

## Mercury exposure and cutaneous disease

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Human contact with mercury has been ongoing for centuries and was previously considered a legitimate means of treating different cutaneous and systemic conditions. Toxicity from this heavy metal may occur from exposure to elemental, inorganic, and organic forms of mercury. This article outlines the signs and symptoms of mercury poisoning and the different clinical conditions with assorted cutaneous findings. (J Am Acad Dermatol 2000;43:81-90.)

**H**uman exposure to mercury has been present for centuries. This heavy metal was administered therapeutically in the European syphilis pandemic of the late 1400s.<sup>1</sup> Industrial exposure to methylmercury was responsible for numerous deaths in the late 19th and early 20th centuries. Two physicians noted the constellation of symptoms caused by the poisoning and the syndrome now bears their names: Hunter-Russell syndrome.<sup>2</sup> In the 1950s more than 2500 persons were affected in and around Minimata Bay, Japan after consuming seafood contaminated by methylmercury pollution from nearby paper mills.<sup>1</sup> Most recently, a large outbreak of mercury poisoning in Iraq occurred after people ate grain treated with mercury-containing fungicides.<sup>3</sup>

Mercury is unique in that it is the only metal existing in liquid form and capable of evaporating at room temperature.<sup>4</sup> It occurs in 3 forms: metallic or elemental, organic, and inorganic.<sup>1,5</sup> Health consequences depend on the metallic form of exposure as well as the timing and dosage. Not all exposures result in cutaneous disease.

We describe a patient with cutaneous mercury deposits and outline the different forms of the metal that may affect patients and the clinical presentations of cutaneous disease.

### CASE REPORT

A 42-year-old previously healthy man presented with complaints of slightly tender "warts" on the left hand of 3 months' duration. He reported cutting himself on a sharp object while blindly reaching inside the wall of a house he was renovating. He denied any history of exposure to fish tanks, farm animals, or roses.

On the dorsum of his left wrist was a slightly erythematous nodule measuring 4 × 2 cm (Fig 1). A smaller nodule on the hand measured 2 × 3 cm. No drainage was noted. The patient was afebrile and without palpable adenopathy. A tissue culture was negative for bacteria, fungus, and mycobacteria. Ten weeks of intermittent topical and oral antibiotics failed to clear the lesions.

Histologically, the tissues demonstrated fibrosis with an inflammatory infiltrate of neutrophils, histiocytes, and scattered eosinophils. Granulomatous changes, including giant cells, were also present. Variably sized, circular aggregates of black material were seen adjacent to and within tissue vacuoles (Fig 2). A tentative diagnosis of a mercury granuloma was made. Scanning electron microscopy and energy dispersive x-ray spectroscopy confirmed the foreign material as elemental mercury (Fig 3).

An x-ray examination of the affected limb demonstrated a well-defined area of involvement along the dorsal hand, wrist, and forearm (Fig 4). Results of a chest x-ray examination were normal.

The affected area was excised and the wound covered with a split-thickness skin graft. Residual elemental mercury was noted in the tissues at surgery. The patient recovered uneventfully.

A 24-hour urinalysis yielded 86.6 µg of mercury (normal < 10.0 µg/24 hr). Whole blood mercury was 32.4 µg/L (normal < 14.9 µg/L). Renal and hepatic functions were normal and his blood count and leukocyte differential were unremarkable.

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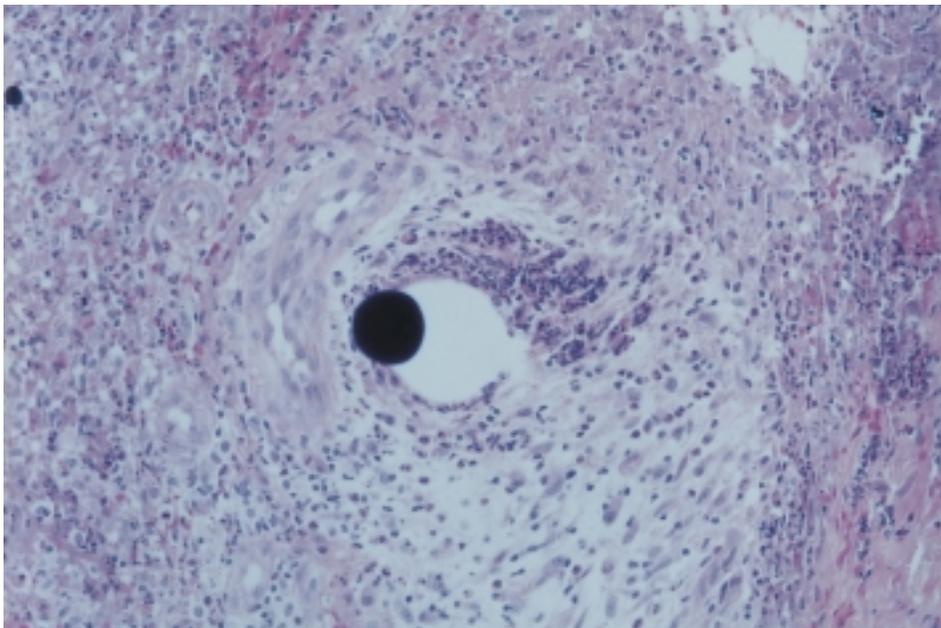
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**Fig 1.** Erythematous and flesh-colored nodules on dorsal wrist and hand.



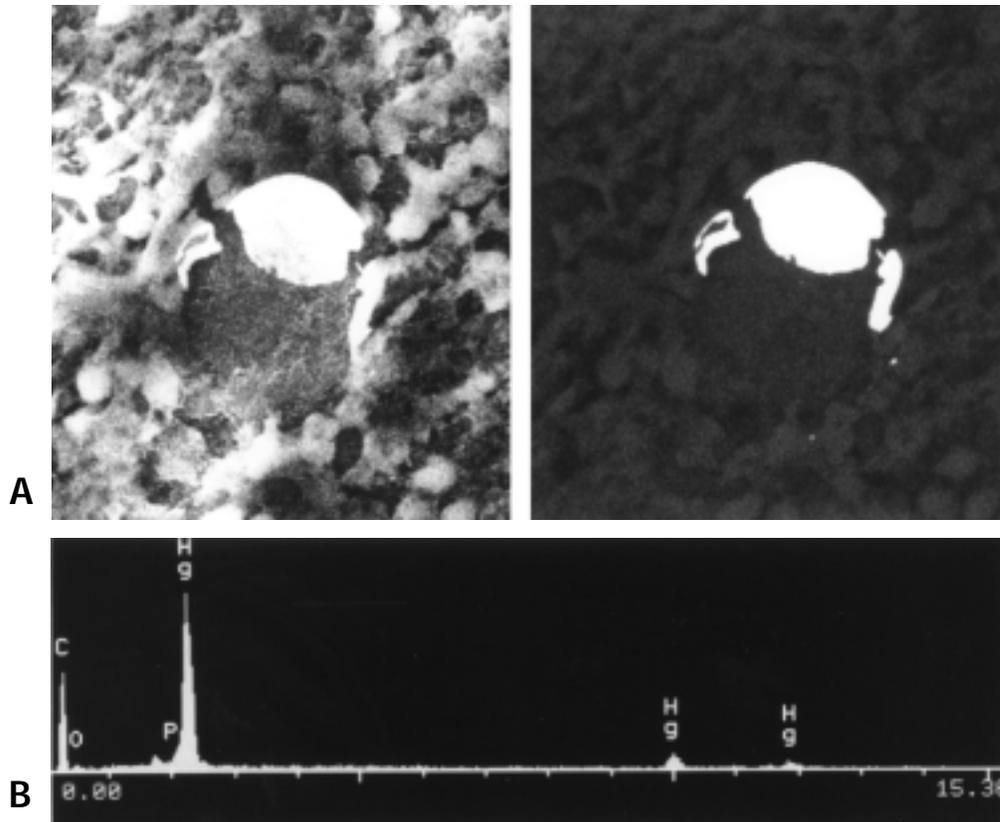
**Fig 2.** Black globules of mercury surrounded by fibrosis and suppurative inflammatory response.

A neuropsychiatric evaluation was performed and disclosed a mild tremor, vague neurovegetative symptoms, and clinical depression. It was unclear whether the depression was antecedent to the injury, resulted from his exposure to the mercury, or has occurred because of his loss of employment. The patient has subsequently been lost to follow-up.

## FORMS OF MERCURY

### Elemental

Elemental mercury vapor is absorbed readily by the lungs and transported through the blood to the brain and other tissues.<sup>6,7</sup> It is oxidized, presumably in red blood cells, to mercuric ions that combine with sulfhydryl groups on cell membranes and enzymes.<sup>1</sup>



**Fig 3.** **A**, Scanning electron microscopic image with backscatter (*left*) and secondary electron image (*right*) showing bright remnant of spherical droplet of mercury and surrounding cellular tissue. (Original magnification  $\times 1000$ .) **B**, Mercury composition confirmed by energy-dispersive x-ray spectrum.

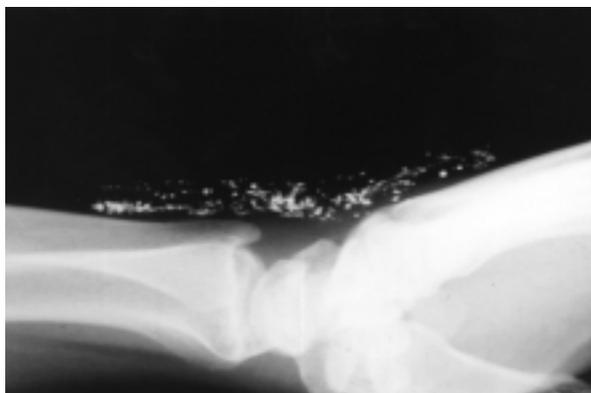
Interestingly, metallic mercury is absorbed negligibly after oral ingestion.<sup>8</sup> Unless regurgitation and aspiration occur, swallowing this element poses no health hazard. Common sources of metallic mercury exposure include mercury switches, thermostats, barometers, and thermometers.<sup>6</sup> When this heavy metal is spilled onto upholstery and carpeting it may slowly volatilize over time, thereby resulting in toxic air concentrations, a common scenario for pediatric poisoning.<sup>6</sup> Contaminated items must be discarded because removal of the metal is difficult.

Toxic exposure results in 3 symptomatic stages. Initially, the patient experiences a flu-like syndrome with fever, headache, myalgias, chills, and dryness of the mouth and throat.<sup>9</sup> It is often mistaken for a viral illness. The second stage begins after 2 weeks and includes multiorgan symptoms involving the central nervous system (CNS) as well as the respiratory and urologic systems. Gastrointestinal complaints are often preeminent and consist of a metallic taste in the mouth, thirst, abdominal pain, nausea and vomiting, constipa-

tion, and anorexia.<sup>1</sup> The symptoms during the third stage are primarily neuropsychiatric and take place over a prolonged period (Table I). The constellation of memory loss, irritability, excitability, depression, diminished self control, and drowsiness is termed "erethism" and is typical for patients with heavy metal poisoning.<sup>6</sup> These sequelae suggest a parkinsonian syndrome involving the basal ganglia and cerebellum.<sup>6</sup> An intention tremor is the most common finding. There likely exists a dose-response relationship between the degree of mercury exposure and the profundity of the neurologic deficits.<sup>1</sup> Some of these deficits are permanent.

Cutaneous findings are few, although the gums may demonstrate a blue line along the alveolar margin similar to that seen in long-term lead or bismuth exposure.<sup>6,11</sup> A lichenoid drug reaction has also been described.<sup>12</sup>

The half-life of elemental mercury is approximately 60 days.<sup>6,9</sup> It is excreted primarily by the kidneys where it accumulates and induces the most damage. Long-term sequelae often include renal failure.<sup>1</sup>



**Fig 4.** Radiographic presentation of metallic mercury diffusely in tissues of dorsal forearm, wrist, and hand.

Evaluation of body fluids for mercury is performed by reference laboratories. Although there is some controversy as to what constitutes toxicity, blood evaluation is recommended, particularly for acute intoxications.<sup>1</sup> Normal levels rarely exceed 15  $\mu\text{g/L}$ . Mercury levels in the plasma may be elevated for prolonged periods because of slow release from erythrocytes after oxidation.<sup>3</sup> Urinary excretion should be evaluated over 24 hours because spot-checked levels are often inaccurate.<sup>1</sup> Rarely is more than 50  $\mu\text{g}$  of mercury excreted in 24 hours unless active chelation is ongoing. Concentrations higher than 300  $\mu\text{g/L}$  are considered the threshold of toxicity, and symptoms rarely occur until mercury excretion rises to this level.<sup>1</sup> Analysis of hair strands by means of x-ray fluorescence for mercury contamination is also possible but may be falsely elevated in persons residing in environments with increased ambient atmospheric concentrations or in populations consuming methylmercury-contaminated seafood.<sup>1,6,13</sup>

### Inorganic

Inorganic mercurials include ammoniated mercury, mercuric chloride, mercuric oxide, mercuric sulfide, mercurous chloride, mercuric iodide, and the phenylmercuric salts.<sup>1</sup> These have been previously used as laxatives (mercurous chloride, calomel) and as anthelmintic agents.<sup>14,15</sup> Toxicity from laxative abuse is uncommon but may still occur.<sup>16</sup> Most exposure today occurs with pesticides, antiseptics, and germicides.<sup>6</sup> Cutaneous compounds for skin lightening, infected eczema or impetigo, psoriasis, and secondary syphilis may contain inorganic mercury compounds and are still available, particularly in developing countries.<sup>17-19</sup>

Ingested inorganic mercury is corrosive to the gastrointestinal tract.<sup>1</sup> Patients typically present with gin-

**Table I.** Neuropsychiatric features of elemental mercury poisoning<sup>1,6,9,10</sup>

#### Neurologic

- Altered gait (ataxia)
- Constricted visual fields
- Deafness
- EEG slowing
- Seizures
- Scotoma
- Tremor
- Diminished short-term memory
- Dysphagia
- Neurasthenia
- Decreased strength
- Decreased sensation
- Spasticity
- Paresthesias
- Abnormal reflexes

#### Psychiatric

- Confusion
- Hallucinations
- Lethargy
- Diminished libido
- Manic-depressive episodes
- Neurotic reaction
- Psychomotor skill diminishment
- Suicidal ideation
- Temper instability

givitis, burning tongue, abdominal pain, nausea, vomiting, and esophageal erosions.<sup>16</sup> Unlike elemental mercury, the inorganic salts are readily absorbed by the gut and are excreted through the kidneys and gastrointestinal system.<sup>7,20</sup> Only about 10% of an ingested dose is absorbed, but the half-life is approximately 40 days.<sup>7</sup> Mercury salts interfere with sulfhydryl-containing enzyme systems.<sup>21</sup> Symptoms of poisoning are slow and insidious. They include neurologic sequelae such as dementia and tremor, but renal failure is often the terminal event.<sup>16</sup>

### Organic

Unlike inorganic toxicity, toxicity from organic mercurials is more fulminant. It includes neurologic decompensation with mental deterioration, ataxia, spasms, paresthesia, deafness, and eventually coma. These compounds include ethylmercury, methylmercury, phenylmercuric salts, thimerosal (merthiolate), and merbromin (mercurochrome).<sup>1</sup> The greatest danger with these compounds is their capacity for inducing birth defects in children exposed in utero. Ethyl- and methylmercury cross the placental barrier and are concentrated in the fetus and breast milk.<sup>1</sup> Affected children display a characteristic constellation of birth defects including severe mental retardation, seizures,

spasticity, chorea, atheototic movements, tremors, ataxia, deafness, cataracts, small birth weight, anemia, and renal dysfunction. Adult men exposed to these chemicals may experience teratospermia.<sup>1</sup>

Thimerosal is the most common organic mercurial inducing cutaneous disease, which results from its use as an antiseptic and preservative in cosmetics, topical medications, and vaccines.

### Therapy

Treating patients with acute or chronic mercurialism has traditionally centered on chelation therapy. Dimercaprol (British anti-Lewisite [BAL]; 2,3-dimercapto-*l*-propanol) and *D*-penicillamine have been the most popular agents used for this treatment. It is now known that in patients with methylmercury poisoning, BAL may increase the CNS levels and exacerbate toxicity.<sup>1,22</sup> DMSA (meso 2,3-dimercaptosuccinic acid) is useful in children with lead poisoning and may be beneficial in treating mercury intoxication.<sup>1</sup> It is superior to *D*-penicillamine with fewer side effects and can almost completely prevent methylmercury uptake by erythrocytes and hepatocytes.<sup>1,9</sup> DMPS (2,3-dimercaptopropane-*l*-sulfonate) is under review by the Food and Drug Administration for mercury poisoning.<sup>6</sup> *N*-acetyl-penicillamine has been successfully given to patients with mercury-induced neuropathies and chronic toxicity, although it is not approved for such uses.

Hemodialysis with and without the addition of *L*-cysteine as a chelating agent has been used in some patients experiencing acute renal failure from mercury toxicity.<sup>1,6</sup> Peritoneal dialysis and plasma exchange may also be of benefit.<sup>7,23</sup>

### CUTANEOUS CONDITIONS ASSOCIATED WITH MERCURY EXPOSURE

Some of the skin manifestations from contact with mercury or mercury-containing compounds are well described and are classified as distinct syndromes.

#### Acrodynia (pink disease)

This condition is perhaps the best known in dermatology because many of the signs and symptoms are referable to the skin. Acrodynia was initially described in the latter part of the 19th century.<sup>24</sup> From 1920 to 1950 cases were common in England, Australia, and the United States because mercury-containing medications were in widespread use. In 1980, a large outbreak in Buenos Aires, Argentina occurred in children exposed to commercially laundered diapers containing a mercurial antibacterial agent.<sup>25</sup>

Acrodynia is typically restricted to infants and young children.<sup>24</sup> Newborns and adults do not appear

to be susceptible. Only a certain subset of exposed patients are affected, suggesting that it represents an idiosyncratic hypersensitivity response.<sup>24,26</sup>

Pink disease occurs in children exposed to mercury for prolonged periods.<sup>24</sup> This may result from elemental mercury vapor, calomel-containing teething and diaper powders, fungicides in paint, repeated gamma-globulin injections, anthelmintics, termite-protected wood (mercury bichloride), ingestion of watch batteries, laxative use, and ammoniated mercury ointments applied as antibacterial agents.<sup>1,6,24,27,28</sup> Most of these substances are rare today, but mercuric oxide is still considered by some clinicians the therapy of choice for eyelid mites.<sup>29</sup>

Affected patients are initially listless, anorexic, and irritable.<sup>24</sup> Their blood pressure and heart rate increase. Significant pain occurs in the hands and feet preventing sleep. Children often rub their palms together in an attempt to diminish this discomfort. Eventually the hands and feet will swell, becoming a dusky pink along with the nose. The palms and soles sweat profusely and desquamate as the disease abates. One author termed this "puffy, pink, painful, paresthetic, perspiring, and peeling hands."<sup>6</sup> The skin is cold and moist from excessive perspiration, supporting the hypothesis that acrodynia involves an element of sympathovascular dysfunction.<sup>24</sup> Excoriation with lichenification may ensue as the children rub and scratch their skin. Excessive salivation with red and swollen gums is common.<sup>6</sup> Ulceration of these mucosa and tooth loss are seen. Alopecia often occurs from the patient pulling the hair out. Nail loss has been reported. Photophobia arises and children may hide their eyes. Muscle weakness affects the pectoral and pelvic girdle.<sup>1</sup> This is not a paralysis but rather diffuse hypotonia. Patients may assume the "salaam position" in which they sit with their heads between their legs and rub their hands together.<sup>24</sup> Older children tend to have less morbidity.

Cutaneous biopsy specimens are nonspecific with hyperplastic sweat glands and a variable dermal inflammatory infiltrate.<sup>30</sup> Mercury blocks the action of catechol methyl transferase leading to increased amounts of vanillylmandelic and homovanillic acid in the urine.<sup>6</sup>

Treatment initially involves discerning the source of mercury poisoning and preventing further exposure. The chelating agent DMSA appears to increase mercury excretion more than penicillamine.<sup>6</sup> Therapy clears the condition in many children; however, long-term morbidity and death have been reported.<sup>24,28</sup>

#### Mucocutaneous lymph node syndrome (Kawasaki's disease)

The signs and symptoms of acrodynia are similar to those of the mucocutaneous lymph node syn-

drome, prompting Cheek<sup>31</sup> to suggest that this entity may be caused by mercury poisoning. Orłowski and Mercer<sup>32</sup> later evaluated 6 patients with a clinical diagnosis of Kawasaki's disease and found all with increased urinary mercury excretion. A subsequent report found no association between the two diseases.<sup>15</sup> Given the similarity between these conditions it seems advisable to test patients believed to have the mucocutaneous lymph node syndrome for mercury exposure.

### **Tattoo reaction**

Persons with tattoos containing red pigment from mercuric sulfide (cinnabar-vermillion, Chinese red) and occasionally cadmium sulfide may experience inflammation restricted to these sites, usually within 6 months of tattooing.<sup>33-37</sup> The areas become swollen, crusted, and scaly with modest discomfort. A psoriasiform, verrucous reaction has also been described.<sup>36</sup> One patient traumatized the red area of his tattoo and experienced a generalized eczematous eruption that required hospitalization.<sup>33</sup>

Histologically the epidermis demonstrates lichenoid features with sawtoothing.<sup>34,37</sup> Vacuolar changes and dyskeratotic cells may be present. An interface inflammatory infiltrate of lymphocytes, histiocytes, plasma cells, and occasional neutrophils is seen. The tattoo pigment is present as clumps and irregular granules, is usually extracellular, and is not refractile.<sup>33</sup> Direct immunofluorescence has shown globular aggregates of IgM, IgG, and IgA with a shaggy band of fibrin along the dermoepidermal junction. Some specimens demonstrate a granulomatous infiltrate with a tuberculoid or sarcoidal pattern.<sup>36</sup> A pseudolymphoma inflammatory pattern has also been reported.<sup>35</sup>

It is assumed that the presence of mercuric sulfide is responsible for promoting this reaction.<sup>36,38</sup> Cinnabar is insoluble in water and must develop a degree of solubility within the dermis. The pigment may disassociate and form organic compounds, which act as haptens.<sup>36</sup> Stjskal et al<sup>39</sup> described mercury specific lymphocytes and believe that a cell-mediated hypersensitivity reaction is active. Some investigators do not believe that mercury induces this phenomenon.<sup>34</sup>

Patch testing has proven disappointing.<sup>34,38</sup> In one study, only 1 of 9 patients tested reacted to mercurial antigens.<sup>37</sup> Another patient reacted to patch testing with 5% ammoniated mercury cream.<sup>33</sup>

Alternative dyes have become more popular. Cadmium red, sienna/red ochre (ferric hydrate), and organic substances such as sandalwood and brazilwood have replaced the use of mercuric sulfide in many establishments.<sup>37</sup>

### **Mercury exanthem**

The elicitation of an exanthem from mercury exposure may represent an example of a systemically induced allergic contact dermatitis.<sup>3,40,41</sup> Most commonly provoked by inhalation of mercury vapors, it is often initiated by previous exposure to organic mercury compounds such as merthiolate and mercurochrome.

A diffuse and symmetric erythematous maculopapular eruption begins on the flexural areas and proximal extremities within a few days of exposure.<sup>31</sup> A V-shaped pattern of redness on the medial thighs mimics the "baboon syndrome."<sup>41,42</sup> The eruption often has a burning or pruritic quality. Small, non-follicular sterile pustules may form as the disease progresses. Purpura is seen in severe cases.<sup>41</sup> Fever, malaise, and thirst are common.<sup>4</sup> The condition clears with extensive desquamation, particularly on the hands and feet, at around 14 days. The pustules show a subcorneal collection of neutrophils with epidermal spongiosis.<sup>4,41,42</sup> The dermis is nonspecifically edematous with scattered mononuclear cells and polymorphonuclear leukocytes. Intrafollicular neutrophils have also been reported.<sup>4</sup>

Most cases are subsequent to exposure to metallic mercury, usually from a broken thermometer; however application of mercury-containing creams, topical antiparasitics, or antiseptics may also provoke this reaction.<sup>42-44</sup> Dental mercury exanthems arise in persons with an allergic reaction to their amalgam fillings. Other sources of exposure include vaccines, toxoids, gamma globulin preparations, contact lens solutions, and antitoxins.<sup>39</sup> A disproportionate number of cases have occurred in Japan, probably because of the high incidence of sensitization from mercurochrome, a popular disinfectant in homes.<sup>4</sup>

Patients are typically patch test positive to mercury antigens including elemental mercury, mercuric chloride, mercuric oxide, ammoniated mercury, thimerosal, and mercurochrome.<sup>4,41,44</sup> Patch testing with metallic mercury and ammoniated mercury is recommended.<sup>44</sup>

### **Dental amalgams**

One of the most prevalent uses for mercury is that of dental restoration, specifically the production of amalgams for filling teeth. More than 100 tons of the metal are used annually by dentists in the United States with the average private practitioner using 2 to 3 pounds.<sup>6,45</sup> One hundred million fillings yearly involve the use of mercury.<sup>46</sup> Such amalgams are 50% mercury by weight.<sup>47</sup> The gradual corrosion of these fillings releases 20 to 30  $\mu\text{g/day}$  of inorganic mercury.<sup>6,48</sup>

There is believed to exist an association between these dental fillings and the presence of oral lichenoid papules.<sup>49,50</sup> Such lesions are often, but not always, adjacent to mercury-containing amalgams. These are typically brown to violet papules and plaques with occasional reticulation. Ulceration may be noted in more advanced lesions. Histologically a lichenoid infiltrate reminiscent of lichen planus is noted.

Lesions are rarely symptomatic, and many patients are unaware of their existence. Removal of the offending fillings may result in clearing of the lichenoid plaques.<sup>49,50</sup> Patients whose lesions are in direct contact with the fillings have a better prognosis. The presence or absence of a positive patch test to mercury antigens may be meaningless.<sup>49,50</sup> Patch testing to mercuric chloride 0.1%, elemental mercury 0.5%, and mercury ammonium chloride 1.0% in petrolatum is recommended along with a reading at 1 to 2 weeks to avoid missing a delayed reaction.<sup>49</sup> Removal and replacement of dental restorative materials is a significant undertaking, and it is important to demonstrate a state of hypersensitivity before undertaking such a process.

The constant exposure to mercury, albeit minimal, may induce a state of sensitization with an increased susceptibility to oral lichenoid lesions.<sup>39</sup> Mercury binding to SH on endogenous proteins produces a change in antigenicity making them vulnerable to attack by immunocompetent cells and eventuating in oral lichenoid lesions.

### Cutaneous hyperpigmentation

Historically, one of the most common uses for mercury-containing compounds has been to alleviate cutaneous hyperpigmentation.<sup>11</sup> Mercurous chloride, mercurous oxide, and ammoniated mercury are often used topically for skin bleaching.<sup>11,51</sup> Many such medicaments are available over the counter, even in developed countries.<sup>51</sup> There is no restriction on the percentage of inorganic mercury that may be incorporated into these creams, and no warnings are required on packaging or inserts.

An unexpected side effect to the continuous application of these medications has been worsening cutaneous hyperpigmentation. This was initially described in 1922 by Goeckermann.<sup>52</sup> Long-term application may also result in significantly increased urinary mercury excretion and proteinuria.<sup>6</sup> Dyall-Smith and Scurry<sup>51</sup> described a patient with an 18-year history of continuous application to her face of a cream containing 17.5% mercuric ammonium chloride. In addition to profound cutaneous hyperpigmentation she also exhibited increased blood and urine mercury levels and neuropsychiatric changes including depression, anxiety, and paranoid delu-

sions. Such psychologic disturbances may not be reversible despite normalization of systemic mercury levels.

The mercury compounds are readily absorbed through the skin, perhaps via appendages. They induced depigmentation by competing with copper in the enzyme tyrosinase.<sup>51</sup>

Patients present with a "slate-gray" or light brown pigmentation of treated skin. In contrast to the pigmentation from other heavy metals, in mercury toxicity cutaneous folds of the nose, eyelids, and neck demonstrate increased darkening.<sup>11,53</sup> Long-term application of creams around the eyes may result in discoloration of the lens ("mercurialitis"), which is detectable by slit lamp examination.<sup>53</sup>

Mercury is demonstrable as coarse, refractile brown-black granules within the papillary dermis.<sup>54</sup> Iron and melanin stains are negative.<sup>11,51</sup> The granules aggregate in macrophages and around capillaries as well as lying free in the dermis. They are often associated with elastic fibers. The epidermis may demonstrate increased melanin production.<sup>11</sup>

Treatment consists of discontinuing the use of these creams and lotions. Often the hyperpigmentation improves rapidly.

### Contact dermatitis

Acute contact dermatitis from exposure to mercury-containing compounds presents with mild swelling, vesiculation, scaling, and irritation. Some investigators believe this is the most common dermatologic manifestation of mercury toxicity.<sup>26</sup> Thimerosal (merthiolate) is the most often cited offender. It is present in numerous antiseptics and disinfecting agents, nasal sprays, contact lens solutions, and vaccine/antitoxin preservatives.<sup>55</sup> Other mercurials such as mercurochrome, phenylmercuric salts, ammoniated mercury, mercuric oxide, and mercurous chloride are also capable of producing allergic cutaneous reactions. Patients allergic to one form of mercury may cross react with another. Patch test positivity to numerous mercurial agents may result despite the provocation of the allergy by a single substance.<sup>56</sup> Dental amalgams may induce allergic contact stomatitis as well as glabrous eczematous dermatitis, urticaria, and erythema.<sup>57</sup> Anaphylactic reactions have been reported.<sup>12</sup>

### Cutaneous granulomas

The elicitation of dermal granulomatous inflammation from elemental mercury is uncommon but histologically distinct. Fewer than 100 cases have been reported in the world literature.<sup>22</sup> The majority of such incidents represent a deliberate attempt at injecting the metal, typically with accompanying suicidal ideation.<sup>21</sup> Intravenous access is usually being

sought. In other patients the deposition of mercury is a manifestation of an underlying psychiatric disease. More unusual scenarios include an attempted homicide,<sup>58</sup> previous assault with a mercury tipped bullet,<sup>22</sup> impalation by a broken thermometer,<sup>18</sup> misguided attempts to make a boxer's punches "quicker" (quicksilver),<sup>59,60</sup> protection against assault with bullets,<sup>21</sup> and after accidental exposure in a dog bite wound.<sup>61</sup> Jun et al<sup>7</sup> described a patient with a cutaneous mercury granuloma who claimed to have been exposed 18 years earlier by consumption of duck soup containing the metal. Suchard and co-workers<sup>62</sup> later disputed these findings, instead proposing that the patient had deliberately injected himself. Anaerobic blood sampling with mercury sealed syringes, leaking mercury-containing intestinal intubation tubes, and repeated application of mercuric ointments and creams to cutaneous wounds have induced these granulomas.<sup>21,22</sup>

Patients typically present as ours did weeks to months later with a mass at the site of injection.<sup>22</sup> Most lesions are flesh colored to moderately red, although hyperpigmentation mimicking a nodular melanoma has been described.<sup>63</sup> Percutaneous extrusion of mercury has been reported.<sup>64</sup> Embolization to visceral organs, particularly the lungs, is common and has resulted in death.<sup>65</sup> The mercury is slowly converted to oxides and organic compounds with subsequent excretion by the kidneys.<sup>63</sup> Accumulation occurs in the kidney, spleen, and liver. Elevated urinary and blood levels of the metal may be present, although signs of systemic toxicity have been reported in only 5 patients including the one described here.<sup>21,66-68</sup> Functional impairment may not be present despite increased blood and urine levels of mercury.<sup>21</sup>

Evaluation of gross pathology specimens may demonstrate small aggregates of shiny metallic material within the dermis and subcutaneous tissues.<sup>21</sup> The histologic features from our patient's biopsy specimen are typical in that the mercury appears as spherical dark gray to black globules within tissue spaces surrounded by collagen necrosis.<sup>69</sup> Some deposits are encased in an eosinophilic capsulelike material.<sup>70</sup> A mixed inflammatory infiltrate of neutrophils, eosinophils, and histiocytes is present. Scattered giant cells are seen. Older lesions demonstrate greater fibrosis and granulomatous changes.

Definitive evaluation of the foreign material requires analysis by scanning electron microscopy/energy-dispersive x-ray, or the gold lysis test.<sup>7</sup> On scanning electron microscopy, the mercury appears as spherical to egg shaped globules measuring 400 to 900 nm in diameter.<sup>21</sup> The metal is typically free in the dermis, although some may be present in tissue

macrophages.<sup>52</sup> Individual lysosomes phagocytose 12-nm particles.

Most cases have been managed with surgical excision of the injection site.<sup>22,70,71</sup> X-ray control of such surgeries is often beneficial because the mercury tends to disperse when the tissue is manipulated.<sup>22,69</sup> Preoperative and postoperative blood and urine levels should be determined.<sup>70</sup> A return to normal values after the operation has been reported.<sup>72</sup>

Chelation therapy is controversial.<sup>22</sup> Intramuscular injection of dimercaprol (BAL) and oral penicillamine have been administered to patients after intravenous or intra-arterial injection of mercury but without demonstrable evidence of benefit.<sup>22</sup> There is no proof that such therapy induces significant removal of subcutaneous mercury, and even in patients demonstrating increased elimination clinical benefit may not be apparent. Treatment with DMSA or DMPS is believed to be more useful in such patients. There is no specific therapy for deposits of mercury from systemic embolization other than frequent follow-up examinations.<sup>63</sup> Monitoring of central nervous system and renal function is recommended, as is a neuropsychiatric evaluation.<sup>70</sup>

#### REFERENCES

1. Graeme KA, Pollack CV. Heavy metal toxicity, part I: arsenic and mercury. *J Emerg Med* 1998;16:45-56.
2. Hunter D, Russell DS. Focal cerebral and cerebellar atrophy in a human subject to organic mercury compounds. *J Neurol Neurosurg Psychiatry* 1954;17:235-41.
3. Houeto P, Sandouk P, Baud FJ, Levillain P. Elemental mercury vapour toxicity: treatment and levels in plasma and urine. *Hum Exp Toxicol* 1994;13:848-52.
4. Nakayama H, Shono M, Hada S. Mercury exanthem. *J Am Acad Dermatol* 1984;11:137-9.
5. Adler R, Boxstein D, Schaff P, Kelly D. Metallic mercury vapor poisoning simulating mucocutaneous lymph node syndrome. *J Pediatr* 1982;101:967-8.
6. Ellenhorn MJ, Schonwold S, Ordag G, Wasserberger J, editors. Metals and related compounds. In: *Ellenhorn's medical toxicology*. 2nd ed. Baltimore: William and Wilkins; 1997. p. 1532-613.
7. Jun JB, Min PK, Kim DW, Chung SL, Lee KH. Cutaneous nodular reaction to oral mercury. *J Am Acad Dermatol* 1997;37:131-3.
8. Gerstner HB, Huff JE. Clinical toxicology of mercury. *J Toxicol Environ Health* 1977;2:491-526.
9. Bluhm RE, Bobbitt RG, Welch LW, Wood AJJ, Bonfiglio JF, Sarzen C, et al. Elemental mercury vapor toxicity, treatment and prognosis after acute, intensive exposure in chloralkali plant workers. Part I: history, neuropsychological findings and chelator effects. *Hum Exp Toxicol* 1992;11:201-10.
10. Zillmer EA, Lucci KA, Barth JT, Peake TH, Spyker DA. Neurobehavioral sequelae of subcutaneous injection with metallic mercury. *Clin Toxicol* 1986;24:91-110.
11. Granstein RD, Sober AJ. Drug- and heavy metal-induced hyperpigmentation. *J Am Acad Dermatol* 1981;5:1-18.
12. Schrällhammer-Benkler K, Ring J, Przybilla B, Meruer M, Landthaler M. Acute mercury intoxication and lichenoid drug eruption followed by mercury contact allergy and development of antinuclear antibodies. *Acta Derm Venereol (Stockh)* 1992;72:294-6.

13. Nielsen JB, Grandjean P. Mercury in hair—but from where? [letter] *Lancet* 1999;353:502.
14. Williams CT. Black deposit in the large intestine from the presence of mercury. *Tr Path Soc Lond* 1867;18:111-5.
15. Aschner M, Aschner JL. Mucocutaneous lymph node syndrome: is there a relationship to mercury exposure? *Am J Dis Child* 1989;143:1133-4.
16. Wands JR, Weiss SW, Yardley JH, Maddrey WC. Chronic inorganic mercury poisoning due to laxative abuse: a clinical and ultrastructural study. *Am J Med* 1974;57:92-101.
17. Silverberg DS, McCall JT, Hunt JC. Nephrotic syndrome with use of ammoniated mercury. *Arch Intern Med* 1967;120:581-6.
18. Bourgeois M, Doooms-Goossens A, Knockaert D, Sprengers D, Van Boven M, Van Tittelboom T. Mercury intoxication after topical application of a metallic mercury ointment. *Dermatologica* 1986;172:48-51.
19. De Bont B, Lauwerys R, Govaerts H, Moulin D. Yellow mercuric oxide ointment and mercury intoxication. *Eur J Pediatr* 1986; 145:217-8.
20. Barregard L, Sallsten G, Jarvholm B. Mortality and cancer incidence in chloralkali workers exposed to inorganic mercury. *Br J Ind Med* 1990;47:99-104.
21. Lupton BP, Kao GF, Johnson FB, Graham JH, Helwig EB. Cutaneous mercury granuloma. *J Am Acad Dermatol* 1985;12: 296-303.
22. Bradberry SM, Feldman MA, Braithwaite RA, Shortland-Webb W, Vale JA. Elemental mercury-induced skin granuloma: a case report and review of the literature. *Clin Toxicol* 1996;34:209-16.
23. Leumann EP, Brandenberger H. Hemodialysis in a patient with acute mercuric cyanide intoxication. Concentration of mercury in blood, dialysate, urine, vomitus, and feces. *Clin Toxicol* 1977;11:301-8.
24. Dinehart SM, Dillard R, Raimer SS, Diven S, Cobos R, Pupo R. Cutaneous manifestations of acrodermia (pink disease). *Arch Dermatol* 1988;124:107-9.
25. Astalfi A, Goelli C. *Monitoreo Biologico: Proceedings of Academia Nacional de Medicina de Buenos Aires Conference: Nov 3, 1981; Buenos Aires, Argentina.*
26. Gebauer K, Connor B. Cutaneous mercury granuloma. *Australas J Dermatol* 1991;32:129-32.
27. Dathan JG. Acrodermia associated with excessive intake of mercury. *Br Med J* 1954;1:247-9.
28. Warkany J. Acrodermia: postmortem of a disease. *Am J Dis Child* 1966;112:146-56.
29. Ashkenazi I, Desatnik HR, Abraham FA. Yellow mercuric oxide: a treatment of choice for phthiriasis palpebrum. *Br J Ophthalmol* 1991;75:356-8.
30. Wyllie WG, Stern RU. Pink disease: the morbid anatomy, with a note on treatment. *Arch Dis Child* 1931;6:137-56.
31. Cheek DB. Comment on mucocutaneous lymph node syndrome: could it be a heavy metal poisoning? *Pediatrics* 1975;56: 335-6.
32. Orłowski JP, Mercer RD. Urine mercury levels in Kawasaki's disease. *Pediatrics* 1980;66:633-6.
33. Biro L, Klein WP. Unusual complications of mercurial (cinnabar) tattoo. *Arch Dermatol* 1967;96:165-7.
34. Taaffe A, Knight AG, Marks R. Lichenoid tattoo hypersensitivity. *Br Med J* 1978;1:616-8.
35. Zinberg M, Heilman E, Glickman F. Cutaneous pseudolymphoma resulting from a tattoo. *J Dermatol Surg Oncol* 1982; 8:955-8.
36. Bagley MP, Schwartz RA, Lambert WC. Hyperplastic reaction developing within a tattoo. *Arch Dermatol* 1987;123:1557, 1560-1.
37. Sowden JM, Byrne JP, Smith AG, Hiley C, Suarez V, Wagner B, et al. Red tattoo reactions: x-ray microanalysis and patch-test studies. *Br J Dermatol* 1991;124:576-80.
38. Davis RG. Hazards of tattooing: report of two cases of dermatitis caused by sensitization to mercury (cinnabar). *US Armed Forces Med J* 1960;118:261-80.
39. Stjskal VDM, Forsbeck M, Cederbrant KE, Asteman O. Mercury specific lymphocytes: an indication of mercury allergy in man. *J Clin Immunol* 1996;16:31-40.
40. Rogers M, Goodhew P, Szafraniec T, McColl I. Mercury exanthem. *Australas J Dermatol* 1987;27:70-7.
41. Muzio GF, Guarrera M, Rongioletti F. The case of the mercury heart. *Acta Derm Venereol (Stockh)* 1994;74:149-50.
42. Descamps V, Lejoyeux F, Marck Y, Bouscarat F, Crickx B, Belaich S. Erysipelas-like mercury exanthem. *Contact Dermatitis* 1997;36: 277-8.
43. Roujeau JC, Bioulac-Sage P, Bourseau C, Guillaume JC, Bernard P, Lok C, et al. Acute generalized exanthematous pustulosis: analysis of 63 cases. *Arch Dermatol* 1991;127:1333-8.
44. Barraza V, Meunier P, Escande JP. Acute contact dermatitis and exanthematous pustulosis due to mercury. *Contact Dermatitis* 1998;38:361.
45. Naleway C, Sakaguchi R, Mitchell E, Muller T, Ayer WA, Hefferren JJ. Urinary mercury levels in US dentists, 1975-1983: review of health assessment program. *J Am Dent Assoc* 1985;222:3742.
46. Hancocks S. Is dental amalgam bad for you? [letter] *Br Med J* 1991;302:488.
47. Nadarajah V, Neiders ME, Aguirre A, Cohen RE. Localized cellular inflammatory responses to subcutaneously implanted dental mercury. *J Toxicol Environ Health* 1996;49:113-25.
48. Begerow J, Zander D, Freier I, Dunemann L. Long-term mercury excretion in urine after removal of amalgam fillings. *Arch Occup Environ Health* 1994;17:263-8.
49. Koch P, Bahmer FA. Oral lichenoid lesions, mercury hypersensitivity, and combined hypersensitivity to mercury and other metals: histologically proven reproduction of the reaction by patch testing with metal salts. *Contact Dermatitis* 1995;33:323-8.
50. Par-Olov O, Anneroth G, Skoglund A. Amalgam-associated oral lichenoid reactions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;81:459-65.
51. Dyll-Smith DJ, Scurry JP. Mercury pigmentation and high mercury levels from the use of a cosmetic cream. *Med J Aust* 1990;153:409-15.
52. Goeckermann WH. A peculiar discoloration of the skin: probably resulting from mercurial compounds (calomel) in proprietary face creams. *JAMA* 1922;79:605-7.
53. Kennedy C, Molland EA, Henderson WJ, Whiteley AM. Mercury pigmentation from industrial exposure: an ultrastructural and analytical electron microscopic study. *Br J Dermatol* 1977;96: 367-74.
54. Burge KM, Winkelmann RK. Mercury pigmentation: an electron microscopic study. *Arch Dermatol* 1970;102:51-61.
55. Reitschel RL, Fowler JF. Antiseptics and disinfectants. In: Fisher's contact dermatitis. 4th ed. Baltimore: Williams & Wilkins; 1995. p. 184-204.
56. Thomas P, Rueff F, Przybilla B. Airborne allergic contact dermatitis from mercury in a chemistry student. *Contact Dermatitis* 1997;37:297.
57. Bleiker TO, English JSC. Acute contact allergy to dental amalgam. *Contact Dermatitis* 1998;38:112.
58. Kumar A, Jain R, Sawhney S, Goel AK, Chattopadhyay K. Intravenous administration of metallic mercury with homicidal intent. *J Assoc Physicians India* 1992;40:640-1.
59. Kern FB, Condo F, Michel SL. Mercury granuloma with systemic absorption. *JAMA* 1972;222:88-9.

60. Krohn IT, Solof A, Mobini J, Wagner DK. Subcutaneous injection of metallic mercury. *JAMA* 1980;243:548-9.
61. Cole JK, Holbrook JL. Focal mercury toxicity: a case report. *J Hand Surg* 1994;19:602-3.
62. Suchard J, Wallace, Graeme K, LoVecchio F, Stephens D, Harrington-Zautra L, et al. Cutaneous nodular reaction or oral mercury. *J Am Acad Dermatol* 1998;38:784-5.
63. Grenga TE, Pietrocola DM. Subcutaneous injection of mercury mimicking nodular melanoma. *NY State J Med* 1982;82:1231-3.
64. Lathem W, Lesser GT, Messinger WJ, Galdston M. Peripheral embolism by metallic mercury during arterial blood sampling. *Arch Intern Med* 1954;93:550-5.
65. Popper L. Tod nach thermometerverletzung. *Wien Med Wochenschr* 1960;116:779-80.
66. Maranzana P, Finulli M. Mercury poisoning following accidental penetration of metallic mercury into subcutaneous tissue. *Med Lav* 1965;56:357-66.
67. Arcadio F, Thuivolet J, Perrot H. Acrodynic syndrome after accidental subcutaneous infiltration of mercury. *Bull Soc Fr Dermatol Syphiligr* 1968;75:509-10.
68. Fichte B, Ritzau F, Assmann H. Metallic mercury poisoning: case report. *Radiology* 1984;24:95-7.
69. Allen CC, Lund KA, Treadwell P. Elemental mercury foreign body granulomas. *Int J Dermatol* 1992;31:353-4.
70. Sau P, Solivan G, Johnson FB. Cutaneous reaction from a broken thermometer. *J Am Acad Dermatol* 1991;25:915-9.
71. Netscher DT, Friedland JA, Guzewicz RM. Mercury poisoning from intravenous injection: treatment by granuloma resection. *Ann Plast Surg* 1991;26:592-6.
72. Hill DM. Self-administration of mercury by subcutaneous injection. *Br Med J* 1967;1:342-3.