings to Chisso executives, they ordered him to stop the experiment and to kill the remaining cats in secrecy (60). Chisso also refused to comply with victims and used to offer despicable financial compensation to victims. Its disregard for dignity of life and human rights was later condemned in court (60).

For further details, the recent work of Yokoyama (62) is a complete study of the Minamata case.

Mercurial Medications: Not Entirely in the Past

There is a popular belief that the difference between a medicine and poison is merely the dose. This statement applies well to mercury.

It has been previously shown that it is possible to find in medical literature from the 19th and 20th centuries authors who advocate(d) the use of mercurial compounds in the treatment of diseases, as well as others that abhor it. This discrepancy in opinion is due to the fact that mercury toxicity, which is responsible for its microbicidal effects, is also responsible for this substance's side effects. In some cases, side effects were minimal; in others, serious and even fatal. Whether they will be serious or fatal depends on the dose administered, the chemical species employed in the treatment, and human physiology. So, the question still remains: should or should we not ban production and marketing of mercury medicines?

The use of mercury compounds in drugs is still defended today, as shown by the work of Mohite and Bhatnagar (63), which demonstrated the efficacy of using Mercurochrome 1% as an antiseptic for burns.

In spite of its effectiveness as a medicine in many situations, in order to respond to this question, we must expand our judgment beyond its usefulness as a medicine and analyze other aspects, especially in regard to environmental issues. Is the utility of mercury medicines so fundamental that it justifies direct and indirect consequences to the environment as a result of its production? Because of this discussion, it is no wonder that the Minamata Convention on Mercury was agreed in 2013.

The Minamata Convention on Mercury (MCM) is an international treaty aimed at protecting human health and the environment from damages caused by mercury. It was agreed on 19 January 2013 in Geneva, at the 50th session of the Intergovernmental Negotiating Committee on mercury and adopted in October 2013, in Kumamoto, Japan, at a Diplomatic Conference (Conference of Plenipotentiaries) (64). The MCM entered into force in August 2017, after the deposit of the 50th instrument of ratification, acceptance, approval or accession. Its aim is to control anthropogenic releases of mercury throughout its lifecycle (mercury emission, storage and disposal) (64).

Before consuming a product, we must evaluate the various stages of its production process, from obtaining raw materials to waste generation. For example, for medicines, one of the ways of generating waste is through excretion with subsequent disposal in sewage networks.

Moreover, when it comes to public health, the use of mercury amalgams in dentistry still generates much controversy among professionals. Amalgam, in addition to being more efficient in many types of procedures, has a much lower cost than resins and other materials. This theme well illustrates the importance of socioeconomic development to be in keeping with scientific development: expensive alternative materials will not be able to replace mercury amalgam in poorer regions of the world, like many cities in Brazil.

Environmental Considerations

Currently, there are numerous reports in the scientific literature about cases of mercury contamination at home and at school. Pediatric cases of elemental mercury poisoning from exposure to mercury by skin contact or inhalation have been reported in schools in different provinces of Turkey (65, [66]). Several cases are related to the fact that children carry liquid mercury from school to home, and heat it on the stove (67, 68, 69). A case was reported of mercury intoxication of two children (a 9-month boy and a 2.5-year-old girl) who were exposed to mercury from a barometer in a private residence in the Netherlands (70). Sasan and collaborators (71) report a case in Iran about mercury poisoning of two boys who had played with mercury. Also, a case was reported in Iran about two sisters presenting classical mercury contamination symptoms (pain in extremities, itchy rashes, sweating, salivation, weakness, and mood changes) after using a mercury compound for treatment of pediculosis (infestation by lice) (72).

Despite all these tragic events in the past, people keep dying from mercury contamination, as it is the case of a seven-year-old girl who died in August 2015 on an Indonesian island, where small-scale gold mining is an important part of the economy (73). In many developing countries, poor people keep living and working in close proximity to mercury emissions, in artisanal and small-scale gold mining. It is not the purpose of the present work to address pollution caused by artisanal mining, but countless papers in the literature report environmental, socioeconomic and political problems related to this practice. For example, in Antioquia, Colombia, guerrilla and paramilitary activities in rural areas pushed miners to towns so they could process their gold. Because of this, Antioquia developed the world's highest per capita mercury pollution. According to Webster, upon arriving in Antioquia one can feel a metallic taste on the tongue (74).

As previously mentioned, poisoning symptomatology depends on the dose and exposure rate. Moreover, other important factors are nutrition, co-exposures and preexisting conditions, all of which are strongly related to poverty (75).

Within the current pessimistic scenario caused by the environmental impacts generated by irresponsible anthropogenic activities, the Minamata Convention brought light to the end of the tunnel. According to the Minamata Convention, each party shall report on the measures it has taken to carry out the Convention's provisions, the effectiveness of these measures and challenges to achieve the goals of the Convention (64).

Conclusions

Mercury is released by a variety of natural and anthropogenic sources. Its singular physical properties and high toxicity make it a controversial element. Mercury is connected to medical events in history, as the Mad Hatter and Minamata diseases.

Mercury was employed in the past as a medicine because of its bactericidal properties. On the other hand, it also made countless victims through both accidental and intentional actions, in addition to occupational diseases and accidents at work.

Nowadays, there is a global effort represented by the Minamata Convention to minimize the damage caused by mercury to the environment and human health. Nevertheless, poverty places a hard challenge to achieve the goals of this Convention. Therefore, all countries must create public health commitments for combating social and economic inequities that are the greatest environmental threats.

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Notes from Europe

EuChemS Historical Landmarks Award

The call for submissions for the EuChemS Historical Landmarks Award, which aims at celebrating the important link between history, cultural heritage and chemistry, is open for submissions. Deadline is 31 December 2020.

Find out more about the award and enter your submission on the webpage https://www.euchems.eu/awards/euchems-historical-landmarks/.

The EuChemS Historical Landmarks Award for 2019 have been designated for:

- Mines of Almadén, Spain, for the European Level
  https://www.euchems.eu/euchems-historical-landmarks-award-2019-european-level/
- Edessa Cannabis Factory Museum, Greece, for the Regional Level
  https://www.euchems.eu/euchems-historical-landmarks-award-2019-regional-level/

13ICHC Postponed to May 2023

The 13th International Conference on History of Chemistry (13ICHC) organized by the EuChemS Working Party on the History of Chemistry (WPHC), in cooperation with Vilnius University had been announced to be held in Vilnius, Lithuania, from the 18th to the 22nd of May 2021. See: https://www.ichc2021vilnius.chgf.vu.lt/. Due to the evolution of the Covid-19 pandemic, the conference has been postponed to May 2023, still in Vilnius. The new date of May 2023 has been chosen to maintain the biennial schedule of the WPHC.

A one-day online activity will be organized by the WPHC for one of the originally scheduled 2021 conference days.