Goodman & Gilman's The Pharmacological Basis of THERAPEUTICS

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the preceding laboratory abnormalities and, usually, nonspecific, mild symptoms of lead poisoning. Clear symptoms of lead poisoning are associated with concentrations that exceed 75 μg/dl of whole blood, and lead encephalopathy usually is apparent when lead concentrations are greater than 100 μg/dl. In persons with moderate-to-severe anemia, interpretation of the significance of concentrations of lead in blood is improved by correcting the observed value to approximate that which would be expected if the patient's hematocrit were within the normal range.

The urinary concentration of lead in normal adults generally is less than 80 μg/L (0.4 μM). Most patients with lead poisoning show concentrations of lead in urine of 150 to 300 μg/L (0.7 to 1.4 μM). However, in persons with chronic lead nephropathy or other forms of renal insufficiency, urinary excretion of lead may be within the normal range, even though blood lead concentrations are significantly elevated.

Because the onset of lead poisoning usually is insidious, it often is desirable to estimate the body burden of lead in individuals who are exposed to an environment that is contaminated with the metal. In the past, the edetate calcium disodium ($CaNa_2EDTA$) provocation test was used to determine whether there is an increased body burden of lead in those for whom exposure occurred much earlier. The provocation test is performed by intravenous administration of a single dose of $CaNa_2EDTA$ (50 mg/kg), and urine is collected for 8 hours. The test is positive for children when the lead excretion ratio (micrograms of lead excreted in the urine per milligram of $CaNa_2EDTA$ administered) is greater than 0.6; it also may be useful for therapeutic chelation in children with blood levels of 25 to 45 μg/dl. This test is not used in symptomatic patients or in those whose concentration of lead in blood is greater than 45 μg/dl because these patients require the proper therapeutic regimen with chelating agents (*see* below). Neutron activation analysis or fluorometric assays, available only as research methods, may offer a unique *in vivo* approach to the diagnosis of lead burden in the future.

Organic Lead Poisoning. Tetraethyl lead and tetramethyl lead are lipid-soluble compounds that are absorbed readily from the skin, GI tract, and lungs. The toxicity of tetraethyl lead is believed to be due to its metabolic conversion to triethyl lead and inorganic lead.

The major symptoms of intoxication with tetraethyl lead are referable to the CNS: insomnia, nightmares, anorexia, nausea and vomiting, diarrhea, headache, muscular weakness, and emotional instability (Seshia *et al.*, 1978). Subjective CNS symptoms such as irritability, restlessness, and anxiety are next evident, usually accompanied by hypothermia, bradycardia, and hypotension. With continued exposure, or in the case of intense short-term exposure, CNS manifestations progress to delusions, ataxia, exaggerated muscular movements, and finally, a maniacal state.

The diagnosis of poisoning by tetraethyl lead is established by relating these signs and symptoms to a history of exposure. The urinary excretion of lead may increase markedly, but the concentration of lead in blood remains nearly normal. Anemia and basophilic stippling of erythrocytes are uncommon in organic lead poisoning. There is little effect on the metabolism of porphyrins, and erythrocyte protoporphyrin concentrations are inconsistently elevated (Garrettson, 1983). In the case of severe exposure, death may occur within a few hours or may be delayed for several weeks. If the patient survives the acute phase of organic lead poisoning, recovery usually is complete; however, instances of residual CNS damage have been reported.

Treatment of Lead Poisoning. Initial treatment of the acute phase of lead intoxication involves supportive measures. Prevention of further exposure is important. Seizures are treated with *diazepam* or *phenytoin* (*see* Chapter 19), fluid and electrolyte balances must be maintained, and cerebral edema is treated with *mannitol* and *dexamethasone* or controlled hyperventilation. The concentration of lead in blood should be determined or at least a blood sample obtained for analysis prior to initiation of chelation therapy.

Chelation therapy is indicated in symptomatic patients or in patients with a blood lead concentration in excess of 50 to 60 μg/dl (about 2.5 μM). Four chelators are employed: *edetate calcium disodium* ($CaNa_2EDTA$), *dimercaprol* [British antilewisite (BAL)], *D-penicillamine*, and *succimer* [2,3-dimercaptosuccinic acid (DMSA), CHEMET]. $CaNa_2EDTA$ and dimercaprol usually are used in combination for lead encephalopathy.

$CaNa_2EDTA$. $CaNa_2EDTA$ is initiated at a dose of 30 to 50 mg/kg per day in two divided doses either by deep intramuscular injection or slow intravenous infusion for up to 5 consecutive days. The first dose of $CaNa_2EDTA$ should be delayed until 4 hours after the first dose of dimercaprol. An additional course of $CaNa_2EDTA$ may be given after an interruption of 2 days. Each course of therapy with $CaNa_2EDTA$ should not exceed a total dose of 500 mg/kg. Urine output must be monitored because the chelator–lead complex is believed to be nephrotoxic. Treatment with $CaNa_2EDTA$ can alleviate symptoms quickly. Colic may disappear within 2 hours; paresthesia and tremor cease after 4 or 5 days; and coproporphyrinuria, stippled erythrocytes, and gingival lead lines tend to decrease in 4 to 9 days. Urinary elimination of lead usually is greatest during the initial infusion.

Dimercaprol. Dimercaprol is given intramuscularly at a dose of 4 mg/kg every 4 hours for 48 hours, then every 6 hours for 48 hours, and finally, every 6 to 12 hours for an additional 7 days. *The combination of dimercaprol and $CaNa_2EDTA$ is more effective than is either chelator alone* (Chisolm, 1973).

D-Penicillamine. In contrast to $CaNa_2EDTA$ and dimercaprol, penicillamine is effective orally and may be included in the regimen at a dosage of 250 mg given four times daily for 5 days. During chronic therapy with penicillamine, the dose should not exceed 40 mg/kg per day.

Succimer. Succimer is the first orally active lead chelator available for children, with a safety and efficacy profile that surpasses that of D-penicillamine. Succimer usually is given every 8 hours (10 mg/kg) for 5 days and then every 12 hours for an additional 2 weeks.

General Principles. In any chelation regimen, the blood lead concentration should be reassessed 2 weeks after the regimen has been completed; an additional course of therapy may be indicated if blood lead concentrations rebound.

Treatment of organic lead poisoning is symptomatic. Chelation therapy will promote excretion of the inorganic lead produced from the metabolism of organic lead, but the increase is not dramatic.

Mercury

Mercury was an important constituent of drugs for centuries as an ingredient in many diuretics, antibacterials, antiseptics, skin ointments, and laxatives. More specific, effective, and safer modes of therapy now have replaced the mercurials, and drug-induced mercury poisoning has become rare. However, mercury has a number of impor-

Table 65–2
Occupational and Environmental Exposure to Mercury

INDUSTRIAL USES OF MERCURY	% OF TOTAL MERCURY EXPOSURE
Chloralkali, *e.g.*, bleach	25
Electrical equipment	20
Paints	15
Thermometers	10
Dental	3
Laboratory	2

tant industrial uses (Table 65–2), and poisoning from occupational exposure and environmental pollution continues to be an area of concern. There have been epidemics of mercury poisoning among wildlife and human populations in many countries. With very few exceptions and for numerous reasons, such outbreaks were misdiagnosed for months or even years. Reasons for these tragic delays included the insidious onset of the affliction, vagueness of early clinical signs, and the medical profession's unfamiliarity with the disease (Gerstner and Huff, 1977).

Chemical Forms and Sources of Mercury. With regard to the toxicity of mercury, three major chemical forms of the metal must be distinguished: mercury vapor (elemental mercury), salts of mercury, and organic mercurials. Table 65–3 indicates the estimated daily retention of various forms of mercury from various sources.

Elemental mercury is the most volatile of the metal's inorganic forms. Human exposure to mercury vapor is mainly occupational. Extraction of gold with mercury and then heating the amalgam to drive off the mercury is a technique that has been used extensively by gold miners and still is used today in some developing countries. Chronic exposure to mercury in ambient air after inadvertent mercury spills in poorly ventilated rooms, often scientific laboratories, can produce toxic effects. Mercury vapor also can be released from silver–amalgam dental restorations. In fact, this is the main source of mercury exposure to the general population, but the amount of mercury released does not appear to be of significance for human health (Eley and Cox, 1993) except for allergic contact eczema seen in a few individuals.

Salts of mercury exist in two states of oxidation—as monovalent mercurous salts or as divalent mercuric salts. Mercurous chloride (Hg_2Cl_2), or *calomel,* the best-known mercurous compound, was used in some skin creams as an antiseptic and was employed as a diuretic and cathartic. Mercuric salts are the more irritating and acutely toxic form of the metal. Mercuric nitrate was a common industrial hazard in the felt-hat industry more than 400 years ago. Occupational exposure produced neurological and behavioral changes depicted by the Mad Hatter in Lewis Carroll's *Alice's Adventures in Wonderland.* Mercuric chloride (Hg_2Cl_2), once a widely used antiseptic, also was used commonly for suicidal purposes. Mercuric salts still are employed widely in industry, and industrial discharge into rivers has introduced mercury into the environment in many parts of the world. The main industrial uses of inorganic mercury today are in chloralkali production and in electronics. Other uses of the metal include the manufacturing of plastics, fungicides, and germicides and the formulation of amalgams in dentistry.

The organomercurials in use today contain mercury with one covalent bond to a carbon atom. Members of this heterogeneous group of compounds have varying abilities to produce toxic effects. The alkylmercury salts are by far the most dangerous of these compounds; methylmercury is the most common. Alkylmercury salts have been used widely as fungicides and have produced toxic effects in humans. Major incidents of human poisoning from the inadvertent consumption of mercury-treated seed grain have occurred in Iraq, Pakistan, Ghana, and Guatemala. The most catastrophic outbreak occurred in Iraq in 1972. During the fall of 1971, Iraq imported large quantities of seed (wheat and barley) treated with methylmercury and distributed the grain for spring planting. Despite official warnings, the grain was ground into flour and made into bread. As a result, 6530 victims were hospitalized, and 500 died (Bakir *et al.*, 1973, 1980).

Table 65–3
Estimated Average Daily Retention of Total Mercury and Mercury Compounds in the General Population Not Occupationally Exposed to Mercury

EXPOSURE	ESTIMATED MEAN DAILY RETENTION OF MERCURY COMPOUNDS, μg MERCURY/DAY		
	Mercury Vapor	*Inorganic Mercury Salts*	*Methylmercury*
Air	0.024	0.001	0.0064
Food			
Fish	0.0	0.04	2.3
Nonfish	0.0	0.25	0.0
Drinking water	0.0	0.0035	0.0
Dental amalgams	3–17	0.0	0.0
Total	*3–17*	*0.3*	*2.31*

Minamata disease also was due to methylmercury. In the Japanese town of Minamata, the major industry was a chemical plant that emptied its effluent directly into Minamata Bay. The chemical plant used inorganic mercury as a catalyst, and some of it was methylated before it entered the bay. In addition, microorganisms can convert inorganic mercury to methylmercury; the compound then is taken up rapidly by plankton algae and is concentrated in fish *via* the food chain. Residents of Minamata who consumed fish as a large portion of their diet were the first to be poisoned. Eventually, 121 persons were poisoned, and 46 died (McAlpine and Araki, 1958; Smith and Smith, 1975; Tamashiro *et al.*, 1985). In the United States, human poisonings have resulted from ingestion of meat from pigs fed grain treated with an organomercurial fungicide. Because of concerns about methylmercury accumulation in fish, the Food and Drug Administration (FDA) recommends that pregnant or nursing women, women of childbearing age, and young children avoid eating large fish (*e.g.*, shark, swordfish, king mackerel, and tilefish) and limit their intake of albacore tuna to 6 ounces per week.

In other instances, exposure to mercury was intentional. For example, thimerosal (CH_3CH_2—Hg—S—C_6H_4—COOH) has been used as an antibacterial additive to biologics and vaccines since the 1930s. However, concerns about the possibility of health risks from thimerosal in vaccines have been debated, especially the possibility that the ethylmercury thiosalicylate preservative in hepatitis B immunoglobulin (HBIG) could release ethylmercury and cause severe mercury intoxication (Lowell *et al.*, 1996; Ball *et al.*, 2001). These concerns were based on the assumption that ethylmercury, for which there is limited toxicologic information, is toxicologically similar to its close chemical relative, methyl mercury (CH_3—Hg^+), about which much is known (Clarkson, 2002).

A study by the FDA determined that that there is a significant safety margin incorporated into all the acceptable mercury exposure limits. Furthermore, there are no data or evidence of any harm caused by the level of exposure that some children may have encountered in following the existing immunization schedule. Nevertheless, the availability of vaccines with alternate preservatives led to a statement calling for removal of all vaccines containing thimerosal (Joint Statement of the American Academy of Pediatrics and the United States Public Health Service, 1999; Ball *et al.*, 2001). This practice remains in place today, even though subsequent studies have failed to demonstrate any health risk associated with vaccines containing thiomerosal (Verstraeten *et al.*, 2003; Heron *et al.*, 2004).

Chemistry and Mechanism of Action. Mercury readily forms covalent bonds with sulfur, and it is this property that accounts for most of the biological properties of the metal. When the sulfur is in the form of sulfhydryl groups, divalent mercury replaces the hydrogen atom to form mercaptides, X—Hg—SR and $Hg(SR)_2$, where X is an electronegative radical and R is protein. Organic mercurials form mercaptides of the type R—Hg—SR'. Even in low concentrations, mercurials are capable of inactivating sulfhydryl groups of enzymes and thus interfering with cellular metabolism and function. The affinity of mercury for thiols provides the basis for treatment of mercury poisoning with such agents as dimercaprol and penicillamine. Mercury also combines with phosphoryl, carboxyl, amide, and amine groups.

Absorption, Biotransformation, Distribution, and Excretion. *Elemental Mercury.* Elemental mercury is not particularly toxic when ingested because of very low absorption from the GI tract; this is due to the formation of droplets and because the metal in this form cannot react with biologically important molecules. However, inhaled mercury vapor is completely absorbed by the lung and then is oxidized to the divalent mercuric cation by catalase in the erythrocytes (Magos *et al.*, 1978). Within a few hours, the deposition of inhaled mercury vapor resembles that after ingestion of mercuric salts, with one important difference: Because mercury vapor crosses membranes much more readily than does divalent mercury, a significant amount of the vapor enters the brain before it is oxidized. CNS toxicity is thus more prominent after exposure to mercury vapor than to divalent forms of the metal.

Inorganic Salts of Mercury. The soluble inorganic mercuric salts (Hg^{2+}) gain access to the circulation when taken orally. GI absorption is approximately 10% to 15% of that ingested, and a considerable portion of the Hg^{2+} may remain bound to the alimentary mucosa and the intestinal contents. Insoluble inorganic mercurous compounds, such as calomel (Hg_2Cl_2), may undergo some oxidation to soluble compounds that are more readily absorbed. Inorganic mercury has a markedly nonuniform distribution after absorption. The highest concentration of Hg^{2+} is found in the kidneys, where the metal is retained longer than in other tissues. Concentrations of inorganic mercury are similar in whole blood and plasma. Inorganic mercurials do not readily pass across the blood–brain barrier or the placenta. The metal is excreted in the urine and feces with a half-life of about 60 days (Friberg and Vostal, 1972); studies in laboratory animals indicate that fecal excretion is quantitatively more important (Klaassen, 1975).

Organic Mercurials. Organic mercurials are absorbed more completely from the GI tract than are the inorganic salts because they are more lipid soluble and less corrosive to the intestinal mucosa. Their uptake and distribution are depicted in Figure 65–3A. More than 90% of methylmercury is absorbed from the human GI tract. The organic mercurials cross the blood–brain barrier and the placenta and thus produce more neurological and teratogenic effects than do the inorganic salts. Methylmercury combines with cysteine to form a structure similar to methionine, and the complex is transported by the large neutral amino acid carrier present in capillary endothelial cells (Clarkson, 1987) (Figure 65–3B). Organic mercurials are distributed more uniformly to the various tissues than are the inorganic salts (Klaassen, 1975). A significant portion of the body burden of organic mercurials is in the red blood cells. The ratio of the concentration of organomercurial in erythrocytes to that in plasma varies with the compound; for methylmercury, it approximates 20:1 (Kershaw *et al.*, 1980). Mercury concentrates in hair because of its high sulfhydryl content. The carbon–mercury bond of some organic mercurials is cleaved after absorption; with methylmercury, the cleavage is quite slow, and the inorganic mercury formed is not thought to play a major role in methylmercury toxicity. Aryl mercurials, such as mercurophen, usually contain a labile mercury–carbon bond; their toxicity is similar to that of inorganic mercury. Methylmercury in humans is excreted mainly in the feces in the form of a glutathione conjugate; less than 10% of a dose appears in urine (Bakir *et al.*, 1980). The half-life of methylmercury in the blood of humans is between 40 and 105 days (Bakir *et al.*, 1973).

Toxicity. *Elemental Mercury.* Short-term exposure to the vapor of elemental mercury may produce symptoms within several hours, including weakness, chills, metallic taste, nausea, vomiting, diarrhea, dyspnea, cough, and a feeling of tightness in the chest. Pulmonary toxicity may progress to an interstitial pneumonitis with severe compromise of respiratory function. Recovery, although usually complete, may be complicated by residual interstitial fibrosis.

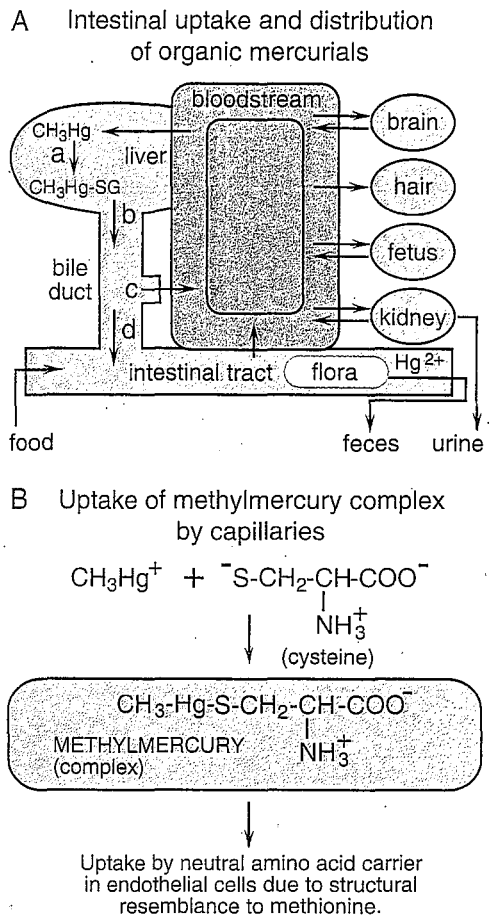


Figure 65–3. *Uptake and relative distribution of organic mercurials.* ***A.*** The intestinal uptake and subsequent distribution of organic mercurials, such as methylmercury, throughout the body. ***a.*** Conjugation with glutathione (GSH), shown as CH_3—Hg—SG. ***b.*** Secretion of conjugate into bile. ***c.*** Reabsorption in gallbladder. ***d.*** Remaining Hg enters intestinal tract. ***B.*** Uptake of the methylmercury complex by capillaries. The ability of organic mercurials to cross the blood–brain barrier and the placenta contributes to their greater neurological and teratogenic effects when compared with inorganic mercury salts. Note the structural similarity of the methylmercury complex to methionine, $CH_3SCH_2CH_2$—$CH(NH_3^+)COO^-$.

Chronic exposure to mercury vapor produces a more insidious form of toxicity that is dominated by neurological effects (Friberg and Vostal, 1972). The syndrome, termed the *asthenic vegetative syndrome,* consists of neurasthenic symptoms in addition to three or more of the following findings: goiter, increased uptake of radioiodine by the thyroid, tachycardia, labile pulse, gingivitis, dermographia, and increased mercury in the urine (Goyer and Clarkson, 2001). With continued exposure to mercury vapor, tremor becomes noticeable, and psychological changes consist of depression, irritability, excessive shyness, insomnia, reduced self-confidence, emotional instability, forgetfulness, confusion, impatience, and vasomotor disturbances (such as excessive perspiration and uncontrolled blushing, which together are referred to as *erethism*). Common features of intoxication from mercury vapor are severe salivation and gingivitis. The triad of increased excitability, tremors, and gingivitis has been recognized historically as the major manifestation of exposure to mercury vapor when mercury nitrate was used in the fur, felt, and hat industries. Renal dysfunction also has been reported to result from long-term industrial exposure to mercury vapor. The concentrations of mercury vapor in the air and mercury in urine that are associated with the various effects are shown in Figure 65–4.

Inorganic Salts of Mercury. Inorganic ionic mercury (*e.g.,* mercuric chloride) can produce severe acute toxicity. Precipitation of mucous membrane proteins by mercuric salts results in an ashen-gray appearance of the mucosa of the mouth, pharynx, and intestine and also causes intense pain, which may be accompanied by vomiting. The vomiting is perceived to be protective because it removes unabsorbed mercury from the stomach; assuming that the patient is awake and alert, vomiting should not be inhibited. The local corrosive effect of ionic inorganic mercury on the GI mucosa results in severe hematochezia with evidence of mucosal sloughing in the stool. Hypovolemic shock and death can occur in the absence of proper treatment, which can overcome the local effects of inorganic mercury.

Systemic toxicity may begin within a few hours of exposure to mercury and last for days. A strong metallic taste is followed by stomatitis with gingival irritation, foul breath, and loosening of the teeth. The most serious and frequent systemic effect of inorganic mercury is renal toxicity. Acute tubular necrosis occurs after short-term exposure, leading to oliguria or anuria. Renal injury also follows long-term exposure to inorganic mercury, where glomerular injury predominates. This results from direct effects on the glomerular basement membrane and later indirect effects mediated by immune complexes (Goyer and Clarkson, 2001).

The symptom complex of acrodynia (pink disease) also commonly follows chronic exposure to inorganic mercury ions. Acrodynia is an erythema of the extremities, chest, and face with photophobia, diaphoresis, anorexia, tachycardia, and either constipation or diarrhea. This symptom complex is seen almost exclusively after ingestion of mercury and is believed to be the result of a hypersensitivity reaction (Matheson *et al.*, 1980).

Organic Mercurials. Most human toxicological data about organic mercury concern methylmercury and have been collected as the unfortunate result of large-scale accidental exposures. Symptoms of exposure to methylmercury are mainly neurological and consist of visual disturbance (scotoma and visual-field constriction), ataxia, paresthesias, neurasthenia, hearing loss, dysarthria, mental deterioration, muscle tremor, movement disorders, and with severe exposure, paralysis and death (Table 65–4). Effects of methylmercury on the fetus can occur even when the mother is asymptomatic; mental retardation and neuromuscular deficits have been observed.

Diagnosis of Mercury Poisoning. A history of exposure to mercury, either industrial or environmental, is obviously valuable in making the diagnosis of mercury poisoning. Otherwise, clinical suspicions can be confirmed by laboratory analysis. The upper limit of a nontoxic concentration of mercury in blood generally is considered to be 3 to 4 μg/dl (0.15 to 0.20 μM). A concentration of mercury in blood in excess of 4 μg/dl (0.20 μM) is unexpected in normal, healthy adults and suggests the need for environmental evaluation and medical examination to assess the possibility of adverse health effects. Because methylmercury is concentrated in erythrocytes and inorganic mercury is not, the

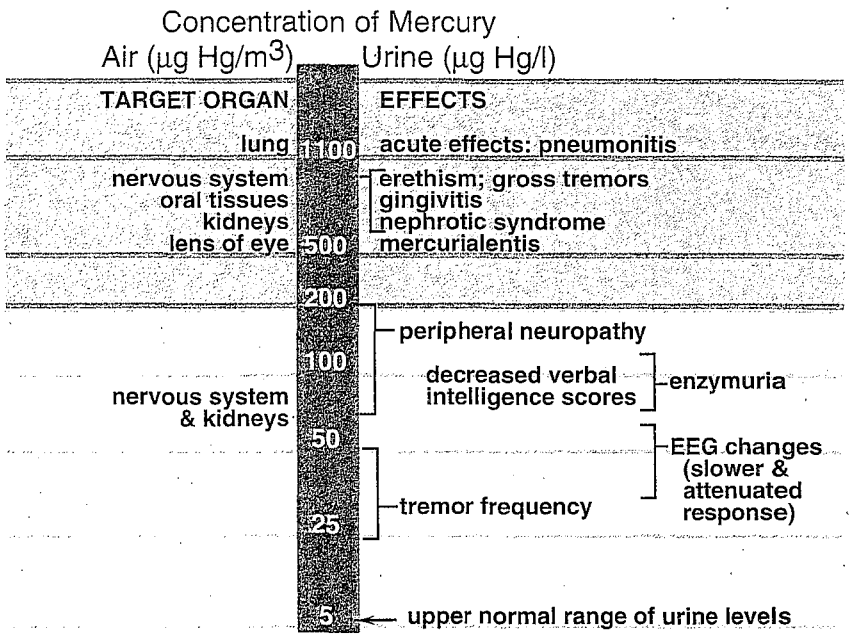


Figure 65–4. *The concentration of mercury vapor in the air and related concentrations of mercury in urine associated with a variety of toxic effects.*

distribution of total mercury between red blood cells and plasma may indicate whether the patient has been poisoned with inorganic or organic mercury. Measurement of total mercury in red blood cells gives a better estimate of the body burden of methylmercury than it does for inorganic mercury. A rough guide to the relationship between concentrations of mercury in blood and the frequency of symptoms that result from exposure to methylmercury is shown in Table 65–4. Concentrations of mercury in plasma provide a better index of the body burden of inorganic mercury, but the relationship between body burden and the concentration of inorganic mercury in plasma is not well documented. This may relate to the importance of timing of measurement of the blood sample relative to the last exposure to mercury. The relationship between the concentration of inorganic mercury in blood and toxicity also depends on the form of exposure. For example, exposure to vapor results in concentrations in brain approximately 10 times higher than those that follow an equivalent dose of inorganic mercuric salts.

The concentration of mercury in the urine also has been used as a measure of the body burden of the metal. The normal upper limit for excretion of mercury in urine is 5 μg/L. There is a linear relationship between plasma concentration and urinary excretion of mercury after exposure to vapor; in contrast, the excretion of mercury in urine is a poor indicator of the amount of methylmercury in the blood because it is eliminated mainly in feces (Bakir *et al.*, 1980).

Table 65–4

Frequency of Symptoms of Methylmercury Poisoning in Relation to Concentration of Mercury in Blood

CONCENTRATION OF MERCURY IN BLOOD, μg/ml (μM)	CASES WITH SYMPTOMS (%)					
	Paresthesias	*Ataxia*	*Visual Defects*	*Dysarthria*	*Hearing Defects*	*Death*
0.1–0.5 (0.5–2.5)	5	0	0	5	0	0
0.5–1 (2.5–5)	42	11	21	5	5	0
1–2 (5–10)	60	47	53	24	5	0
2–3 (10–15)	79	60	56	25	13	0
3–4 (15–20)	82	100	58	75	36	17
4–5 (20–25)	100	100	83	85	66	28

SOURCE: Based on data in Bakir *et al.*, 1973.

Hair is rich in sulfhydryl groups, and the concentration of mercury in hair is about 300 times that in blood. Human hair grows about 20 cm a year, and a history of exposure may be obtained by analysis of different segments of hair.

Treatment of Mercury Poisoning. Measurement of the concentration of mercury in blood should be performed as soon as possible after poisoning with any form of the metal.

Elemental Mercury Vapor. Therapeutic measures include immediate termination of exposure and close monitoring of pulmonary status. Short-term respiratory support may be necessary. Chelation therapy, as described below for inorganic mercury, should be initiated immediately and continued as indicated by the clinical condition and the concentrations of mercury in blood and urine.

Inorganic Mercury. Prompt attention to fluid and electrolyte balance and hematological status is of critical importance in moderate-to-severe oral exposures. Emesis can be induced if the patient is awake and alert, although emesis should not be induced where there is corrosive injury. If ingestion of mercury is more than 30 to 60 minutes before treatment, emesis may have little efficacy. With corrosive agents, endoscopic evaluation may be warranted, and coagulation parameters are important. *Activated charcoal* is recommended by some, although it lacks proven efficacy. Administration of charcoal may make endoscopy difficult or impossible.

Chelation Therapy. Chelation therapy with dimercaprol (for high-level exposures or symptomatic patients) or penicillamine (for low-level exposures or asymptomatic patients) is used routinely to treat poisoning with either inorganic or elemental mercury. Recommended treatment includes dimercaprol 5 mg/kg intramuscularly initially, followed by 2.5 mg/kg intramuscularly every 12 to 24 hours for 10 days. Penicillamine (250 mg orally every 6 hours) may be used alone or following treatment with dimercaprol. The duration of chelation therapy will vary, and progress can be monitored by following concentrations of mercury in urine and blood. The orally effective chelator succimer appears to be an effective chelator for mercury (Campbell *et al.*, 1986; Fournier *et al.*, 1988; Bluhm *et al.*, 1992), although it has not been approved by the FDA for this purpose.

The dimercaprol–mercury chelate is excreted into both bile and urine, whereas the penicillamine–mercury chelate is excreted only into urine. Thus penicillamine should be used with extreme caution when renal function is impaired. In fact, hemodialysis may be necessary in the poisoned patient whose renal function declines. Chelators still may be used because the dimercaprol–mercury complex is removed by dialysis (Giunta *et al.*, 1983).

Organic Mercury. The short-chain organic mercurials, especially methylmercury, are the most difficult forms of mercury to mobilize from the body presumably because of their poor reactivity with chelating agents. Dimercaprol is contraindicated in methylmercury poisoning because it increases brain concentrations of methylmercury in experimental animals. Although penicillamine facilitates the removal of methylmercury from the body, it is not clinically efficacious, and large doses (2 g/day) are needed (Bakir *et al.*, 1980). During the initial 1 to 3 days of administration of penicillamine, the concentration of mercury in the blood increases before it decreases, probably reflecting the mobilization of metal from tissues to blood at a rate more rapid than that for excretion of mercury into urine and feces.

Methylmercury compounds undergo extensive enterohepatic recirculation in experimental animals. Therefore, introduction of a nonabsorbable mercury-binding substance into the intestinal tract should facilitate their removal from the body. A *polythiol resin* has been used for this purpose in humans and appears to be effective (Bakir *et al.*, 1973). The resin has certain advantages over penicillamine. It does not cause redistribution of mercury in the body with a subsequent increase in the concentration of mercury in blood, and it has fewer adverse effects than do sulfhydryl agents that are absorbed. Clinical experience with various treatments for methylmercury poisoning in Iraq indicates that penicillamine, *N*-acetylpenicillamine, and an oral nonabsorbable thiol resin all can reduce blood concentrations of mercury; however, clinical improvement was not clearly related to reduction of the body burden of methylmercury (Bakir *et al.*, 1980).

Conventional hemodialysis is of little value in the treatment of methylmercury poisoning because methylmercury concentrates in erythrocytes, and little is contained in the plasma. However, it has been shown that L-*cysteine* can be infused into the arterial blood entering the dialyzer to convert methylmercury into a diffusible form. Both free cysteine and the methylmercury–cysteine complex form in the blood and then diffuse across the membrane into the dialysate. This method has been shown to be effective in humans (Al-Abbasi *et al.*, 1978). Studies in animals indicate that succimer may be more effective than cysteine in this regard (Kostyniak, 1982).

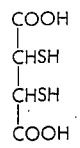
Arsenic

Arsenic was used more than 2400 years ago in Greece and Rome as a therapeutic agent and as a poison. The foundations of many modern concepts of chemotherapy derive from Ehrlich's early work with organic arsenicals, and such drugs once were a mainstay of chemotherapy. Although use of arsenicals as chemotherapeutics has declined, reports still emerge about their effectiveness, as shown by the use of *arsenic trioxide* in the treatment of acute promyelocytic leukemia (Chen *et al.*, 1996; Soignet *et al.*, 1998) (*see* Chapter 51). Arsenicals also remain important in the treatment of certain tropical diseases, such as African trypanosomiasis (*see* Chapter 40). In the United States, the impact of arsenic on health is predominantly from industrial and environmental exposures. (For a review, *see* NRC, 1999.)

Arsenic is found in soil, water, and air as a common environmental toxicant. Well water in sections of Argentina, Chile, and Taiwan has especially high concentrations of arsenic, which results in widespread poisoning. Large numbers of people in Bangladesh and West Bengal, India, are exposed to high concentrations of arsenic in their well water used for drinking. There also are high concentrations of arsenic in the water in many parts of the western United States. The element usually is not mined as such but is recovered as a by-product from the smelting of copper, lead, zinc, and other ores. This can release arsenic into the environment. Mineral-spring waters and the effluent from geothermal power plants leach arsenic from soils and rocks containing high concentrations of the metal. Arsenic also is present in coal at variable concentrations and is released into the environment during combustion. Application of pesticides and herbicides containing arsenic has increased its environmental dispersion. The major source of occupational exposure to arsenic-containing compounds is from the manufacture of arsenical herbicides and pesticides (Landrigan, 1981). Fruits and vegetables sprayed

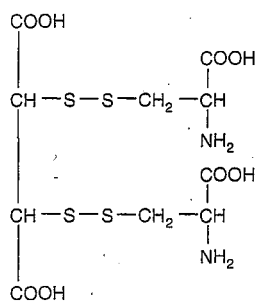
Succimer

Succimer (2,3-dimercaptosuccinic acid, CHEMET) is an orally effective chelator that is chemically similar to dimercaprol but contains two carboxylic acids that modify both the distribution and chelating spectrum of the drug. Succimer has the following structure:



SUCCIMER

After its absorption in humans, succimer is biotransformed to a mixed disulfide with cysteine (Aposhian and Aposhian, 1990), the structure of which is as follows:



Succimer produces a lead diuresis with a subsequent lowering of blood lead levels and attenuation of the untoward biochemical effects of lead, manifested by normalization of δ-ALA dehydrase activity (Graziano *et al.*, 1992). The succimer–lead chelate also is eliminated in bile; the fraction eliminated undergoes enterohepatic circulation.

A desirable feature of succimer is that it does not significantly mobilize essential metals such as zinc, copper, or iron. Animal studies suggest that succimer is effective as a chelator of arsenic, cadmium, mercury, and other metals (Aposhian and Aposhian, 1990).

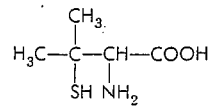
Toxicity with succimer is less than that with dimercaprol perhaps because its relatively lower lipid solubility minimizes its uptake into cells. Nonetheless, transient elevations in hepatic transaminases are observed following treatment with succimer. The most commonly reported adverse effects of succimer treatment are nausea, vomiting, diarrhea, and loss of appetite. Rashes also have been reported that may necessitate discontinuation of therapy.

Succimer has been approved in the United States for treatment of children with blood lead levels in excess of 45 μg/dl.

Penicillamine

Penicillamine was first isolated in 1953 from the urine of patients with liver disease who were receiving penicillin. Discovery of its chelating properties led to its use in patients with Wilson's disease and heavy-metal intoxications.

Chemistry. Penicillamine is D-β,β-dimethylcysteine. Its structure is as follows:



PENICILLAMINE

The D-isomer is used clinically, although the L-isomer also forms chelation complexes. Penicillamine is an effective chelator of copper, mercury, zinc, and lead and promotes the excretion of these metals in the urine.

Absorption, Distribution, and Excretion. Penicillamine is well absorbed (40% to 70%) from the GI tract and therefore has a decided advantage over many other chelating agents. Food, antacids, and iron reduce its absorption. Peak concentrations in blood are obtained between 1 and 3 hours after administration (Netter *et al.*, 1987). Unlike cysteine, its nonmethylated parent compound, penicillamine is somewhat resistant to attack by cysteine desulfhydrase or L-amino acid oxidase. As a result, penicillamine is relatively stable *in vivo*. Hepatic biotransformation is responsible for most of the degradation of penicillamine, and very little is excreted unchanged. Metabolites are found in both urine and feces (Perrett, 1981).

Therapeutic Uses. Penicillamine (CUPRIMINE, DEPEN) is available for oral administration. For chelation therapy, the usual adult dose is 1 to 1.5 g/day in four divided doses (*see* sections under individual metals). The drug should be given on an empty stomach to avoid interference by metals in food. In addition to its use as a chelating agent for the treatment of copper, mercury, and lead poisoning, penicillamine is used in Wilson's disease (hepatolenticular degeneration owing to an excess of copper), cystinuria, and rheumatoid arthritis (rarely). For the treatment of Wilson's disease, 1 to 2 g/day usually is administered in four doses. The urinary excretion of copper should be monitored to determine whether the dosage of penicillamine is adequate.

N-Acetylpenicillamine is more effective than penicillamine in protecting against the toxic effects of mercury presumably because it is even more resistant to metabolism.

The rationale for the use of penicillamine in cystinuria is that penicillamine reacts with the poorly soluble cysteine in a thiol–disulfide exchange reaction and forms a relatively water-soluble cysteine–penicillamine mixed disulfide. In cystinuria, the urinary excretion of cystine is used to adjust dosage, although 2 g/day in four divided doses usually is employed.

The mechanism of action of penicillamine in rheumatoid arthritis remains uncertain, although suppression of the disease may result from marked reduction in concentrations of IgM rheumatoid factor. A single daily dose of 125 to 250 mg usually is used to initiate therapy, with dosage increases at intervals of 1 to 3 months as necessary to a typical range of 500 to 750 mg/day. Because of toxicity, the drug is used rarely today in this setting.

Other experimental uses of penicillamine include the treatment of primary biliary cirrhosis and scleroderma. The mechanism of action of penicillamine in these diseases also may involve effects on immunoglobulins and immune complexes (Epstein *et al.*, 1979).