Perils of Mercury*

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ABSTRACT

The historical items pertaining to mercury are outlined, and its toxicity and former medicinal uses are discussed. The diversity of the toxic effects by the different forms of mercury as well as the routes of administration are illustrated in three case reports. The importance of diaphoresis in the treatment of mercury poisoning as well as the status of the use of chelating agents are reviewed. The need for the surveillance of mercury and the prevention of exposure to mercury from environmental and dietary sources are emphasized. The importance of excluding mercury toxicity in patients with psychiatric and neurological disorders is stressed.

Introduction

For three thousand years, mercury and its compounds have been widely used in medicine and in industry. Today, the uses of mercury in industry are increasing while the uses of mercurials in medicine are being discarded and, at long last, are gradually falling into oblivion.‡ In the history of medicine, no other ingredients of drugs have been credited with such a diversity of remedial and therapeutic actions as have the mercurials, – vermifuge, cathartic, diuretic, antisypyilitic, antiseptic, antipruritic, antiphlogistic, antiparasitic, and as an alterative, to mention a few. In retrospect, it is amazing that the mercurials had attained such prominence as therapeutic agents and that they were used medicinally with confidence for a score of centuries; especially since the awesome, horrible maladies caused by the occupational exposure to these same compounds were also described and recognized by learned physicians covering the same span of ages.§ Noteworthy historical items pertaining to mercury are listed in table I.

† Send reprint requests to author at Institute for Clinical Science, 1833 Delancey Place, Philadelphia, PA 19103.
‡ In a casual survey of several local pharmacists, it was found that the only mercurial that is still occasionally prescribed is yellow mercuric oxide ophthalmic ointment. It is noteworthy that amalgams are still used by some dentists for filling tooth cavities, and many cosmetics contain organic mercurial compounds.

§ The earliest known book describing diseases from exposures to metals was written by Ulrich Ellenbog, a native of Swabia, Germany. His book, entitled "Von den Giftgegen Beseb Tempfen von Reuchen der Metal", was first printed in Augsburg in 1524, although it had probably been written about 50 years earlier.13,17,43
TABLE I

Noteworthy Historical Items Pertaining to Mercury

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1100 B.C.</td>
<td>Chinese used cinnabar (HgS) - vermillion - Chinese red.</td>
</tr>
<tr>
<td>700 B.C.</td>
<td>Phoenicians reputed to have mined cinnabar.</td>
</tr>
<tr>
<td>415 B.C.</td>
<td>Mercury mined in Almaden, Spain by slaves and convicts.</td>
</tr>
<tr>
<td>400+ B.C.</td>
<td>Aristotle called mercury &quot;quick silver.&quot;</td>
</tr>
<tr>
<td>c. 0</td>
<td>Mesopotamians associated metals with planets. Mercury is the only metal which has retained the name of a planet.</td>
</tr>
<tr>
<td>c. 50</td>
<td>Dioscorides, a Greek physician, wrote that cinnabar has medical uses, such as healing burns, but that the ore itself was poisonous. He called mercury &quot;liquid silver.&quot;</td>
</tr>
<tr>
<td>c. 77</td>
<td>Pliny referred to mercury as hydrargyrum (water silver), hence the symbol, Hg. Pliny was concerned with respiratory hazards in mercury workers and advised them to protect their faces with masks made from thin bladder tissue. Pliny called mercury intoxication a disease of slaves and convicts.</td>
</tr>
<tr>
<td>c. 850</td>
<td>Leech book of the Druids of Wales and wandering Celtic monks gave the formula against lice: &quot;One pennyweight of quick silver and two of old butter.&quot;</td>
</tr>
<tr>
<td>980-1036</td>
<td>Medieval textbook, the &quot;Canon&quot; of Avicenna, advocated use of mercury inunctions for the treatment of chronic skin diseases. No differentiation made between syphilis, leprosy, typhus, etc.</td>
</tr>
<tr>
<td>1258+</td>
<td>Gilbertus Anglicanus described method of &quot;extinguishing&quot; mercury to make blue ointment.</td>
</tr>
<tr>
<td>1473</td>
<td>Ulrich Ellenbog in Germany wrote first treatise on industrial metal poisons. He recognized that the inhalation of metallic vapors was oftentimes more dangerous than exposure to the metals themselves.</td>
</tr>
<tr>
<td>1553</td>
<td>Paracelsus described mercury poisoning in the miners of Idria, Italy (now Yugoslavia).</td>
</tr>
<tr>
<td>1665</td>
<td>First legislative measures of industrial hygiene taken to protect mercury miners in Idria by shortening the working day to six hours.</td>
</tr>
<tr>
<td>1600+</td>
<td>Oswald Crollius in Basilica Chymica described method for making mercurous chloride.</td>
</tr>
<tr>
<td>1600+</td>
<td>de Mayerne, physician to Henry IV of France, is said to have coined the name &quot;calomel.&quot; The etymology is in doubt, but the name is presumed to be derived from the Greek Kalo, meaning beautiful, and from Mele, meaning honey. Calomel was called &quot;sweet mercury.&quot;</td>
</tr>
<tr>
<td>1550-1940</td>
<td>Mercury was used in the therapy of syphilis. It was the sole treatment before arsphenamine was introduced in 1905.</td>
</tr>
<tr>
<td>1713</td>
<td>Ramazzini wrote a monumental treatise on Diseases of Workers. He described ill effects on surgeons giving their patients mercury inunctions for syphilis.</td>
</tr>
</tbody>
</table>
TABLE I continued

Noteworthy Historical Items Pertaining to Mercury

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1721</td>
<td>Antoine de Jussieu described symptoms of salivation, ulceration of gums, and tremors in mercury miners in Almaden, Spain. Sweating was found to be effective treatment for tremors.</td>
</tr>
<tr>
<td>1741</td>
<td>Schlichting used calomel as a diuretic for cardiac dropsy.</td>
</tr>
<tr>
<td>1776</td>
<td>Falck published first comprehensive monograph devoted exclusively to extolling the use of mercury and its preparations as therapeutic agents. In Philadelphia, calomel was drug of choice for colic. Benjamin Rush considered it the &quot;sovereign remedy in yellow fever, typhus, and other malignant affections.&quot; Rush gave calomel routinely along with jalop and repeated bleedings to all patients with yellow fever in the Philadelphia epidemics.</td>
</tr>
<tr>
<td>1799</td>
<td>Proust was first to demonstrate mercury to be present in seawater.</td>
</tr>
<tr>
<td>1800-1940</td>
<td>In many hospitals, &quot;blue mass&quot; was given routinely as a cathartic to patients on admission. &quot;Blue mass&quot; is made by triturating metallic mercury with honey and licorice. It contains one-third of its weight as metal.</td>
</tr>
<tr>
<td>1803</td>
<td>Fire in mercury mine in Idria, Yugoslavia spread mercury vapor over countryside. Mercurial tremor reported to have developed in 900 persons.</td>
</tr>
<tr>
<td>1810</td>
<td>British sloop, Triumph, had some mercury containers broken in hold. All birds and cattle aboard died; 200 sailors developed symptoms of mercury poisoning, and three of them died.</td>
</tr>
<tr>
<td>1892</td>
<td>Osler's Textbook of Medicine delineates treatment of syphilis with mercury.</td>
</tr>
<tr>
<td>1906</td>
<td>H. C. Wood's authoritative text books on Therapeutics list mercury as an alterative (tonic).</td>
</tr>
<tr>
<td>1919</td>
<td>Osler included mercury in his list of &quot;real medicines.&quot;</td>
</tr>
<tr>
<td>1940-1950</td>
<td>Development of chelating agents for treatment of metal intoxications, including mercury.</td>
</tr>
<tr>
<td>1953</td>
<td>Minamata Bay, Japan disease - outbreak of poisoning by organic mercury compounds in community of fishermen was traced to poisoning of fish from the effluent of a factory making vinyl chloride using mercuric chloride as a catalyst.</td>
</tr>
<tr>
<td>1956-1960</td>
<td>Mass poisoning of peasants in Iraq from seed dressing used in preparation of homemade bread. The seed dressing was ethyl mercury para toluene sulfonanilide.</td>
</tr>
<tr>
<td>1967</td>
<td>Threshold limit for mercury vapor for 8 hours per day set at 100 ug/M³ in USA. OSHA decrees threshold limit to 50 ug/M³. Limit in Soviet Union since 1944 is 10 ug/M³.</td>
</tr>
<tr>
<td>1974</td>
<td>Trakhenberg directed attention to a syndrome observed in Soviet Union which has been labelled &quot;micromercurialism.&quot; He suggested that the threshold limit for mercury vapor in the working environment should be below 10 ug/M³.</td>
</tr>
<tr>
<td>1980</td>
<td>Medicinal uses of mercurial compounds have been practically discarded.</td>
</tr>
<tr>
<td>1984</td>
<td>Finnish workers found a statistically significant correlation between impairment of memory and the concentration of mercury in blood.</td>
</tr>
</tbody>
</table>
Toxicity of Mercury

In his brilliant, perceptive treatise on Diseases of Workers, Ramazzini,59 in 1713, lauded the use of mercury for the treatment of syphilis and stated, “Of all the remedies discovered by medical skill for curbing the ferocity of the French disease (i.e., syphilis), mercury won first place and after the unbroken experience of two centuries still holds it.” Later on in the same treatise, he states, “We all know what terrible maladies are contracted by the goldsmiths from exposure to mercury by gilding with gold amalgams.” He noted, “Very few of them reach old age and even when they do not die young, their health is so terribly undermined that they pray for death.” In commenting about the poor health of mirror-makers and the hazards of their exposure to mercury, Ramazzini stated, “You may see these men gazing with reluctance and scowling at the reflections of their own sufferings in their mirrors and cursing the trade they have adopted.”

It seems apparent that poisoning from the therapeutic use of mercurials in past ages was either not clearly recognized clinically or was circumvented without reason. Despite the sizable literature on mercury poisoning, it is noteworthy that the diagnosis is still infrequently considered in routine hospital practice. The belief seems to be prevalent that random exposures to mercury are harmless. Mercury and its compounds have no known metabolic function, and their presence in the cells and fluids of living organisms, including man, represents contamination from natural and man-made sources. The presence of mercury in the tissues of man may therefore be regarded as undesirable.

The atmosphere plays an important role in the mobilization of mercury. The mercury concentration of the air over mineral deposits containing mercury is significantly higher than that of air over non-mineralized areas. Mercury vapor is believed to be released into the atmosphere by evaporation from the ground surface.44 The release of mercury in the environment also comes from the burning of fossil fuels, from coal-fired power plants, and from such operations as mining, and smelting.47,54,61,70 It is noteworthy that mercury released in the environment becomes available for potential methylation.48

In any discussion of the toxicity of mercury, it is necessary to distinguish between its physical and chemical forms. These forms may be classified broadly as inorganic and organic.46 Examples are given in Table II in which the anion is depicted as chloride. A variety of anions may be combined with the mercury cation without appreciable effect on its toxicity. Elemental mercury vapor and the inorganic salts are the forms of hazardous exposure more generally encountered in industrial operations, and the organic salts (such as methyl mercuric chloride)52 are the forms more frequently encountered in food poisoning.4,23,48

Two major Japanese outbreaks of methyl mercury in Minamata Bay and in Niigata were caused by the industrial release of methyl mercury and by its subsequent accumulation in edible fish.48 During the winter of 1971–72, the largest outbreak of methyl mercury poisoning ever recorded occurred in Iraq. This was the result of the con-
sumption of homemade bread prepared from seed wheat that had been treated with a methyl mercury fungicide.\textsuperscript{4,48}

Organic mercury accumulates in the tissues of higher organisms, probably by diffusion.\textsuperscript{38,48} Even low concentrations of methyl mercury in water will lead to increased concentrations in the tissues of fish and other aquatic life. After methyl mercury has diffused through cell membranes, it becomes bound to sulfhydryl groups.

Case Reports

Mercury toxicity is characterized by the diversity of effects that the metal and its salts may cause as well as the routes of administration, – ingestion, skin absorption, inhalation, and whether the exposure is acute or chronic.\textsuperscript{15,39} Over the years, a number of patients with mercury poisoning have come under our medical care. Pertinent data from three patients were selected in order to illustrate the diversity of findings that may be observed from poisoning by each of the three routes of administration as well as by three different mercurials.

Case 1 Poisoning from Ingestion of Bichloride of Mercury

The patient was a white male, 30 years of age, who stated, when first seen at the Hospital of the University of Pennsylvania in 1928, that he had swallowed, with suicidal intent, five 0.5 gram tablets of bichloride of mercury two hours previously.\textsuperscript{41} Before admission, he had vomited several times and had watery stools. After admission, the patient developed complete anuria accompanied by frequent liquid stools containing blood. Within 48 hours after taking the bichloride of mercury, the patient developed convulsions, became irrational, and presented the clinical features of acute renal failure. The patient was anuric for six days, became uremic, and developed a distorted serum electrolyte pattern, as shown in table III.\textsuperscript{66} The decreased concentrations in serum chloride and bicarbonate were compensated by increased concentrations of phosphate, sulfate, and organic acids. The non-protein nitrogen concentration became elevated to 282 mg per dl. The relative rise in phosphate, sulfate, and organic acids with displacement of chloride is attributed to the loss of selective excretion through the kidneys of these anions which are constantly being liberated in the metabolism.  

The patient was treated by decapsulation of both kidneys and the intravenous administration of copious quantities of physiological saline. A kidney biopsy revealed extensive nephrosis. The convoluted tubules were necrotic; however, the glomeruli revealed minimal change. Two weeks after admission, the patient began to secrete urine and gradually became rational. He returned to a relatively normal status in approximately five months after the poisoning.

Case 2 Poisoning from Skin Absorption

Delayed skin sensitivity reactions appear to occur more often in persons exposed to organic rather than inorganic mercury. Such a reaction previously reported by us\textsuperscript{67} was a research chemist who accidentally spilled 30 ml of a saturated solution of phenylmercuric acetate (in benzene as solvent) over his right hand. The solvent evaporated rapidly leaving a white crust of the mercurial on his hand. The patient immediately washed his hand with soap and warm water. He developed no immediate discoloration or discomfort. Eight hours after exposure, the patient developed pruritus and erythema on the back of the hand. Vesicles began to form approximately 13 hours after exposure, developing into bullae as shown in figures 1 and 2. The concentration of protein in the

\begin{table}[h]
\centering
\caption{Analyses of Serum from Patient with Bichloride of Mercury Poisoning by Ingestion}
\begin{tabular}{|l|l|l|l|}
\hline
 & Patient & Average & Normal & Difference \\
 & mg/dL & mg/dL & mg/dL \\
\hline
Total Base* & 146.5 & 154.7 & -8.2 \\
Cl - & 72.2 & 104.0 & -31.8 \\
[\text{H}_2\text{PO}_4^-] & 22.2 & 25.8 & -3.6 \\
[\text{H}_2\text{PO}_4^- + \text{H}_2\text{PO}_4^-] & 9.4 & 3.0 & +6.4 \\
\text{B}_{2}\text{SO}_4 & 12.0 & 1.0 & +11.0 \\
\text{B}_{2}\text{PO}_4 & 18.0 & 16.0 & +2.0 \\
\text{B} \text{organic acids} & 8.4 & 4.9 & +3.5 \\
\text{PH} & 7.31 & 7.31 & 0.00 \\
\hline
Non-protein nitrogen & & & \\
mg per 100 dl & 282.0 & 25 & \\
Freezing point depression & 0.63° C. & 0.55° C. & \\
\hline
\end{tabular}
\begin{flushleft}
* Total base was chemically determined. It denotes the summation of the inorganic cation concentration of serum (exclusive of \text{NH}_4), i.e., sodium, potassium, calcium, and magnesium concentrations in serum. \\
† [\text{H}_2\text{PO}_4^-] = \frac{1}{2}[\text{CO}_2] - 1.27 \\
‡ \text{B}_{2}\text{PO}_4 \text{ at pH 7.31} = \frac{77}{23} \text{[PO}_4^-] = 5.3 \text{mM per L} \\
§ \text{B}_{2}\text{PO}_4 + \text{B}_{2}\text{PO}_4^- = 9.4 \text{mEq} \\
\| \text{B}_{2}\text{PO}_4 + \text{H}_2\text{PO}_4^- = 0.95 \text{Pr (pH = 5.26); Pr} = \text{g protein per dl} \\
\| Calculated by difference
\end{flushleft}
\end{table}
serous fluid was only about 60 percent of the concentration in the serum; however, the ratios of the albumin to globulin were essentially the same. It is noteworthy that the concentration of gamma globulin in the serous fluid was greater than in the serum.

The patient's serum electrolytes were essentially within the normal range of values. Urinalysis remained within normal limits. The lesion healed without scar formation in two to three weeks. The only residual affect was the loss of hair over the exposed areas.

Poisoning from the skin absorption of inorganic mercury salts was especially prevalent during the last century among workers in the felt hat industry. The disability in these workers has given rise to such expressions as "the mad hatter," "chattering away to himself like a mad hatter," and "Danbury shakes." Danbury, Connecticut was a center in the United States for the manufacture of felt hats, and the expression, "Danbury shakes," refers to the tremors that were prevalent among the hatters of Danbury. 22,43,60

**Figure 1.** Lesions on palm of right hand five days after exposure to phenylmercuric acetate.

**Figure 2.** Lesions on dorsum of right hand five days after exposure to phenylmercuric acetate.

**Figure 3.** Callouses on palmar surface of the hand of a hatter.
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The danger of mercurialism among hatters occurs mainly during the process of felting the fine hairs from the furs of rabbits, muskrats, and beavers. The smooth, straight, and resilient hairs are roughened and twisted by treatment with an acid solution of mercuric nitrate. This alteration of the hair is essential for felting. Figure 3 is a photograph of a hatter's hand and shows the callouses on the hypothenar area and the palmar surface that resulted from wetting down fur for felting.

**Case 3 Poisoning from Mercury Vapor Inhalation**5,6,12,19,20,28,31,33,40,42

The inhalation of mercury vapor is undoubtedly the most common form of mercurialism that is presently encountered. The patient whom we studied and treated over a protracted period was a 41-year-old man who had been employed in the manufacturing of thermometers for 13 years. The patient had been extensively studied for six months before our contacts with him and was diagnosed as suffering from a psychosis with essential tremor with the recommendation that he be committed for mental institutional care. An alert resident obtained the history of exposure to mercury which finally led to the diagnosis of mercury vapor poisoning after the finding of 2.9 mg of mercury in a 24 hour collection of urine (normal 0.006 to 0.02 μg) and an increased concentration of 240 μg of mercury per dl of serum (normal 5 to 20 μg). After extensive treatment with BAL, penicillamine, and sweats, the patient made a complete and uneventful recovery. A resume of the clinical data are given in table IV. Specimens of the patient's handwriting before treatment and after treatment are shown.

### Table IV
Resumé of Clinical Data

<table>
<thead>
<tr>
<th>Date</th>
<th>Therapeutic Agents</th>
<th>Hg Urine mg/day</th>
<th>Hg Serum μg/l</th>
<th>Hg Sweat μg/l</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/15</td>
<td>Before therapy</td>
<td>2.9</td>
<td>240</td>
<td></td>
<td>Severe reaction.</td>
</tr>
<tr>
<td>1/16-17</td>
<td>BAL (1st day)</td>
<td>25.2</td>
<td>235</td>
<td></td>
<td>Rapt improvement. Severe ulcerative stomatitis.</td>
</tr>
<tr>
<td>1/17-30</td>
<td>BAL (average 3 days)</td>
<td>14.8</td>
<td>340</td>
<td></td>
<td>Return of symptoms.</td>
</tr>
<tr>
<td>1/31-2/13</td>
<td>Penicillamine (average 3 days)</td>
<td>0.5</td>
<td>255</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/14-16</td>
<td>None</td>
<td>0.4</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/17-3/4</td>
<td>Dithiocarb (average 4 days)</td>
<td>1.2</td>
<td>240;</td>
<td>370</td>
<td>Mental confusion, dermatitis &amp; urticaria.</td>
</tr>
<tr>
<td>3/5-7</td>
<td>BAL</td>
<td>1.4</td>
<td>290</td>
<td></td>
<td>Favorable response, alert.</td>
</tr>
<tr>
<td>3/8-6/20</td>
<td>Sweats &amp; physio-therapy</td>
<td>0.7</td>
<td>290;</td>
<td>100; 32</td>
<td>Mentation &amp; aids for daily living improved.</td>
</tr>
<tr>
<td>6/20-11/17</td>
<td>Sweats &amp; physio-therapy</td>
<td>0.2-0.08</td>
<td>40; 4</td>
<td>45</td>
<td>No defects of mentation, calculation or judgment.</td>
</tr>
<tr>
<td>After 6 months</td>
<td>Continuing sweats &amp; physio-therapy</td>
<td>0.2-0.08</td>
<td>40; 4</td>
<td>45</td>
<td>Slight intention tremor, eventually disappeared.</td>
</tr>
<tr>
<td>After 1 year</td>
<td></td>
<td>0.017</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The photograph was taken by the author in 1924 at the Pennsylvania Hospital.

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5 The photograph was taken by the author in 1924 at the Pennsylvania Hospital.

6 British antilewisite, 2,3-dimercaptopropanol (usually called dimercaprol or BAL).

7 Sodium diethyl dithiocarbamate.
complete recovery are shown in figures 4 and 5. Initially, the patient experienced most of the neuropsychological symptoms associated with elemental mercury vapor poisoning. A description of the patient's course and the analytical method for the measurement of mercury have been published.65,67,68

In a study of laboratory technicians using mercury-filled volumetric apparatuses for gas analysis, Harrington found concentrations of mercury in urine as high as 2.4 mg per liter. (The normal range is 6 to 20 μg.) Harrington expressed concern that the laboratory workers were ignorant of the potential dangers from chronic exposure to mercury vapor. In a survey of 40 laboratory technicians exposed to metallic mercury for several years, Lauwerys and Buchet found a significant correlation between the concentrations of mercury in urine and the extent of the exposure to mercury. The expanding uses of mercury in scientific instruments, electrical devices, lighting equipment, rectifiers, fungicides, pigments, and catalysts will tend to increase dangers from mercury intoxication.

Treatment of Mercury Poisoning

The time-honored treatment for persons ill from exposure to mercury in mining and industrial operations has been, in the main, directed to diaphoresis and physiotherapy.7,65 The beneficial effects of sweating in patients poisoned by mercury inhalations have been recognized for centuries. Some 300 years ago, Olaus Borch (1626–1690), a professor of chemistry and botany in Copenhagen, was reported to have developed “asphyxia and palsy to the point of death” while working with quicksilver and to have been restored to health by sweating.7 Health regulations in Spain, that are two centuries old, limit cinnabar (mercuric sulfide, HgS) miners to a work period of only eight days per month. As a consequence, these men hold second jobs in the various trades, and their exposure to mercury is intermittent and limited. Nonetheless, many become chronically ill from exposure to mercury vapor. Putnam describes the treatment given in a hospital in Almaden, Spain. The hospital contains a special room lined with heat lamps and has a floor marked with a circular path. “Sometimes a man inhales too much mercury vapor in the mine and develops a tremor. If it’s a severe case, the doctors send him here (i.e., the room), for treatment. He strips and walks round and round (the circular path) in the heat, sweating out the mercury. Most respond rapidly and return to work. A few don’t; they are pensioned.”

In the early part of this century, the treatment of mercury poisoning was directed, for the most part, to persons attempting suicide by the ingestion of lethal amounts of mercuric chloride.63 For this purpose, Lambert and Patterson advocated the use of diuretics, both orally and by rectum, supplemented by diaphoresis. These measures were combined with the administration of albumin in the form of milk and frequent flushings of the stomach and colon.

As an adjunct to the diuretic and diaphoretic treatment of Lambert and Patterson in 1915, Hayman and Priestley in 1928 advocated the decapsulation of the kidneys and the administration of appropriate saline fluids as replacement therapy and for the correction of electrolyte imbalance. Sanchez-Sigilia and colleagues in 1963 recommended the use of hemodialysis in the treatment of acute mercurial intoxication.62

The use of chelating agents in the treatment of heavy metal poisoning has been under investigation since the development of BAL during World War II as an antidote for arsenic poisoning. In general, BAL and d-penicillamine have been recommended as antidotes of choice for mercury poison-

† Van Slyke, Haldane, Martin, etc.
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However, as Gabard14 has pointed out, the experimental and clinical data upon which these recommendations were based have been meager and contradictory. Within the past four years, two separate reports36,45 have been published on the treatments of two different families of four and seven persons, respectively, who were exposed to mercury vapors and for whom penicillamine did not produce any significant increase in the excretions of mercury. The therapeutic value of penicillamine in both reports was uncertain. It should also be noted that most of the reports on the response of chelating agents, and particularly penicillamine, placed emphasis on their use in the treatment of intoxication from organic mercury, especially methyl mercury. Dithiocarbamate compounds have had limited success in the treatment of inorganic mercury poisoning.41,65 There have been comparatively few studies that pertained to chelation therapy of poisoning from the inhalation of mercury vapor or the ingestion of inorganic mercury compounds. However, within the past two years, Campbell, Clarkson, and Omar8 reported 2,3-dimercaptopropane-1-sulfonate to be effective in two patients suffering with heavy intoxication from elemental mercury vapor.

Mercurials in the Environment11,18,29,47,48,54,61,70

The ecological effects of mercury on health have been extensively studied and reported by the World Health Organization.70 A number of studies have been undertaken in an effort to set acceptable tolerances for mercury in food. Although no firm limits have been set, nevertheless, a Food Additives World Health (FAO/WHO) commission set as a provisional tolerable weekly intake (PTWI) for human beings 5 μg per kilogram of body weight for the intake of methylmercury expressed as mercury.48 Toxic effects from the dietary intake of methyl mercury are reported to be in the range of 250 to 420 μg per day. According to Clarkson,10 adverse health effects become manifest in occupational exposures to elemental mercury vapor in atmospheric concentrations above 100 μg per cubic meter, although deleterious effects have been claimed in concentrations of 10 to 100 μg per cubic meter.2,26 Lauwers and Buchet35 pointed out that there is no international agreement of the allowable concentrations of mercury vapor to which people may be exposed. In the Soviet Union, the maximum allowable concentration for mercury in air was set in 1944 for industry to be 10 μg per cubic meter. Trakhtenberg, however, suggests that this low value has little margin of safety.69 According to Trakhtenberg, Soviet investigators have shown that warm blooded animals chronically exposed to concentrations of mercury vapor from 6 to 50 μg per cubic meter develop a syndrome, which is referred to as micromercurialism. Finnish workers56 have recently recommended an atmospheric exposure limit of 25 μg per cubic meter to avoid adverse effects in humans. These workers also reported a statistically significant correlation between the impairment of memory and the concentrations of mercury in blood. They suggested that the monitoring of mercury concentrations in blood should provide useful information in programs of health surveillance.

Comments on Previous Therapeutic Uses of Mercury and Its Compounds

In past centuries, mercurial compounds were used extensively as therapeutic agents. In his Treatise on the Medical Qualities of Mercury published in 1776, Falck13 stated, "There is no temperament, constitution, sex, or
period of life, exempt from receiving benefit from mercury and its preparations; and I don't know a disease incident to mankind, where it can with propriety be deemed improper; unless used to excess, and disproportioned to circumstances. The truth of this I have experienced with success both by internal and external applications; not only in the venereal, but inflammatory and chronic distempers."

**Calomel and Blue Mass as Cathartics**

Before World War II, calomel (mercurous chloride) and Blue Mass (metallic mercury triturated with honey and licorice) were widely used as cathartics. In fact, these mercurial cathartics were prescribed routinely to almost every patient (excluding those with appendicitis, bleeding ulcers, etc.) admitted to most of the hospitals in this country. Gradually, the toxic, renal, and allergic effects of these compounds became recognized and they were finally discarded, in spite of the pleas from distinguished professors of medicine. My beloved teacher, O. H. Perry Pepper in 1953, made a plea that calomel be given another chance and suggested that the fate of calomel might be in part due to the excessive dosage, to unqualified claims and also of the invasion of well-advertised and more profitable substitutes.

**Blue Ointment in the Treatment of Syphilis**

In several centuries before 1940 when penicillin first came into use, patients undergoing treatment for syphilis could be observed every day in the medical wards of our hospitals rubbing blue ointment into their bodies. The ointment was applied according to the directions given in most of the medical textbooks published earlier in this century. The course of treatment usually extended over a period of a year and led to the adage that "a night with Venus was the prelude to a year with Mercury."

The following excerpt taken from Osler and McCrae's textbook in 1920 relates to the use of mercury in the treatment of syphilis:

"Mercury should always be given after arsphenamine. . . . It is well to push the administration so that the patient is under its influence as rapidly as possible. Inunction is the most effective means of administration. One-half of a dram (2 to 4 grams) of mercurial ointment or olate of mercury is thoroughly rubbed into the skin, on areas free from hair, daily for six days; on the seventh a warm bath is taken. It is well to apply the ointment on successive days. The sides of the chest and abdomen and the inner surface of the arms and thighs are the best positions. Thirty inunctions is an average number for each course."

In his concise *History of Medicine*, Sir William Osler included mercury in his list of the "few real medicines or healing agents which must be used" in the treatment of patients.

**Comments, Suggestions and Conclusions**

Many of the syphilitic patients treated with mercury inunctions became ataxic and spent their last days in mental institutions. One might speculate that in many of those diagnosed as having locomotor ataxia and/or manic-depressive psychosis, the causative factor was the iatrogenically administered mercury and not the wandering spirochete.

Fortunately, the use of mercurial drugs has been almost completely discarded. In addition, recognition of the perils have been helpful in protecting persons from the direct exposure to mercury and its compounds. Some exceptions are still extant, as for example, the use of amalgams for filling tooth cavities and the application of cosmetics, such as mercury-containing mascaras. Hope-
fully, these exceptions will soon be replaced with non-toxic substitutes. The larger problem at the present time is the prevention of indirect and undetected exposures of mercury from environmental and dietary sources. The extensive uses of mercury in industrial instrumentation, thermo-regulators, fluorescent lighting, etc., create hazards that are usually not considered or recognized. Waste water polluted with mercury enters ocean and river beds and contaminates fresh water fish and seafood. Such mercury-contaminated food sources are usually overlooked. Furthermore, mercury vapors from industrial operations, burning of fossil oils, coal-fired power plants, mining and melting operations are uncontrolled and pollute the atmosphere. These sources require surveillance.

It may be presumed that the development of effective methods for safeguarding man from adverse environmental and dietary exposures to mercurials will contribute to the prevention of related metabolic, psychiatric, and neurologic disabilities. From reports in the literature, it would appear that the magnitude of exposure to mercury may be estimated from measurements of the concentrations of mercury in the blood and body fluids. Hence, the analysis of the results of the recent Finnish health surveillance program, which includes the routine measurement of mercury in blood, will require careful study and assessment.

Advancement in our knowledge of the toxicity of mercury will constitute a subject for research in clinical science for many years to come. Relatively little information is available on the metabolic state of inhaled mercury vapor in humans or of the amounts of exposure in which adverse effects first manifest themselves. Adverse effects for elemental mercury vapor appear to become manifest in atmospheric concentrations between 10 and 100 μg per cubic meter and for methyl mercury in the dietary intake between 280 and 420 μg per day. Confirmatory studies are needed to support the dosage ranges. For the protection of man, it obviously becomes important to determine the uptake of mercury and the rates of methylation in the flora and fauna. Animal studies suggest that a number of agents may influence the levels of toxicity. For example, the injection of selenium appears to reduce the toxicity of methylmercury; and alcohol and certain herbicides may influence the degree of absorption of mercury vapor. These factors require further study.

Finally, in patients encountering depressions, behavioral, and neurological disorders, it is our opinion that careful consideration should be given to intoxication from undetected exposure to mercury as a possible cause.

References


