CHAPTER 23

TOXIC EFFECTS OF METALS

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INTRODUCTION

Metals differ from other toxic substances in that they are neither created nor destroyed by humans. Nevertheless, their utilization by humans influences the potential for health effects in at least two major ways: first, by environmental transport, that is, by human or anthropogenic contributions to air, water, soil, and food, and second, by altering the speciation or biochemical form of the element (Beijer and Jernelov, 1986).

Metals are probably the oldest toxins known to humans. Lead usage may have begun prior to 2000 B.C., when abundant supplies were obtained from ores as a by-product of smelting silver. Hippocrates is credited in 370 B.C. with the first description of abdominal colic in a man who extracted metals. Arsenic and mercury are cited by Theophrastus of Erebus (370–287 B.C.) and Pliny the Elder (A.D. 23–79). Arsenic was obtained during the melting of copper and tin, and an early use was for decoration in Egyptian tombs. In contrast, many of the metals of toxicologic concern today are only recently known to humans. Cadmium was first recognized in ores containing zinc carbonate in 1817. About 80 of the 105 elements in the periodic table are regarded as metals, but less than 30 have been reported to produce toxicity in humans. The importance of some of the rarer or lesser known metals such as indium or gallium might increase with new applications in microelectronics, antitumor therapy, or other new technologies.

Metals are redistributed naturally in the environment by both geologic and biological cycles (Fig. 23-1). Rainwater dissolves rocks and ores and physically transports material to streams and rivers, depositing and stripping materials from adjacent soil and eventually transporting these substances to the ocean to be precipitated as sediment or taken up in rainwater to be relocated elsewhere on earth. The biological cycles include bioconcentration by plants and animals and incorporation into food cycles. These natural cycles may exceed the anthropogenic cycle, as is the case for mercury. Human industrial activity, however, may greatly shorten the residence time of metals in ore, may form new compounds, and may greatly enhance worldwide distribution not only by discharge to land and water but also to the atmosphere. When discharged in gaseous or fine particulate forms, metal may be trans-

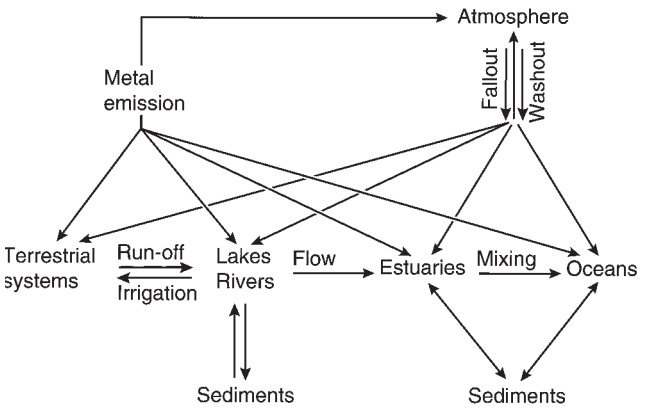

Figure 23-1. Routes for transport of trace elements in the environment. [From Beijer and Jernelöv (1986).]

ported in the atmosphere over global distances. The role of human activity in the redistribution of metals is demonstrated by the 200-fold increase in lead content of Greenland ice, beginning with a natural low level (about 800 B.C.) and continuing with a gradual rise in lead content of ice through the evolution of the industrial age and finally a nearly precipitous rise in lead corresponding to the period when lead was added to gasoline in the 1920s (Ng and Patterson, 1981). Metal contamination of the environment therefore reflects both natural sources and a contribution from industrial activity.

The conceptual boundaries of what is regarded as the toxicology of metals continue to broaden. Historically, metal toxicology largely concerned acute or overt effects, such as abdominal colic from lead toxicity or the bloody diarrhea and suppression of urine formation from ingestion of corrosive (mercury) sublimate. There must continue to be knowledge and understanding of such effects, but they are uncommon with present-day occupational and environmental standards. There is, however, growing interest in, and inquiry into, subtle, chronic, or long-term effects in which cause-and-effect relationships are not obvious or may be subclinical. These might include a level of effect that causes a change in an important index of affected individuals' performance—that is, lower than expected IQs due to childhood lead exposure. Assigning responsibility for such toxicologic effects is extremely difficult and sometimes impossible, particularly when the endpoint in question lacks specificity, in that it may be caused by a number of agents or even combinations of substances. The challenges for the toxicologist, therefore, are many. The major ones include the need for quantitative information regarding dose and tissue levels as well as greater understanding of the metabolism of metals, particularly at the tissue and cellular levels, where specific effects may occur. Depending on the dose, most metals affect multiple organ systems; but at the lowest dose where effects occur, each metal tends to effect first a specific organ or tissue.

There is increasing emphasis on the use of biomarkers of exposure, toxicity, and suseptiblity to toxic metals. Biomarkers of exposure, also called biological monitors, such as metal concentrations in blood, and urine, have a long history of use, but the advent of molecular biology has greatly expanded the possiblities for all three types of biomarkers. Thus in the case of chromium, DNA-protein complexes may serve as a biomarker of both exposure and carcinogenic potential. The induction of genes known to play a protective role against metal toxicity—for example, the metallothionein and heme oxygenase genes—show promise as markers of both effect and susceptiblity. The use of such biomarkers provides guidelines for preventive measures or therapeutic intervention.

DOSE–EFFECT RELATIONSHIPS

Estimates of the relationship of dose or level of exposure to toxic effects for a particular metal are in many ways a measure of the dose–response relationships discussed in greater detail in Chap. 2. Relationships between sources of exposure, transport, and distribution to various organs and excretory pathways are shown in Fig. 23-2. The dose or estimate of exposure to a metal may be a multidimensional concept and is a function of time as well as the concentration of metal. The most precise definition of dose is the amount of metal within cells of organs manifesting a toxicologic effect. Results from single measurements may reflect recent exposure or longer-term or past exposure, depending on retention time in the particular tissue.

A critical determinant of retention of a metal is its biological half-life, that is, the time it takes for the body or organ to excrete half of an accumulated amount. The biological half-life varies according to the metal as well as the organ or tissue; in the case of many metals, more than one half-life is needed to fully describe the retention time. For example, the biological half-lives of cadmium in kidney and lead in bone are 20 to 30 years, whereas for some metals, such as arsenic or lithium, they are only a few hours or days. The half-life of lead in blood is only a few weeks, as compared to the much longer half-time in bone. After inhalation of mercury vapor, at least two half-lives describe the retention in brain—one of the order of a few weeks and the other measured in years.

Blood, urine, and hair are the most accessible tissues in which to measure an exposure or dose; they are sometimes referred to as *indicator tissues*. In vivo, the quantitation of metals within organs is not yet possible, although techniques such as neutron activation and x-ray fluorescence spectroscopy are emerging technologies. Indirect estimates of quantities of toxic metals in specific organs may be calculated from metabolic models derived from autopsy data. Blood and urine concentrations usually reflect recent exposure and correlate best with acute effects. An exception is urinary cadmium, which may reflect renal damage related to an accumulation of cadmium in the kidney. Partitioning of metal between cells and plasma and between filterable and nonfilterable components of plasma should provide more precise information regarding the presence of biologically active forms of a particular metal. For example, most of the methyl mercury in blood is protein-bound, whereas the transportable species—believed to be a complex with low-molecular-weight thiol amino acids—accounts for a tiny fraction. Such partitioning is now standard laboratory practice for blood calcium; ionic calcium is by far the most active form of the metal. Other specific metal complexes, such as chromate and arsenate anions, have now been shown to be the species transported into cells. Speciation of toxic metals in urine may also provide diagnostic insights. For example, cadmium metallothionein in plasma or urine may be of greater toxicologic significance than total cadmium.

Hair might be useful in assessing variations in exposure to metals over the long term. Analyses may be performed on segments of the hair, so that metal content of the newest growth can be compared with past exposures. Hair levels of mercury have been found to be a reliable measure of exposure to alkyl or methyl mercury. For most other metals, however, hair is not a reliable tissue

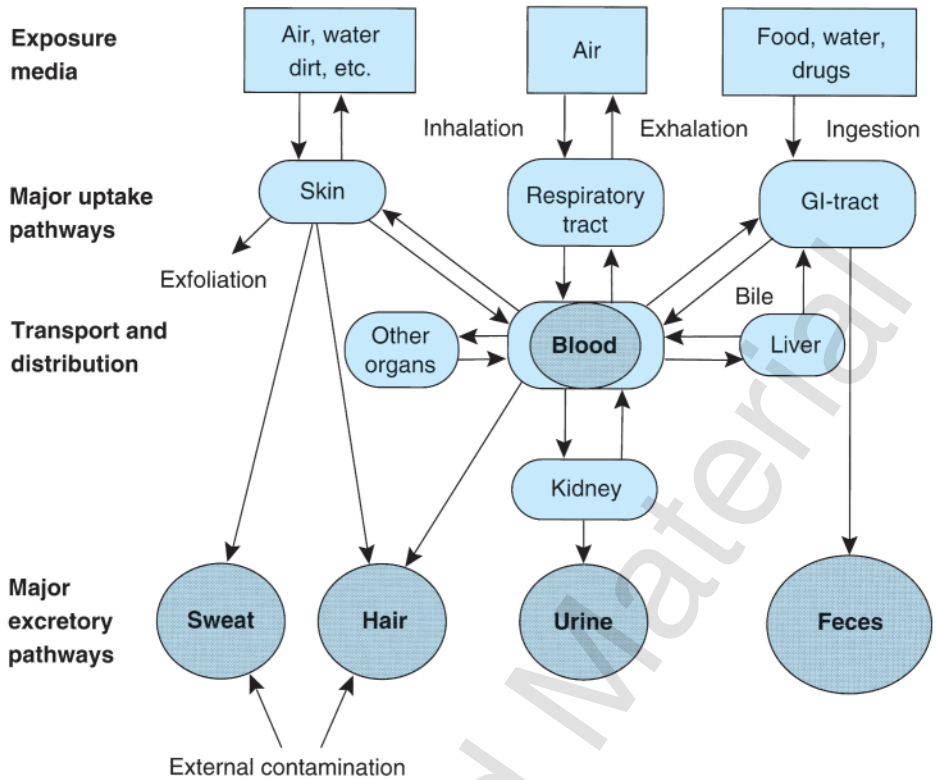

Figure 23-2. Metabolism after exposure to metals via skin absorption, inhalation and ingestion.

The arrows indicate how the metals are transported and distributed. Tissues that are particularly useful for biological monitoring are identified in shaded areas. [From Elinder et al. (1994), with permission.]

for measuring exposure because of metal deposits from external contamination that complicate analyses, in spite of washing.

Cellular targets for toxicity are specific biochemical processes (enzymes) and/or receptors on membranes of cells and organelles. The proximate toxic action of the metal may involve an interaction between the free metal ion and the toxicologic target—for example, in the case of alkali and alkaline earth metals such as lithium and barium. Other metals that bind with high affinities to cellular ligands may transfer from a ligand involved in transport of the metal directly to the target ligand. For example, methyl mercury is believed to transfer from one thiol group to another without any intermediary free mercury ion.

Toxicity is determined by dose at the cellular level as well as such factors as valence state and ligand binding. Hexavalent chromium is highly toxic, whereas the trivalent form functions as an essential trace element. Ligand binding is probably the most fundamental chemical process in metal toxicity and in cellular defense against metals. The thiol ligands of metallothionein avidly bind a number of toxic metals as part of a defense system. Lead attaches to thiol ligands on enzymes involved in heme synthesis, trivalent arsenic to the thiol groups of alpha lipoic acid, and uranium to phosphate groups on glucose transporters, all metal ligand interactions underlying toxic action.

Certain metals can form organometallic compounds involving covalent metal-carbon bonds. These "organic" forms differ in toxic properties from the inorganic counterparts. Nonionized alkyl compounds such as tetraethyl lead and dimethyl mercury are lipid soluble and pass readily across biological membranes unaltered by their surrounding medium. They are dealkylated or transformed ultimately to inorganic species. Hence, the patterns of disposition and toxicity of organic forms tend to differ from those of inorganic forms. For example, alkyl mercury is primarily a neurotoxin, whereas mercuric chloride is toxic to the kidneys.

HOST FACTORS INFLUENCING THE TOXICITY OF METALS

Recognition of factors that influence toxicity of a particular level of exposure to a toxic metal are important in determining the risk of toxicity, particularly in susceptible populations. A number of factors influencing the toxicity of metals are shown in Table 23-1. The interaction of toxic with essential metals occurs when the metabolism of a toxic metal is similar to that of the essential element (Goyer, 1995). Absorption of toxic metals from the lung or gastrointestinal tract may be influenced by an essential metal, partic-

Table 23-1
Factors Influencing Toxicity of Metals

Interactions with essential metals
Formation of metal–protein complexes
Age and stage of development
Lifestyle factors
Chemical form or speciation
Immune status of host

ularly if the toxic metal shares or influences a homeostatic mechanism, as occurs for lead and calcium and iron, and for cadmium and iron. There is an inverse relationship between the protein content of the diet and cadmium and lead toxicity. Vitamin C reduces lead and cadmium absorption, probably because of increased absorption of ferrous ion. Toxic metals may influence the role of essential metals as cofactors for enzymes or other metabolic processes (e.g., lead interferes with the calcium-dependent release of neurotransmitters). Lead, calcium, and vitamin D have a complex relationship affecting mineralization of bone, and they have a more direct one involving impairment of 1-25-dihydroxy vitamin D synthesis in the kidney.

Metalloprotein complexes involved in detoxification or protection from toxicity have now been described for a few metals (Goyer, 1984). Morphologically discernible cellular inclusion bodies are present with exposures to lead, bismuth, and a mercury-selenate mixture. Metallothioneins form complexes with cadmium, zinc, copper, and other metals, and ferritin and hemosiderin are intracellular iron-protein complexes. None of these proteins or metal-protein complexes have any known enzymatic activity. The nature and influences of these complexes are discussed below (this chapter) in the discussion of the toxicology of the particular metals involved.

Persons at either end of the life span, whether they are young children or elderly people, are believed to be more susceptible to toxicity from exposure to a particular level of metal than most adults (NRC, 1993). The major pathway of exposure to many toxic metals in children is food, and children consume more calories per pound of body weight than adults. Moreover, children have higher gastrointestinal absorption of metals, particularly lead. Experimental studies have extended these observations to many metals, and a milk diet, probably because of its lipid content, seems to increase metal absorption. The rapid growth and rapid cell division that children's bodies experience represent opportunities for genotoxic effects. Intrauterine toxicity to methyl mercury is well documented. There is no impediment to the transplacental transport of lead, so that fetal blood lead levels are similar to maternal levels.

Lifestyle factors such as smoking or alcohol ingestion may have indirect influences on toxicity. Cigarette smoke by itself contains some toxic metals, such as cadmium, and cigarette smoking may also influence pulmonary effects. Alcohol ingestion may influence toxicity indirectly by altering diet and reducing essential mineral intake.

For metals that produce hypersensitivity reactions, the immune status of an individual becomes an additional toxicologic variable. Metals that provoke immune reactions include mercury, gold, platinum, beryllium, chromium, and nickel. Clinical effects are varied but usually involve any of four types of immune responses. In anaphylactic or immediate hypersensitivity reactions, the antibody IgE reacts with the antigen on the surface of mast cells, releasing vasoreactive amines. Clinical reactions include conjunctivitis, asthma, urticaria, or even systemic anaphylaxis. Cutaneous, mucosal, and bronchial reactions to platinum have been attributed to this type of hypersensitivity reaction. Cytotoxic hypersensitivity is the result of a complement-fixing reaction of IgG immunoglobulin with antigen or hapten bound to the cell surface. The thrombocytopenia sometimes occurring with exposure to organic gold salts may be brought about in this manner. Immune complex hypersensitivity occurs when soluble immune complex forms deposits (antigen, antibody, and complement) within tissues, producing an acute inflammatory reaction. Immune complexes are typically deposited on the epithelial (subepithelial) side of glomerular basement membrane, resulting in proteinuria following exposure to mercury vapor or gold therapy. Cell-mediated hypersensitivity, also known as the *delayed hypersensitivity reaction,* is mediated by thymus-dependent lymphocytes and usually occurs 24 to 48 h after exposure. The histologic reaction consists of mononuclear cells and is the typical reaction seen in the contact dermatitis following exposure to chromium or nickel. The granuloma formation occurring with beryllium and zirconium exposure may be a form of cell-mediated immune response.

METAL-BINDING PROTEINS

Protein binding of metals has been the subject of a recent major review on the molecular biology of metal toxicology (Zalups and Koropatnick, 2000). Several kinds of metal-protein interactions may be considered. A protein may be the target of toxicity. Enzymes are the best-documented targets. The protein may play a protective role, reducing the activity (toxicity of the metal). The metallothioneins are the best-known example.

Many different classes of proteins are known to play a role in the disposition of metals in the body. Nonspecific binding to proteins, such as serum albumin or hemoglobin, plays a role in metal transport in the bloodstream and in the distribution of metals between red cells and plasma. Metals bound to albumin may be carried into cells by endocytotic mechanisms. The distribution of methyl mercury between red cells and plasma depends upon genetically determined species of hemoglobin molecules differing in their content of cysteine residues. In addition, proteins with specific metal binding properties play a special role in both the transport of metals from plasma to tissues and in the transport of metals across cell membranes and within the cell.

Specific Metal-Binding Proteins

The metallothioneins, discovered over 40 years ago, may have several diverse functions, including essential metal homeostasis and protection against metal toxicity. They have low molecular weights (about 6000 Da) and are rich in thiol ligands. These ligands provide the basis for high-affinity binding of several essential and nonessential but toxic metals such as Cd, Cu, Hg, Ag, and Zn. In most cases but not all, the metallothioneins are highly inducible by a number of metals and other stimulants. Metallothioneins can interact with metals in complex physiologic and biochemical pathways, as illustrated in the discussion of cadmium, below.

Transferrin is a glycoprotein that binds most of ferric iron in plasma. Transport of iron across cell membranes occurs by receptor-mediated endocytosis of ferric transferrin. The receptor is a disulfide-linked membrane glycoprotein whose affinity for apotransferrin is two orders of magnitude lower than that for ferric transferrin. Once inside the cell, iron is separated from transferrin by an acidification process within the endosomes. This protein also transports Al^{3+} and Mn^{2+}.

Ferritin is primarily a storage protein for iron in the reticuloendothelial cells of liver, spleen, and bone. It plays a major role in hepatic turnover of iron. Kupffer cells release iron acquired from the phagocytosis of red cells in the form of ferritin, which is efficiently internalized by hepatocytes via their ferritin receptors. It has been suggested that ferritin may serve as a general metal detoxicant, since it binds a variety of toxic metals including Cd, Zn, Be and Al.

Ceruloplasmin is a copper-containing glycoprotein oxidase in plasma that converts ferrous to ferric iron, which then binds to transferrin. This protein also stimulates iron uptake by a transferrin-independent mechanism.

Membrane Carrier Proteins

In addition to the cases discussed above, a rapidly increasing number of carrier proteins are being discovered that transport metals across cell membranes and organelles inside the cells. Although certain metals may be transported in the free ionic forms, as through calcium channels, many metals are transported as complexes with endogenous ligands on transport systems intended for the ligand itself. This is made possible because many of these carriers are generally multispecific, accepting substrates that differ considerably in their chemical structure and are not able to discriminate between substrates whose only modification is the attachment of a metal ion.

The phosphate and sulfate transporters can carry a number of metal oxyanions across the plasma membrane. Vanadate and arsenate are structurally similar to phosphate and can compete with phosphate for transport as well as intracellular binding sites. In fact, their toxicity may be related to this competition. Similarly, chromate, molybdate, and selenate are structurally similar to sulfate and are carried on the sulfate transporter.

Amino acid and peptide transporters and organic solute carriers also accept metals as complexes with endogenous molecules such as amino acids, peptides, and bicarbonate. Cellular uptake of copper or zinc may occur as complexes with the amino acid histidine. Methyl mercury crosses cell membranes as a complex with cysteine on the large neutral amino acid carrier and is exported from hepatocytes into bile as a complex with glutathione. Zinc appears to be taken up into red blood cells as an anionic complex with bicarbonate, $Zn(HCO_3)_2$, through the anion exchanger. Bicarbonate complexes of lead may follow a similar route.

Other examples of metal transporters have been the subject of a recent review (Ballatori, 2000a). These include divalent cation transporters and ATP-activated membrane pumps. For example, Wilson's and Menke's diseases are due to genetic errors in copper metabolism related to ATP-activated copper carriers. It has been estimated (Ballatori, 2000b) that the human genome may contain upwards of 9000 genes coding for transporter proteins, of which 2000 are concerned with the transport of drugs and other xenobiotics. This rapidly expanding field is still not sufficiently developed to identify polymorphisms of these protein carriers. The future holds promise that identification and measurement of expression of these carriers in cells and tissues will result in valuable biomarkers of metal effects and of individual susceptibility to metal toxicity.

COMPLEXATION AND CHELATION THERAPY

Treatment of poisoning from toxic metals is sometimes warranted to prevent or reverse toxicity and therefore remains an important topic, particularly for those metals that are cumulative and persistent (e.g., lead). It must be emphasized, however, that treatment is only a secondary alternative to reduction or prevention of exposures to toxic metals.

Complexation is the formation of a metal ion complex in which the metal ion is associated with a charged or uncharged electron donor, referred to as a *ligand.* The ligand may be monodentate, bidentate, or multidentate; that is, it may attach or coordinate using one, two or more donor atoms. *Chelation* occurs when bidentate ligands form ring structures (*chelate* comes from the Greek word for claw) that include the metal ion and the two ligand atoms attached to the metal (Williams and Halstead, 1982). Metals may react with O-, S-, and N-containing ligands present in the form of OH, COOH, SH, NH_2, NH, and N. A resultant metal complex is formed by coordinate bonds (coordination compound), in which both electrons are contributed by the ligand (Klaassen, 1990).

Chelating[1] agents (drugs) vary in their specificity for toxic metals. Ideal chelating agents should be water-soluble, resistant to biotransformation, able to reach sites of metal storage, capable of forming nontoxic complexes with toxic metals, and of being excreted from the body; they should also have a low affinity for essential metals, particularly calcium and zinc (Klaassen, 1990). The challenge in the development of safer and more effective chelating agents is to design all of the desirable chemical, physiologic, and pharmacologic properties into the drug (Jones, 1992).

The general properties of chelating agents that are of current interest are briefly described below. Additional details and comments are provided later in the chapter with discussions of specific metals.

BAL (British Anti-Lewisite)

BAL (2,3-dimercaptopropanol) was the first clinically useful chelating agent. It was developed during World War II as a specific antagonist to vesicant arsenical war gases, based on the observation that arsenic has an affinity for sulfhydryl-containing substances. BAL, a dithiol compound with two sulfur atoms on adjacent carbon atoms, competes with the critical binding sites responsible for the toxic effects. These observations led to the prediction that the "biochemical lesion" of arsenic poisoning would prove to be a thiol with sulfhydryl groups separated by one or more intervening carbon atoms. This prediction was borne out a few years later with the discovery that arsenic interferes with the function of 6,8-dithiooctanoic acid in biological oxidation (Gunsalus, 1953).

BAL has been found to form stable chelates in vivo with many toxic metals, including inorganic mercury, antimony, bismuth, cadmium, chromium, cobalt, gold, and nickel. However, it is not necessarily the treatment of choice for toxicity to these metals. BAL has been used as an adjunct in the treatment of the acute encephalopathy of lead toxicity. It is a potentially toxic drug, and its use may be accompanied by multiple side effects. Although treatment with BAL will increase the excretion of cadmium, there is a

[1]Chelating agents are a subset of the more general class of complexing agents. However, the terms *chelation* and *chelating agents* are now used to cover all types of metal complexation therapy even though some agents cannot form ring structures—for example, penicillamine, to be discussed later. Also, bidentate complexing agents such as BAL that have the capacity to form ring structures with metals; in fact, they may form complexes without ring structures, depending on the molar ratio of metal to BAL (for further discussion, see Clarkson and DiStefano, 1971). In this text we follow the common practice of using the terms *chelation* and *chelating agent* to cover all types of complexation therapy.

concomitant increase in renal cadmium concentration, so that its use in case of cadmium toxicity is to be avoided. It does, however, remove inorganic mercury from the kidney, but it is not useful in the treatment of alkyl mercury or phenyl mercury toxicity. BAL also enhances the toxicity of selenium and tellurium, so it is not to be used to remove these metals from the body.

DMPS

DMPS (2,3-dimercapto-1-propanesulfonic acid) is a water-soluble derivative of BAL developed in response to BAL's toxicity and unpleasant side effects. DMPS has been shown to reduce blood lead levels in children (Chisholm and Thomas, 1985). It has the advantage over ethylene diamine tetraacetic acid (EDTA) in that it is administered orally and does not appear to have toxic side effects. It has been widely used in the former Soviet Union to treat many different metal intoxications. DMPS has been used experimentally to estimate the renal burden of lead (Twarog and Cherian, 1984) and inorganic mercury (Cherian et al., 1988). Its effectiveness in mobilizing metals from the kidney may be due to the fact that it is transported into kidney cells on the organic anion transport system (Zalups et al., 1998). It increases the urinary excretion of mercury in persons with an increased body burden from industrial exposure, from dentists and dental technicians, from persons with dental amalgams, from those exposed to mercurous chloride in skin creams (Aposhian et al., 1992; Gonzalez-Ramirez et al., 1998). This agent has also been used to assess body burdens of inorganic mercury from dental amalgams and of arsenic ingested from drinking water (Aposhian, 1998).

DMSA

DMSA (meso-2.3.-dimercaptosuccinic acid; succimer), like DMPS, is a chemical analog of BAL. More than 90 percent of DMSA is in the form of a mixed disulfide in which each of the sulfur atoms is in disulfide linkage with a cysteine molecule (Aposhian and Aposhian, 1992). The drug is of current interest clinically because of its ability to lower blood lead levels. It has advantages over EDTA because it is given orally and has greater specificity for lead. It may be safer than EDTA in that it does not enhance excretion of calcium and zinc to the same degree. Studies in rodents showed that a single dose of DMSA primarily removes lead from soft tissues (Smith and Flegal, 1992). A lead mobilzation test with DMSA does not appear to give better information on body burden than measurements of lead in blood, plasma, or urine (Gerhardsson et al., 1999).

The drug has been licensed recently by the U.S. Food and Drug Administration (FDA) specifically for the treatment of lead poisoning in children whose blood lead levels are ≥ 45 μg/dL, and it has been used in Europe. However its effectiveness in improving long-term blood lead levels in children has been questioned (O'Connor and Rich, 1999), nor, according to studies on primates, does it appear effective in removing lead from the brain (Cremin et al., 1999). Its ability to reverse some of the toxic outcomes of lead poisoning, such as negative effects on cognitive and behavioral development, has not been demonstrated.

EDTA

Calcium salt of ethylene diamine tetraacetic acid (EDTA) must be used for clinical purposes because the sodium salt has greater affinity for calcium and will produce hypocalcemic tetany. However, the calcium salt will bind lead, with displacement of calcium from the chelate. EDTA is poorly absorbed from the gastrointestinal tract so it must be given parenterally, which distributes it rapidly throughout the body. It has long been the method of choice for the treatment of lead toxicity. The peak excretion point is within the first 24 h and represents the excretion of lead from soft tissues. Removal of lead from the skeletal system occurs more slowly, with the restoration of equilibrium with soft tissue compartments. Animal experiments indicate that EDTA is not effective in reducing total brain lead (Seaton et al., 1999). Calcium EDTA does have the potential for nephrotoxicity, so it should be administered only when clinically indicated (EPA, 1986). Combination therapy of EDTA with other chelating agents, such as BAL and DMSA, has been used to reduce the risk of side effects from either agent alone, as each agent can be given at a lower dose in combined therapy. Whether BAL or DMSA is used as the second agent, the results are equally effective in reducing blood lead in children (Besunder et al., 1997).

DTPA

DTPA, or diethylenetriaminepentaacetic acid, has chelating properties similar to those of EDTA. The calcium salt ($CaNa_2DTPA$) must be used clinically because of DTPA's high affinity for calcium. It has been used for the chelation of plutonium and other actinide elements, but with mixed success. Experimental studies have shown that various multidentate hydroxypyridinonate ligands are more effective than $CaNa_2DTPA$ for promoting excretion of Pu and other actinides (Durbin et al., 2000).

Desferrioxamine

Desferrioxamine is a hydroxylamine isolated as the iron chelate of *Streptomyces pilosus* and is used clinically in the metal-free form (Keberle, 1964). It has a remarkable affinity for ferric iron and a low affinity for calcium, and it competes effectively for iron in ferritin and hemosiderin but not in transferrin and not for the iron in hemoglobin or heme-containing enzymes. It is poorly absorbed from the gastrointestinal tract, so it must be given parenterally. Clinical usefulness is limited by a variety of toxic effects, including hypotension, skin rashes, and possibly cataract formation. It seems to be more effective in hemosiderosis due to blood transfusion but is less effective in treatment of hemochromatosis. A high-molecular-weight derivative in which desferrioxamine is chemically coupled to hydroxyethyl starch shows promise in human tests as an effective iron chelator, with lower toxicity than the parent compound (Dragsten et al., 2000).

Dithiocarbamate (DTC)

Dithiocarb (diethyldithiocarbamate), or DTC, has been recommended as the drug of choice in the treatment of acute nickel carbonyl poisoning. The drug may be administered orally for mild toxicity and parenterally for acute or severe poisoning (Sunderman, 1979). However, no adequately controlled clinical studies have been performed (Bradberry and Vale, 1999).

DTC has also been used experimentally for removal of cadmium bound to metallothionein (Kojima et al., 1990). A number of DTC compounds with various substitutions of nonpolar, nonionizing groups have been synthesized by Jones and Cher-

ian (1990). Sodium, *N*-(4-methoxybenzyl)-D-glucamine dithiocarbamate (MeOBGDTC), is among the most effective in removing cadmium from tissues. The CdMeOBGDTC complex is excreted in the bile rather than by the kidney, avoiding the nephrotoxicity characteristic of cadmium chelates. To date the use of this compound has been limited to experimental studies in rodents.

Penicillamine and *N*-Acetylcysteine

Penicillamine (β, β-dimethylcysteine), a hydrolytic product of penicillin, has been used for the removal of copper in persons with Wilson's disease and for the removal of lead, mercury, and iron (Walshe, 1964). It is also important to note that penicillamine removes other physiologically essential metals, including zinc, cobalt, and manganese. Attached to its use is the risk of inducing a hypersensitivity reaction with a wide spectrum of undesirable immunologic effects, including skin rash, blood dyscrasia, and possibly proteinuria and nephrotic syndrome. It has cross-sensitivity with penicillin, so it should be avoided by persons with penicillin hypersensitivity. For persons who have developed a sensitivity to penicillamine, an orally active chelating agent, triethylene tetramine 2HCl (Trien), is an alternative for the removal of copper (Walshe, 1983). Reducing the commonly used dose from 25 to 30 mg/kg/day to 15 mg/kg/day maintains the efficacy of d-penicillamine at reducing blood lead with reduced side effects in lead-exposed children (Shannon and Townsend, 2000).

N-acetylcysteine has been widely used clinically as a mucolytic agent (e.g., for cystic fibrosis) and to protect against the toxic effects of a number of chemicals. It is a free-radical scavenger, a precursor to glutathione, and it can form stable water-soluble complexes with mercury and other metals. Its ease of administration (oral), low toxicity, and wide availability in the clinical setting makes it an attractive therapeutic agent. It is effective in accelerating the removal of methyl mercury in animal tests (Ornaghi et al., 1993; Ballatori et al., 1998). It was also effective in extracorporeal complexation hemodialysis (see below) in one case of human exposure to methyl mercury (Lund et al., 1984).

Hemodialysis with Chelation

Hemodialysis is usually not effective in removing metals from the bloodstream because many metals are associated with red blood cells and/or bound to plasma proteins (for example, Sauder et al., 1988). However a chelating agent may transform the metal into a diffusible form amenable to removal by hemodialysis (Kostyniak and Clarkson, 1981). The chelating agent may be given systemically, as in the application of desferrioxamine to remove aluminum in conjunction with hemodialysis (Nakamura et al., 2000). Extracorporeal complexation hemodialysis avoids systemic application of the complexing agent by introducing the agent into the blood as it enters the dialyzer. Hemodialysis then removes the metal chelate and as well as the excess chelating agent. The method was first successfully used to remove methyl mercury from intoxicated patients (Al-Abbasi et al., 1978), and it has subsequently been applied to a case of inorganic poisoning (Kostyniak et al., 1990). The most effective complexing agent appears to be DMSA for mercury removal with hemodialysis (Kostyniak, 1982). The method has been successfully tested in dogs to remove cadmium using a combination of EDTA and glutathione as complexing agents (Sheabar et al., 1989).

MAJOR TOXIC METALS WITH MULTIPLE EFFECTS

Arsenic (As)

Arsenic[1] is particularly difficult to characterize as a single element because its chemistry is so complex and there are many different arsenic compounds. It may be trivalent or pentavalent and is widely distributed in nature. The most common inorganic trivalent arsenic compounds are arsenic trioxide, sodium arsenite, and arsenic trichloride. Pentavalent inorganic compounds are arsenic pentoxide, arsenic acid, and arsenates, such as lead arsenate and calcium arsenate. Organic compounds may also be trivalent or pentavalent, such as arsanilic acid, or may even occur in methylated forms as a consequance of biomethylation by organisms in soil, fresh water, and seawater.

A summary of environmental sources of arsenic as well as their potential health effects is contained in the National Research Council's is report on arsenic in drinking water (NRC, 1999). Inorganic arsenic is released into the environment from a number of anthropogenic sources, which include primary copper, zinc, and lead smelters, glass manufacturers that add arsenic to raw materials, and chemical manufacturers. The National Air Sampling Network tests conducted by the EPA indicate that in areas not influenced by copper smelters, maximum 24-h concentrations do not exceed 0.1 $\mu g/m^3$.

Drinking water usually contains a few micrograms per liter or less. Most major U.S. drinking water supplies contain levels lower than 5 μg/L. It has been estimated that about 350,000 people might drink water containing more than 50 μg/L (Smith et al., 1992). While seafoods contain several times the amount of arsenic in other foods, about 90 percent or more is organic arsenic that is unabsorbed (NRC, 1999). According to the 1991–1997 FDA Total Diet Market Basket Study conducted by the FDA for the 1991–1997 period, daily intake of arsenic from food is less than 10 μg/day (Tao and Bulger, 1998). Assuming consumption of 2000 mL/day of drinking water containing as much as 5 μg/L of arsenic, drinking water also contributes 10 μg/day for a total of 20 μg/day from food and water. Youst et al. (1998) estimated that daily dietary intake of inorganic arsenic ranges from 8.3 to 14 μg/day in the United States and 4.8 to 12.7 μg/day in Canada. Major sources of occupational exposure to arsenic in the United States include the manufacture of pesticides, herbicides, and other agricultural products. High exposure to arsenic fumes and dust may occur in the smelting industries; the highest concentrations most likely are among roaster workers.

Toxicokinetics About 80 to 90 percent of a single dose of arsenite [As(III) or arsenate As(V)] has been shown to be absorbed from the gastrointestinal tract of humans and experimental animals. Arsenic compounds of low solubility (e.g., arsenic selenide, lead arsenide, and gallium arsenide) are absorbed less efficiently than dissolved arsenic. Skin can be a route of exposure to arsenic, and systemic toxicity has been reported in persons having extensive acute dermal contact with solutions of inorganic arsenic (Hostynek et al., 1993). Airborne arsenic is largely trivalent arsenic oxide, but deposition in airways and absorption from lungs is dependent on particle size and chemical form (Morrow et al.,

[1]Atomic weight, 74.92; periodic table group, VA; valence, −3, +3 or +5; discovered in A.D. 1250.

1980). Excretion of absorbed arsenic is mainly via urine. The biological half-life of ingested inorganic arsenic is about 10 h, and 50 to 80 percent is excreted in about 3 days. The biological half-life of methylated arsenic is about 30 h. Arsenic has a predilection for skin and is excreted by desquamation of skin and in sweat, particularly during periods of profuse sweating. It also concentrates in nails and hair. Arsenic in nails produces Mees' lines (transverse white bands across fingernails), which appear about 6 weeks after the onset of symptoms of toxicity. The time of exposure may be estimated from measuring the distance of the line from the base of the nail and the rate of nail growth, which is about 0.3 cm per month or 0.1 mm per day. Arsenic in hair may also reflect past exposure, but intrinsic or systematically absorbed arsenic in hair must be distinguished from arsenic that is deposited from external sources.

Biotransformation The metabolism and potential for toxicity of arsenic is complicated by in vivo transformation of inorganic forms by methylation to monomethyl arsenic (MMA) and dimethyl arsenic (DMA). The methylation of arsenic compounds involves both oxidation states of the element. The liver is the major site for methylation. A substantial fraction of absorbed As(V) is rapidly reduced to AS(III), most of which is then methylated to MMA or DMA. The probable mechanisms of in vivo methylation involve a two-electron process that probably involves thiol oxidation. As(V) is reduced to As(III). The resulting As(III) then reacts with *S*-adenosylmethionine (SAM) in an oxidative addition resulting in the transfer of a methyl group from sulfur to arsenic (Abernathy et al., 1999). Compared with inorganic arsenic, the methylated metabolites are less reactive with tissue constituents, less acutely toxic, less cytotoxic, and more readily excreted in the urine (NRC, 1999). This is presumed to be a process of detoxification of the more toxic inorganic forms, and dimethyl arsenic appears to be a terminal metabolite, which is rapidly formed and rapidly excreted. The liver is the major site for methylation of inorganic arsenic. Studies using primary cultures of normal human hepatocytes have shown that the total methylation yield (MMA and DMA) increased in a dose-dependent manner, but the methylation process is saturable. DMA production was inhibited by As(III) in a concentration-dependent manner and DMA/MMA ratio decreased. At higher concentrations of As(III), both methylated forms of arsenic decreased (Styblo et al., 1999). There are major differences in the biotransformation of inorganic arsenic in different mammalian species (Vahter, 1994; Vahter et al., 1995). For most animal species, DMA is the main metabolite. Studies of marmoset monkeys and chimpanzees show no methylation of inorganic arsenic.

A number of studies in humans in which metabolites of inorganic arsenic in urine have been speciated consistently show average values of 10 to 30 percent inorganic arsenic, 10 to 20 percent MMA, and 55 to 76 percent DMA. Those results were found in human subjects in the general environment and in those exposed at work. However, there are variations in arsenic methylation due to such factors as possible genetic polymorphisms, age, and sex. Studies of native peoples and people of Spanish descent in northern Argentina and Chile exposed to arsenic in drinking water showed that urinary arsenic consisted of only 2 to 4 percent MMA on average (Concha et al., 1998a). On the other hand, a study of exposure to arsenic in drinking water in northeastern Taiwan showed 27 percent MMA in urine—an unusually high percentage (Chiou et al., 1997).

Mechanisms of Toxicity It has been known for some years that trivalent compounds of arsenic are the principal toxic forms and that pentavalent arsenic compounds have little effect on enzyme activity. A number of sulfhydryl-containing proteins and enzyme systems have been found to be altered by exposure to arsenic. Some of these can be reversed by addition of an excess of a monothiol such as glutathione. Effects on enzymes containing two thiol groups can be reversed by dithiols such as 2,3-dimercaptopropanol (British anti-Lewisite, or BAL) but not by monothiol. Arsenic affects mitochondrial enzymes and impairs tissue respiration (Brown et al., 1976), which seems to be related to the cellular toxicity of arsenic. Mitochondria accumulate arsenic, and respiration mediated by NAD-linked substrates is particularly sensitive to arsenic; this is thought to result from a reaction between the arsenite ion and the dihydrolipoic acid cofactor, which is necessary for oxidation of the substrate. Arsenite also inhibits succinic dehydrogenase activity and uncouples oxidative phosphorylation, which results in stimulation of mitochondrial ATPase activity. Arsenic inhibits energy-linked functions of mitochondria in two ways: competition with phosphate during oxidative phosphorylation and inhibition of energy-linked reduction of NAD. Inhibition of mitochondrial respiration results in decreased cellular production of ATP and increased production of hydrogen peroxide, which might cause oxidative stress, and production of reactive oxygen species (ROS). Intracellular production of ROS results in observed induction of major stress protein families (NRC, 1999).

Arsenic compounds induce metallothionein in vivo. Potency is dependent on the chemical form of arsenic. As(III) is most potent, followed by As(V), monomethylarsenate, and dimethylarsenate (Kreppel et al., 1993). Metallothionein is thought to have a protective effect against arsenic toxicity and may be responsible at least in part for its self-induced tolerance. Metallothionein-null mice are more sensitive than wild-type mice to the hepatotoxic and nephrotoxic effects of chronic or injected inorganic arsenicals (Liu et al., 1998). The role of asenical-induced oxidative stress and ROS may play a role in mediating DNA damage and initiating the carcinogenic process (NRC, 1999).

Toxicology Ingestion of large doses (70 to 180 mg) of arsenic may be fatal. Symptoms of acute illness, possibly leading to death, consist of fever, anorexia, hepatomegaly, melanosis, and cardiac arrhythmia, with changes in electrocardiograph results that may point to eventual cardiovascular failure. Other features include upper respiratory tract symptoms, peripheral neuropathy, and gastrointestinal, cardiovascular, and hematopoietic effects. Acute ingestion may be suspected from damage to mucous membranes, such as irritation, vesicle formation, and even sloughing. Sensory loss in the peripheral nervous system is the most common neurologic effect, appearing 1 or 2 weeks after large exposures and consisting of wallerian degeneration of axons, a condition that is reversible if exposure is stopped. Anemia and leukopenia, particularly granulocytopenia, occur a few days following exposure and are reversible. The hematologic consequences of chronic exposure to arsenic are similar to effects from acute exposure. There may also be disturbances in heme synthesis, with an increase in urinary porphyrin excretion.

Chronic exposure to inorganic arsenic compounds may lead to neurotoxicity of both the peripheral and central nervous systems. Neurotoxicity usually begins with sensory changes, paresthesia, and muscle tenderness followed by weakness, progressing from

proximal to distal muscle groups. Peripheral neuropathy may be progressive, involving both sensory and motor neurons leading to demyelination of long axon nerve fibers, but effects are dose-related. Acute exposure to a single high dose can produce the onset of paresthesia and motor dysfunction within 10 days. More chronic occupational exposures producing more gradual, insidious effects may occur over a period of years, and it has been difficult to establish dose–response relationships (Murphy et al., 1981; Donorio et al., 1987).

Liver injury, characteristic of longer-term or chronic exposure, manifests itself initially in jaundice and may progress to cirrhosis and ascites. Toxic effects on hepatic parenchymal cells result in the elevation of liver enzymes in the blood, and studies in experimental animals show granules and alterations in the ultrastructure of mitochondria as well as nonspecific manifestations of cell injury, including loss of glycogen.

The relationship between the prevalence of ingestion of inorganic arsenic in drinking water and cardiovascular disease has been shown in studies in the United States (Engel and Smith, 1994) and in Taiwan (Chiou et al., 1997). Peripheral vascular disease has been observed in persons with chronic exposure to arsenic in drinking water in Taiwan and Chile; it is manifest by acrocyanosis and Raynaud's phenomenon and may progress to endarteritis obliterans and gangrene of the lower extremities (blackfoot disease). This specific effect seems to be related to the cumulative dose of arsenic, but the prevalence is uncertain because of difficulties in separating arsenic-induced peripheral vascular disease (NRC, 1999). Recent studies in southwestern Taiwan (Lai et al., 1994) and cohorts with occupational exposure in Sweden (Rahman and Axelson, 1995) were associated with chronic arsenic ingestion in drinking water and an increase risk of diabetes mellitus. Immunomodulating and immunotoxic effects of arsenic have been suggested from studies in experimental animals, while human studies have shown some effect on lymphocyte replicating ability (Gonsebatt et al., 1994).

Reproductive Effects and Teratogenicity High doses of inorganic arsenic compounds given to pregnant experimental animals produced various malformations, somewhat dependent on time and route of administration, in fetuses and offspring. However, no such effects have been noted in humans with excessive occupational exposures to arsenic compounds. Arsenic readily crosses the placenta in women without known exposure to arsenic. In a fetus and suckling infant in an Andean village where the arsenic content of drinking water was about 200 μg/L, the concentration of arsenic in cord blood was almost as high as that in maternal blood (Concha et al., 1998b). However, more than 90 percent of the arsenic in plasma and urine was in the form of DMA, a percentage that is higher than the percentage in nonpregnant women, suggesting that there is increased methylation during pregnancy. Animal data indicate that less developmental toxicity is caused by the methylated metabolites than by arsenite (NRC, 1999).

Carcinogenicity The potential carcinogenicity of arsenic compounds was recognized over 100 years ago by Hutchinson (1887), who observed an unusual number of skin cancers occurring in patients treated with arsenicals. The IARC (1987) and EPA (1988) classify arsenic as a carcinogen, for which there is sufficient evidence from epidemiologic studies to support a causal association between exposure and skin cancer and lung cancer via inhalation. There is now evidence that arsenic causes cancer of internal organs from oral ingestion (Bates et al., 1992). In humans, chronic exposure to arsenic induces a series of characteristic changes in skin epithelium, proceeding from hyperpigmentation to hyperkeratosis. Diffuse or spotted hyperpigmentation, the initial nonmalignant cutaneous effect, can first appear within 6 months to 3 years of chronic ingestion at concentrations in excess of approximately 0.4 mg/kg/day. Lower exposure rates, on the order of 0.01 mg/kg/day or longer, can result in pigmentation after intervals as long as 5 to 15 years. Palmar-plantar hyperkeratosis usually follows the initial appearance of arsenical hyperpigmentation within a period of years. There may actually be two cell types of arsenic-induced skin cancer—basal cell carcinomas and squamous cell carcinomas—arising in keratotic areas. The basal cell cancers are usually only locally invasive, but squamous cell carcinomas may have distant metastases. The skin cancers related to arsenic differ from ultraviolet light–induced tumors in that they generally occur on areas of the body not exposed to sunlight (e.g., on palms and soles), and they occur as multiple lesions.

The NRC report (1999), utilizing various statistical approaches, cites lifetime cancer risks for bladder cancer from exposure at different levels of arsenic in drinking water. The current EPA maximum contaminant level for arsenic in drinking water is under revision.

Occupational exposure to airborne arsenic may also be associated with lung cancer, usually a poorly differentiated form of epidermoid bronchogenic carcinoma. The time period between initiation of exposure and occurrence of arsenic-associated lung cancer has been found to be on the order of 35 to 45 years. Enterline and Marsh (1980) report a latency period of 20 years in their study of copper smelter workers.

In contrast to most other human carcinogens, it has been difficult to confirm the carcinogenicity of arsenic in experimental animals. Intratracheal installations of arsenic trioxide produced an increased incidence of pulmonary adenomas, papillomas, and adenomatoid lesions, suggesting that arsenic trioxide can induce lung carcinomas (Pershagan et al., 1984), but other studies testing As(III) and As(V) compounds by oral administration or skin application have not shown potential for either promotion or initiation of carcinogenicity. Similarly, experimental studies for carcinogenicity of organic arsenic compounds have been negative.

The mode of action of arsenic carcinogenicity has not been established. Inorganic arsenic and its metabolites have been shown to induce deletion mutations and chromosomal aberrations but not point mutations. Arsenic has also been shown to be comutagenic. Other modes of action that have been suggested include effects on DNA methylation, oxidative stress, and cell proliferation, but that data are not sufficient to draw firm conclusions (NRC, 1999).

Arsine

Arsine gas (AsH_3) is formed by the reaction of hydrogen with arsenic and is generated as a by-product in the refining of nonferrous metals. Arsine is a potent hemolytic agent, producing acute symptoms of nausea, vomiting, shortness of breath, and headache accompanying the hemolytic reaction. Exposure may be fatal and may be accompanied by hemoglobinuria and renal failure and even jaundice and anemia in nonfatal cases when exposure persists (Fowler et al., 1989).

Biomarkers Biomarkers of arsenic exposure are arsenic concentrations in urine, blood, and hair (Table 23-2). Urinary arsenic is the best indicator of exposure because it is the main route of ex-

Table 23-2
Biomarkers of Arsenic Exposure

	NORMAL	EXCESSIVE EXPOSURE
Urine μg/L	5–50	>100 (without seafood)
Blood μg/L	1–4	50
Hair μg/kg	<1	

cretion for most arsenic compounds. The half-time of inorganic arsenic in humans is about 4 days. Urine arsenic level in persons in the general population without seafood intake is usually in the range of 10 μg/L (5 to 50 μg/L). Some marine organisms may contain very high concentrations of organoarsenicals, which do not have significant toxicity and are rapidly excreted in urine without transformation. One serving of seafood might give rise to urinary arsenic concentrations of 1000 μg/L (Norin and Vahter, 1981). Individuals should be advised not to ingest seafood for a day or two before measurement of urinary arsenic. Most of the absorbed inorganic or organic arsenic has a short half-time in blood, so that arsenic concentrations in blood are increased only a short time following absorption. Like lead, arsenic is measured in whole blood, not serum, because most of the arsenic is in red blood cells. Levels are usually very low and expressed per liter of whole blood. High levels of arsenic in drinking water (wells) will increase urine and blood arsenic. In studies carried out in California and Nevada, a water concentration of 400 μg/L corresponded to about 75 μg/L in the urine and about 14 μg/L in the blood (Valentine et al., 1979). Compared with urine, blood is a much less sensitive indicator of arsenic exposure. Hair or even fingernail concentrations of arsenic may be helpful in evaluating past exposures, but interpretation is made difficult because of the problem of differentiating external contamination.

There are no specific biomarkers of arsenic toxicity, and evaluation of clinical effects must be interpreted with knowledge of exposure history.

Treatment For acute toxicity, treatment is symptomatic, with particular attention to fluid volume replacement and support of blood pressure with pressor agents. For acute symptoms, dimercaprol may be given (3 mg/kg intramuscularly every 4 hours) until symptoms subside, followed by oral penicillamine. Succimer (2,3-dimercaptosuccinic acid) is also thought to be effective. For chronic exposures, dimercaprol and/or penicillamine may also be used (Klaassen, 1990).

Beryllium (Be)

Beryllium[1] is an uncommon metal with a few specific industrial uses. Environmental sources and toxicologic effects of beryllium are reviewed in detail in health criteria documents (EPA, 1987; WHO, 1990). Release of beryllium to the environment largely results from coal combustion. The combustion of coal and oil contributes about 1250 or more tons of beryllium to the environment each year (mostly from coal), which is about five times the annual production from industrial use. The major industrial processes that release beryllium into the environment are beryllium extraction plants, ceramic plants, and beryllium alloy manufacturers. These industries also provide the greatest potential for occupational exposure. Currently, the major use for beryllium is as an alloy, but about 20 percent of world production is for applications utilizing the free metal in nuclear reactions, x-ray windows, and other special applications related to space optics, missile fuel, and space vehicles. It is also present in cigarette smoke (Smith et al., 1997). The mean urinary levels of beryllium in the general population are reported as 0.26 μg/L (Apostoli et al., 1989).

Toxicokinetics Knowledge of the toxicokinetics of beryllium has largely been obtained from experimental animals, particularly the rat. Clearance of inhaled beryllium is multiphasic; half is cleared in about 2 weeks, the remainder is removed slowly, and a residuum becomes fixed in the tissues probably within fibrotic granulomata. Gastrointestinal absorption of ingested beryllium probably occurs only in the acidic milieu of the stomach, where it is in the ionized form, but beryllium passes through the intestinal tract as precipitated phosphate. Removal of radiolabeled beryllium chloride from rat blood is rapid, whereas beryllium has a half-life of about 3 h. It is distributed to all tissues, but most goes to the skeleton. High doses go predominantly to the liver, but it is gradually transferred to the bone. The half-life in tissues is relatively short except in the lungs, and a variable fraction of an administered dose is excreted in the urine, where it has a long biological half-life.

Skin Effects Contact dermatitis is the commonest beryllium-related toxic effect. Exposure to soluble beryllium compounds may result in papulovesicular lesions on the skin, which is a delayed-type hypersensitivity reaction. The hypersensitivity is cell-mediated, and passive transfer with lymphoid cells has been accomplished in guinea pigs. If contact is made with an insoluble beryllium compound, a chronic granulomatous lesion develops, which may be necrotizing or ulcerative. If insoluble beryllium-containing material becomes embedded under the skin, the lesion will not heal and may progress in severity. Use of a beryllium patch test to identify beryllium-sensitive individuals may in itself be sensitizing, so any use of this procedure as a diagnostic test is discouraged.

Pulmonary Effects ***Acute Chemical Pneumonitis*** Acute pulmonary disease from inhalation of beryllium is a fulminating inflammatory reaction of the entire respiratory tract, involving the nasal passages, pharynx, tracheobronchial airways, and the alveoli; in the most severe cases, it produces an acute fulminating pneumonitis. This occurs almost immediately following inhalation of aerosols of soluble beryllium compounds, particularly fluoride, an intermediate in the ore extraction process. Severity is dose-related. Fatalities have occurred, although recovery is generally complete after a period of several weeks or even months.

Chronic Granulomatous Disease, Berylliosis Chronic beryllium disease (CBD) was first described among fluorescent lamp workers exposed to insoluble beryllium compounds, particularly beryllium oxide. CBD is an antigen-stimulated, cell-mediated immune response that leads to granulomatous lung disease (Tinkle and Newman, 1997). The major symptom is shortness of breath, which in severe cases may be accompanied by cyanosis and clubbing of fingers (hypertrophic osteoarthropathy, a characteristic manifestation of chronic pulmonary disease). Chest x-rays show miliary mottling. Histologically, the alveoli contain small interstitial granulomas resembling those seen in sarcoidosis. In the early stages, the lesions are composed of fluid, lymphocytes, and plasma cells.

[1]Atomic weight, 9.01; periodic table group, IIA; valence, +2; discovered in 1828.

Multinucleated giant cells are common. Later, the granulomas become organized with proliferation of fibrotic tissue, eventually forming small fibrous nodules. As the lesions progress, interstitial fibrosis increases, with loss of functioning alveoli, impairment of effective air–capillary gas exchange, and increasing respiratory dysfunction. CD4+ cells are believed to be involved in the pathogenesis of CBD (Fontenot et al., 1999). The alpha subunit of the soluble IL-2 receptor is elevated in serum and bronchiolar lavage cells of individuals with CBD and correlates with the degree of clinical severity. This soluble receptor may be a useful biomarker for progression of the disease (Tinkle et al., 1997).

Carcinogenicity Evidence for the carcinogenicity of beryllium was first observed in experimental studies beginning in 1946, before the establishment of carcinogenicity in humans. Epidemiologic confirmation in humans has been evolving. Studies of humans with occupational exposure to beryllium prior to 1970 were negative. However, reports of two worker populations and a registry of berylliosis cases studied earlier show a small excess of lung cancer, although the total number of cases is small. These findings of excess cancer risk in humans are supported by a clear demonstration of carcinogenicity in animals (Hayes, 1997). The IARC (1994) states there is sufficient evidence in humans and animals for the carcinogenicity of beryllium and its compounds. In vitro studies of genotoxicity have shown that beryllium will induce morphologic transformation in mammalian cells (Dipaolo and Casto, 1979). Beryllium will also decrease the fidelity of DNA synthesis but is negative when tested as a mutagen in bacterial systems.

Cadmium (Cd)

Cadmium[1] is a modern toxic metal. It was discovered as an element only in 1817, and industrial use was minor until about 50 years ago. But now it is a very important metal with many applications. Because of its noncorrosive properties, its main use is in electroplating or galvanizing. It is also used as a color pigment for paints and plastics and as a cathode material for nickel-cadmium batteries. Cadmium is a by-product of zinc and lead mining and smelting, which are important sources of environmental pollution. The toxicology of cadmium is extensively reviewed by Friberg et al. (1986), WHO (1992), EPA (1997), and ATSDR (1998).

Exposure For persons in the general population, the major source of cadmium is food. Plants readily take up cadmium from soil contaminated by fallout from the air, cadmium-containing water used for irrigation and cadmium-containing fertilizers. Another source of concern about potential sources of cadmium toxicity is the use of commercial sludge to fertilize agricultural fields. Commercial sludge may contain up to 1500 mg of cadmium per kilogram of dry material. Studies from Sweden have shown a slow but steady increase in the cadmium content of vegetables over the years. Shellfish, such as mussels, scallops, and oysters, may be a major source of dietary cadmium and contain 100 to 1000 μg/kg. Shellfish accumulate cadmium from the water in the form of cadmium-binding peptides. Meat, fish, and fruit contain 1 to 50 μg/kg, grains contain 10 to 150 μg/kg, and the greatest concentrations are in the liver and kidney of animals. Total daily intake of cadmium from food, water, and air in North America and Europe varies considerably but is estimated to be about 10 to 40 μg/day.

[1]Atomic weight, 112.41; periodic table group, IIB; valence, +2; discovered in 1817.

Workplace exposure to cadmium is particularly hazardous in the presence of cadmium fumes or airborne cadmium. Airborne cadmium in the present-day workplace environment is generally 0.05 or $\mu g/m^3$ or less. Occupations at risk include electrolytic refining of lead and zinc and other industries that employ thermal processes—e.g., iron production, fossil fuel combustion, and cement manufacture—all of which release airborne cadmium, the metal being a constituent of the natural raw material. Other occupations include the manufacture of paint pigments, cadmium-nickel batteries, and electroplanting (WHO, 1992). A major nonoccupational source of respirable cadmium is cigarettes.

Toxicokinetics Gastrointestinal absorption of cadmium is about 5 to 8 percent. Absorption is enhanced by dietary deficiencies of calcium and iron and by diets low in protein. Low dietary calcium stimulates synthesis of calcium-binding protein, which enhances cadmium absorption. In general, women have higher blood cadmium concentrations than men. This is most likely due to increased gastrointestinal absorption because of low iron stores in women of childbearing age. Women with low serum ferritin levels have been shown to have twice the normal absorption of cadmium (Flanagan et al., 1978; Berglund et al., 1994). Respiratory absorption of cadmium is greater than gastrointestinal absorption and independent on solubility of cadmium compound, but it ranges from about 15 to 30 percent. As much as 50 percent of cadmium fumes, as in cigarette smoke, may be absorbed. One cigarette contains 1 to 2 μg of cadmium, and 10 percent of the cadmium in a cigarette is inhaled (0.1 to 0.2 μg). Smoking one or more packs of cigarettes a day may double the daily absorbed burden of cadmium.

Absorbed cadmium is excreted in urine. While gastrointestinal excretion is possible, particularly in bile as a glutathione complex, there are no available data to indicate net gastrointestinal excretion in humans. Cadmium excretion in urine increases proportionally with body burden (Friberg et al., 1986; ATSDR, 1998).

Cadmium is transported in blood by binding to red blood cells and high-molecular-weight proteins in plasma, particularly albumin; it is distributed primarily to liver and kidney (Fig. 23-3).

In the liver, cadmium induces the synthesis of metallothionein and is then either stored in the liver as Cd-MT complex or transported via blood to the kidney, where it may accumulate in lysosomes. cd-MT complex in lysosomes is slowly catabolized to non-metallothionein-bound cadmium but may again be complexed with metallothionein or may induce renal toxicity (see "Nephrotoxicity," below).

Blood cadmium levels in adults without excessive exposure is usually less than 1 μg/dL. Newborns have a low body content of cadmium, usually less than 1 mg total body burden. The placenta synthesizes metallothionein and may serve as a barrier to maternal cadmium, but the fetus may be exposed with increased maternal exposure. Human breast milk and cow's milk are low in cadmium, with less than 1 μg/kg of milk. About 50 to 75 percent of the body burden of cadmium is in the liver and kidneys; its half-life in the body is not known exactly, but it may be as long as 30 years. With continued retention, there is progressive accumulation in the soft tissues, particularly in the kidneys, through ages 50 to 60, when the cadmium burden in soft tissues begins to decline slowly (Fig. 23-4).

Because of the potential for renal toxicity, there is considerable concern about the levels of dietary cadmium intake for the general population (Nordberg, 1984).

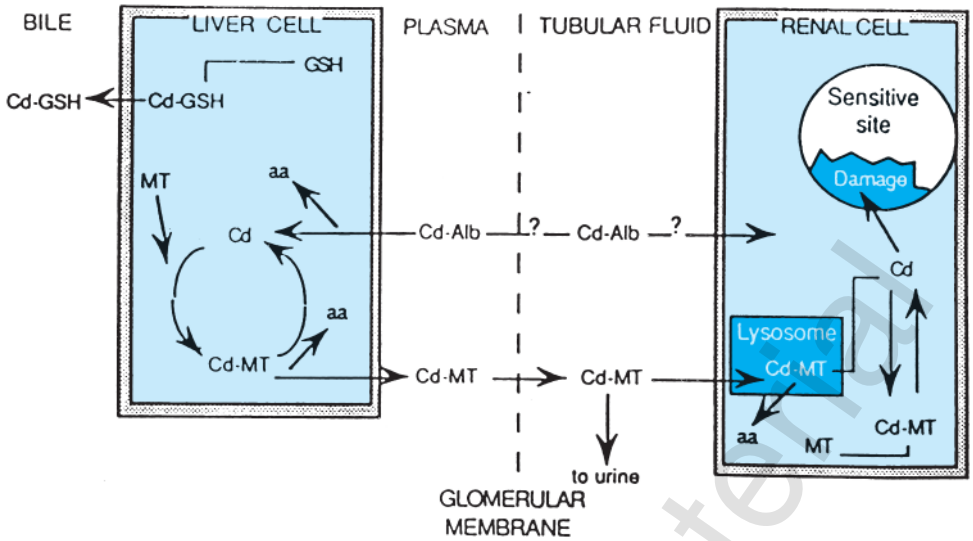

Figure 23-3. A schematic representation of the role of metallothionein in the disposition of cadmium in the liver and kidney. [Adapted from Jarup et al. (1998).]

Acute Toxicity Acute toxicity may result from the ingestion of relatively high concentrations of cadmium, as may occur from contaminated beverages or food. Nordberg (1972) relates an instance in which nausea, vomiting, and abdominal pain occurred from consumption of drinks containing approximately 16 mg/L cadmium. Recovery was rapid, without apparent long-term effects. Inhalation of cadmium fumes or other heated cadmium-containing materials may produce an acute chemical pneumonitis and pulmonary edema. Inhalation of large doses of cadmium compounds may be lethal for humans and experimental animals (ATSDR, 1998). Experimental studies have shown that the chemical form of cadmium can affect its toxicity, probably related to solubility. In acute exposures, the relatively more soluble cadmium chloride, cadmium oxide fume, and cadmium carbonate are more toxic that than the relatively less soluble cadmium sulfide (Klimisch, 1993).

Chronic Toxicity The principal long-term effects of low-level exposure to cadmium are chronic obstructive pulmonary disease and emphysema and chronic renal tubular disease. There may also be effects on the cardiovascular and skeletal systems.

Chronic Pulmonary Disease Toxicity to the respiratory system is proportional to the time and level of exposure. Obstructive lung

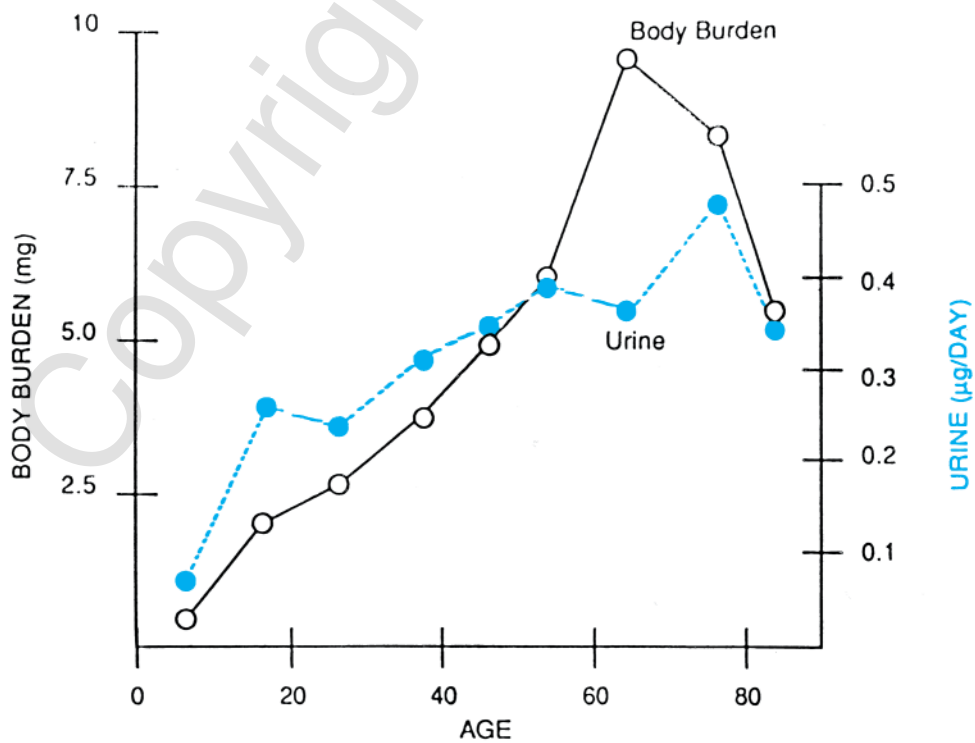

Figure 23-4. Illustration of the accumulation of cadmium with age.

disease results from chronic bronchitis, progressive fibrosis of the lower airways, and accompanying alveolar damage leading to emphysema. The lung disease is manifest by dyspnea, reduced vital capacity, and increased residual volume. The pathogenesis of the lung lesion is the turnover and necrosis of alveolar macrophages. Released enzymes produce irreversible damage to alveolar basement membranes, including the rupture of septa and interstitial fibrosis (Davison, 1988). It has been found that cadmium reduces a_1-antitrypsin activity, perhaps enhancing pulmonary toxicity. However, no difference in plasma a_1-antitrypsin activity could be found between cadmium-exposed workers with and without emphysema (Lauwerys et al., 1979).

Nephrotoxicity Cadmium is toxic to renal tubular cells and glomeruli as reflected by impairment of renal tubular and glomerular function. Morphologic changes are nonspecific and consist of tubular cell degeneration in the initial stages, progressing to an interstitial inflammatory reaction and fibrosis. Analysis of kidney cadmium levels by in vivo neutron activation analysis and x-ray fluorescence has made it possible to study the relationship between renal cadmium levels and the occurrence of effects (Skerfving et al., 1987). The critical concentration of cadmium in the renal cortex that produces tubular dysfunction in 10 percent of the population is about 200 μg/g and about 300 μg/g in 50 percent of the population. There is a pattern in which liver and kidney cadmium levels increase simultaneously until the average cadmium concentration in the renal cortex is about 300 μg/g and the average level in the liver is about 60 μg/g. At higher cadmium liver levels, the level in the renal cortex is disproportionately low, as cadmium is lost from the kidney (Ellis et al., 1984). Daily intake in food of 140 to 260 μg of cadmium per day for more than 50 years or exposure in workroom air of 50 $\mu g/m^3$ for more than 10 years has produced renal dysfunction (Thun et al., 1989; WHO, 1992). An epidemiologic study of the dose–response relationship of cadmium intake from historical data, rice consumption, and β_2-microglobulin as an index of renal tubular dysfunction, found that the total cadmium intake over a lifetime that produced an adverse health effect was 2000 mg for both men and women (Nogawa et al., 1989).

Renal tubular dysfunction is reflected by proteinuria. The proteinuria is principally tubular, consisting of low-molecular-weight proteins whose tubular reabsorption has been impaired by cadmium injury to proximal tubular lining cells. The predominant protein is a β_2-microglobulin (β_2-m), but a number of other low-molecular-weight proteins have been identified in the urine of workers with excessive cadmium exposure, such as retinol-binding protein (RBP), lysozyme, *N*-acetyl-β-D-glucosaminidase (NAG), ribonuclease, α_1-microglobulin, and immunoglobulin light chains (Lauwerys et al., 1980; Buchet et al., 1990). The presence of high-molecular-weight proteins in the urine, such as albumin and transferrin, indicates that some workers may actually have a mixed proteinuria and suggests a glomerular effect as well. The pathogenesis of the glomerular lesion in cadmium nephropathy is not presently understood.

Role of Metallothionein The accumulation of cadmium in the kidneys to some extent without apparent toxic effect is possible because of the formation of cadmium-thionein or metallothionein, a metal–protein complex with a low molecular weight (see "Metal-Binding Proteins," above). Metallothionein is primarily a tissue protein and is ubiquitous in most organs, but it exists in the highest concentration in the liver, particularly following recent exposure to cadmium, and in the kidneys, where it accumulates with age in proportion to cadmium concentration. Cadmium bound to metallothionein within tissues is thought to be nontoxic. However, when the levels of cadmium exceed the critical concentration, it becomes toxic. The protective role of metallothionein is supported by an experiment showing that metallothionein-null mice are more sensitive to cadmium nephrotoxicity than control mice (Liu et al., 1998).

The factors that determine the level of cadmium or of cadmium-metallothionein complex that is toxic are not clear, but experimental studies have shown that repeated injections of low levels of cadmium-metallothionein over several weeks result in a chronic and irreversible nephrotoxicity with renal accumulations of cadmium of only 40 μg/g, less than the 200 μg/g in the renal cortex, which is suggested as the critical level in humans (Wang et al., 1993). Also, renal tubular necrosis occurs in non-cadmium-exposed rats following transplantation of livers from cadmium-toxic animals (Chan et al., 1993). These studies suggest that cadmium nephrotoxicity follows the slow release and renal excretion of cadmium-metallothionein from liver and other soft tissues. Cadmium-metallothionein is toxic when taken up by the proximal tubular cell complex, whereas cadmium chloride at even greater concentrations in proximal tubular cells is not toxic (Dorian et al., 1995).

Skeletal Effects Cadmium toxicity affects calcium metabolism, and individuals with severe cadmium nephropathy may have renal calculi and excess excretion of calcium, probably related to increased urinary loss. With chronic exposure, however, urinary calcium may be less than normal. Associated skeletal changes are probably related to calcium loss and include bone pain, osteomalacia, and/or osteoporosis. Bone changes are part of Itai-Itai disease, a syndrome recognized in postmenopausal multiparous women living in the Fuchu area of Japan prior to and during World War II. The syndrome consists of severe bone deformities and chronic renal disease. Excess cadmium exposure has been implicated in the pathogenesis of the syndrome, but vitamin D and perhaps other nutritional deficiencies are thought to be cofactors. Itai-Itai translates to "ouch-ouch," reflecting the accompanying bone pain. Also, cadmium can affect calcium, phosphorus, and bone metabolism in both industrial workers and people exposed in the general environment. These effects may be secondary to the cadmium effects on the kidneys and/or the direct toxic effect of cadmium on bone metabolism, but there has been little study of calcium metabolism in people with excess exposure to cadmium (Friberg, 1986).

Whether the skeletal effects from cadmium exposure are a product of cadmium toxicity per se or the result of cadmium toxicity plus renal disease and nutritional deficiencies, particularly calcium deficiency, has been debated (Nogawa et al., 1999). Cadmium in bone may interfere with calcification, decalcification, and bone remodeling. Anderson and Danylchuk (1979) found that exposure of beagle dogs for 6 months to cadmium (25 mg/wL) reduced bone turnover rate, consistent with calcium deficiency or osteomalacia. Wang and Battachharyya (1993) showed that cadmium increased release of ^{45}Ca from skeletons of mice and dogs as early as 72 h after the start of dietary cadmium.

A proposed mechanism for the decreased calcium absorption and negative calcium balance in cadmium-exposed rats is that cadmium inhibits activation of vitamin D in the renal cortex (Feldman and Cousins, 1974). Nogawa and colleagues (1987) reported that serum $1,25(OH)_2$ vitamin D levels were lower in Itai-Itai disease patients and in cadmium-exposed subjects with renal damage than in nonexposed subjects. A decrease in serum $1,25(OH)_2$ vitamin D

levels was closely related to serum concentrations of parathyroid hormone, β_2-microglobulin, and the percentage of tubular reabsorption, suggesting that cadmium-induced bone effects were mainly due to a disturbance in vitamin D and parathyroid hormone metabolism. Friberg et al. (1986) suggest that cadmium in the proximal tubular cells depresses cellular functions, which may be followed by the depressed conversion of 25(OH) vitamin D to $1,25(OH)_2$ vitamin D. This is likely to lead to decreased calcium absorption and mineralization of bone, which in turn may lead to osteomalacia. Bhattacharyya and coworkers (1988) found, in studies of mice, that multiparity enhanced cadmium's toxicity to bone. Hypercalciuria is a sensitive indicator for cadmium exposure (Buchet, 1990).

Hypertension and Cardiovascular Effects Epidemiologic studies suggest that cadmium is an etiologic agent for essential hypertension. A study of blood pressures in cadmium workers found an increase in systolic but not diastolic blood pressure (Thun et al., 1989). Studies from Japan have found that the rate of cerebrovascular disease mortality among people who had cadmium-induced renal tubular proteinuria was twice as high as among people in cadmium-polluted areas without proteinuria (Nogawa et al., 1979). Although the population-based U.S. NHANES II study and studies in Belgium (Staessen et al., 1995) have not supported a role for cadmium in the etiology of hypertension and cardiovascular disease in humans, animal studies indicate that cadmium may be toxic to myocardial function. Rats exposed to cadmium in drinking water (Kopp et al., 1983) developed electrocardiographic and biochemical changes in the myocardium and impairment of the functional status of the myocardium. These effects may be related to (1) decreased high-energy phosphate stored in the myocardium, (2) reduced myocardial contractility, and (3) diminished excitability of the cardiac conduction system. Jamall and Sprowls (1987) found that rats whose diets were supplemented with copper, selenium, and cadmium had a marked reduction in heart cytosolic glutathione peroxidase, superoxide dismutase, and catalase. They suggest that heart mitochondria may be the site of the cadmium-induced biochemical lesion in the myocardium.

Neurologic Disorders Epidemiologic studies in humans have suggested a relationship between abnormal behavior and/or decreased intelligence in children and adults exposed to cadmium. However such studies are typically complicated by exposure to other toxic metals. Furthermore, the blood-brain barrier and circumventricular epithelial cells with tight junctions limit the pathways of entrance for cadmium into the central nervous system. In addition, the choroid plexus epithelium accumulates high levels of toxic metals from the blood or cerebrospinal fluid (Murphy, 1997). Metallothionein in glial cells and ependymal cells near circumventricular organs also serves to minimize cadmium diffusion into other parts of the brain.

Carcinogenicity Epidemiologic studies have shown a relationship between occupational (respiratory) exposure to cadmium and lung cancer and possibly prostate cancer. An increase in respiratory cancers was also found in a restudy of a cohort in a U.S. cadmium recovery plant (Thun et al., 1985). Concern has been expressed regarding the influence of confounding factors in the work environment, particularly coexposure to arsenic (Sorahan and Lancashire, 1997). Cadmium has recently been accepted by the International Agency for Research on Cancer as a category 1 (human) carcinogen, based primarily on its relationship to pulmonary tumors (IARC, 1994). There are few studies that examine a relationship between oral intake of cadmium and cancer in humans. A study of cancer incidence among inhabitants with renal tubular dysfunction in a cadmium-polluted area of Japan was negative. The potential relationship between cadmium exposure and prostate cancer in humans remains controversial (Waalkes, 1995).

Cadmium chloride exposure by inhalation produced a dose-dependent increase in the incidence of lung carcinomas in rats (Takenaka et al., 1983; Oldiges, 1989). In rats, cadmium will produce a variety of tumors, including malignant tumors at the site of injection and in the lungs after inhalation. Cadmium chloride, oxide, sulfate, and sulfide produced local sarcomas in rats after their subcutaneous injection, and cadmium powder and cadmium sulfide produced local sarcomas in rats following their intramuscular administration. Other studies have found that oral cadmium exposure was associated with tumor of the prostate, testes, and hematopoietic system in rats. The incidence of lesions was less in zinc-deficient rats, but there was no dose–response relationship (Waalkes, 1995). Other studies have produced cancer in the ventral lobe of the rat prostate by oral or parenteral exposures as well as by direct injection. The lobular structure of the prostate is absent in humans; it is thought that the ventral prostate in rats has no human analog and that tumors of the dorsolateral lobe are more comparable to the human disease (Waalkes and Rehm, 1994). However, subcutaneous injection of cadmium in a particularly cancer-sensitive strain of rat (Noble/Cr) did produce proliferative lesions of the dorsolateral prostate as well as tumors of the testes, pituitary adenomas, and injection-site sarcomas (Waalkes et al., 1999).

Biomarkers of Cadmium Effects Urinary $Beta_2$-microglobulin (β_2m), retinal-binding protein (RBP), *N*-acetyl-β-glucosaminidase (NAG), and metallothionein have been used in conjunction with urinary cadmium levels as a measure of cadmium exposure to cadmium renal tubular dysfunction. Other sensitive indicators include α_1-m, trehalase, and calcium (ATSDR, 1998). The relationship of these indicators to urine cadmium levels were determined in a large population study in Belgium (Buchet, 1990). It was estimated that more than 10 percent of values would be abnormal when urine cadmium excretion rate exceeded 2.87 μg/24 h for RBP, 3.05 μg/24 h for β_2-m, 4.29 μg/24 h for amino acids, and 1.92 μg/24 h for calcium.

Increased excretion of β_2-m is an early indicator of tubular proteinuria, but samples must be controlled for pH. RBP measurements may be a more practical and reliable test of proximal tubular function than β_2-m because sensitive immunologic analytic methods are now available, and β_2-m is less stable in urine (Lauwerys et al., 1984). Activity of the enzyme NAG in urine may be a sensitive indicator of cadmium-induced renal tubular dysfunction, but a dose–response relationship has not been established (Kawada et al., 1998). None of the biomarkers of tubular dysfunction are specific indicators of cadmium effects and their levels must be interpreted in association with a corresponding increase in urinary cadmium. Minor increases in excretion of biomarkers of renal tubular dysfunction may not in themselves indicate an adverse health effect but are indicators of likely possible progression of renal disease if cadmium exposure is continued.

Increase in urinary calcium excretion is a sensitive effect of cadmium-induced renal tubular dysfunction and may contribute to the age-related decline in bone mass (Aoshima et al., 1997). Roels et al. (1993) identified three main groups of thresholds for increased excretion of biomarkers of cadmium effect on the kidney. When calcium levels are at around 2 μg/g creatinine, there was increased

excretion 6-keto prostaglandin and sialic acid; at around 4 μg/g creatinine, there were increases in NAG, albumin, and transferrin; and at around 10 μg/g creatinine, there were increases in excretion of β_2-m, RBP, and antiglomerular basement membrane antibodies.

Biomarkers of Cadmium Exposure The most important measure of excessive cadmium exposure is increased cadmium excretion in urine. In persons in the general population without excessive cadmium exposure, urinary cadmium excretion is both small and constant. Ninety-five percent of U.S. residents excrete less than 2 μg/L in urine and less than 1 percent excrete 4 μg/L (Gunter, 1997). With excessive exposure to cadmium, as might occur in workers, an increase in urinary cadmium may not occur until all of the available cadmium binding sites are saturated. However, when the available binding sites (e.g., metallothionein) are saturated, increased urinary cadmium reflects recent exposure, body burden, and renal cadmium concentration, so that urinary cadmium measurement does provide a good index of excessive cadmium exposure. Most of the cadmium in urine is bound to metallothionein, and there is good correlation between metallothionein and cadmium in urine in cadmium workers with normal or abnormal renal function (Shaikh et al., 1989). Therefore, the measurement of metallothionein in urine provides the same toxicologic information as the measurement of cadmium, and it does not have the problem of external contamination. Radioimmunoassay techniques for measurement of metallothionein are available (Chang et al., 1980) but are not as practical as other biomarkers of cadmium effect.

There is debate as to whether the threshold for preventing cadmium nephropathy is 5 μg/g or 10 μg/g creatinine. Changes in urinary excretion of low-molecular-weight proteins were consistently observed in workers excreting more than 10 μg cadmium per gram of creatinine (Buchet et al., 1980). The American Conference of Governmental Industrial Hygienists biological exposure indexes for cadmium are 5 μg/g creatinine in the urine and 5 μg/L cadmium in the blood (ACGIH, 1996). Roels et al. (1999), recommends that, on the basis of increased excretion of a number of biomarkers (cited above) at urinary cadmium levels ranging from 2.4 to 11.5 μg/g creatinine, occupational exposure to cadmium should not exceed 5 μg of cadmium per gram of creatinine.

Blood cadmium levels generally reflect recent exposure rather than accumulated body burden and are usually in the range of 0.4 to 1.0 μg/L for nonsmokers and somewhat higher for smokers (Lauwerys et al., 1994). Workers with cumulative cadmium exposure equivalent to a blood cadmium concentration of 10 μg/L for 20 years have been shown to have a 14 percent incidence of renal dysfunction (Jarup et al., 1988).

Reversibility of Renal Effects Follow-up studies of persons with renal tubular dysfunction (β_2-microglobulinuria) from occupational exposure to cadmium have shown that the proteinuria is irreversible and that there is a significant increase of creatinine in serum with time, suggesting a progressive glomerulopathy (Roels et al., 1989). Also, persons with renal tubular dysfunction from excess dietary ingestion of cadmium (cadmium-polluted rice) do not have a reversal of the defect as long as 10 years after reduced exposure in cases when the β_2-m exceeds 1000 μg/g of creatinine (Kido et al., 1988). Ellis (1985) has shown, however, that liver cadmium in workers no longer exposed to cadmium gradually declines. Persistence of renal tubular dysfunction after cessation of exposure may reflect the level of body burden and the shifting of cadmium from liver to kidney.

Treatment At the present time, there is no chelation therapy for cadmium toxicity approved for clinical use in humans. Experimentally, DMSA and CaEDTA best reduce acute mortality from cadmium exposure in combination with glutathione. Some DMSA analogs acutely increase biliary excretion of cadmium. However, each of these therapies may result in significant adverse effects (Angle, 1995).

Chromium (Cr)

Chromium[1] is a generally abundant element in the earth's crust and occurs in oxidation states ranging from Cr^{2+} to Cr^{6+}, but only trivalent and hexavalent forms are of biological significance. The trivalent is the more common form. However, hexavalent forms such as chromate compounds are of greater industrial importance. Sodium chromate and dichromate are the principal substances for the production of all chromium chemicals. The major source of chromium is from chromite ore. Metallurgic-grade chromite is usually converted into one of several types of ferrochromium or other chromium alloys containing cobalt or nickel. Ferrochrome is used for the production of stainless steel. Chromates are produced by a smelting, roasting, and extraction process. The major uses of sodium dichromate are for the production of chrome pigments; for the production of chrome salts used for tanning leather, mordant dying, wood preservatives; and as an anticorrosive in cooking systems, boilers, and oil-drilling muds. Overviews of chromium exposures and health effect have been reviewed (Fishbein, 1981; WHO, 1988; O'Flaherty, 1995).

Chromium in ambient air originates from industrial sources, particularly ferrochrome production, ore refining, chemical and refractory processing, the manufacture of cement, and combustion of fossil fuels. Chromium precipitates and fallout are deposited on land and water; land fallout is eventually carried to water by runoff, where it is deposited in sediments. A controllable source of chromium is wastewater from chrome-plating and metal-finishing industries, textile plants, and tanneries. Cobalt-chromium alloy hip replacements lead to elevated blood levels of chromium (Habbab et al., 2000). The daily intake by humans is under 100 μg, mostly from food, with trivial quantities from most water supplies and ambient air.

Human Body Burden Tissue concentrations of chromium in the general population have considerable geographic variation; concentrations as high as 7 μg/kg occur in the lungs of persons in New York or Chicago, with lower concentrations in liver and kidney. In persons without excess exposure, blood chromium concentration is between 20 and 30 μg/L and is evenly distributed between erythrocytes and plasma. With occupational exposure, an increase in blood chromium is related to increased chromium in red blood cells. Chromates readily cross cell membranes on anion carriers as they are isostructural with sulfate and phosphate anions. Urinary excretion is independent of the oxidation state of chromium administered to animals and is less than 10 μg/day for humans in the absence of excess exposure.

[1]Atomic weight, 52; periodic table group, VIB; valence, +6, +3 +2, rare +1, +4, +5; discovered in 1797; isolated in 1798.

Essentiality See the discussion of trivalent chromium—Cr(III)—under "Essential Metals with Potential for Toxicity," below.

Toxicity Systemic toxicity to chromium compounds occurs largely from accidental exposures, occasional attempts to use chromium as a suicidal agent, and from previous therapeutic uses. The major effect from ingestion of high levels of Cr(VI) is acute tubular and glomerular damage. Evidence of kidney damage from lower-level chronic exposure is equivocal (Wadeen 1991). Animal studies of chronic exposure to Cr(VI) have not shown evidence of toxicity (O'Flaherty, 1995). Cr(VI) is corrosive and causes chronic ulceration and perforation of the nasal septum. It also causes chronic ulceration of other skin surfaces, which is independent of hypersensitivity reactions on skin. Allergic chromium skin reactions readily occur with exposure and are independent of dose (Proctor et al., 1998). Occupational exposure to chromium may be a cause of asthma (Bright et al., 1997). The known harmful effects of chromium in humans have been attributed to the hexavalent form, and it has been speculated that the biological effects of Cr(VI) may be related to the reduction to Cr(III) and the formation of complexes with intracellular macromolecules. Cr(III) compounds are considerably less toxic than the hexavalent compounds and are neither irritating nor corrosive. Nevertheless, nearly all industrial workers are exposed to both forms of chromium compounds, and at present there is no information as to whether there is a gradient of risk from predominant exposure to hexavalent or insoluble forms of chromium to exposure to soluble trivalent forms.

Carcinogenicity Exposure to chromium, particularly in the chrome production and chrome pigment industries, is associated with cancer of the respiratory tract (Langard and Norseth, 1986). The mechanism of Cr(VI) carcinogenicity in the lung is believed to be its reduction to Cr(III) and its generation of reactive intermediates.

Animal studies support the notion that the most potent carcinogenic chromium compounds are the slightly soluble hexavalent compounds. Studies on in vitro bacterial systems, however, show no difference between soluble and slightly soluble compounds. Trivalent chromium salts have little or no mutagenic activity in bacterial systems. Because there is preferred uptake of the hexavalent form by cells and it is the trivalent form that is metabolically active and binds with nucleic acids within the cell, it has been suggested that the causative agent in chromium mutagenesis is trivalent chromium bound to genetic material after reduction of the hexavalent form. The intracellular reduction of Cr(VI) involves the oxidation of both small (acorbate and glutathione) and large (macromolecules—DNA and protein) forms and probably plays a role in the carcinogenic process. In fact chromium elicits a variety of effects: (1) at the biochemical level, the formation of coordination covalent interaction of Cr(V) and Cr(III) with DNA and of DNA-DNA and DNA-protein complexes; (2) at the genomic level, the induction of gene expression (oxidant stress and metallothionein and tumor supressor genes), gene mutations, DNA lesions, and inhibition of protein synthesis and arrest of DNA replication; (3) at the cellular level, cell cycle arrest, apoptosis, and neoplastic transformation (Bridgewater et al., 1998; Singh et al., 1998; Klatreider et al., 1999; Dubrovskaya and Wetterhahn, 1998; Solis-Heredia et al., 2000).

Costa and coworkers (1993) have shown that detection of DNA-protein complexes may serve as a biomarker of exposure and of carcinogenic potential from occupational exposure to chromium. There is suggestive evidence that chromium compounds cause cancer at sites other than the respiratory tract (Costa 1997).

Lead (Pb)

If we were to judge of the interest excited by any medical subject by the number of writings to which it has given birth, we could not but regard the poisoning by lead as the most important to be known of all those that have been treated of, up to the present time (Orfila, 1817).

Lead[1] is a ubiquitous toxic metal and is detectable in practically all phases of the inert environment and in all biological systems. Because it is toxic to most living things at high exposures and there is no demonstrated biological need for it, the major issue regarding lead is determining the dose at which it becomes toxic. Specific concerns vary with the age and circumstances of the host, and the major risk is toxicity to the nervous system. The most susceptible populations are children, particularly toddlers, infants in the neonatal period, and the fetus. Several reviews and multiauthored books on the toxicology of lead are available (Goyer and Rhyne, 1973; EPA, 1986; Goyer, 1993; NRC, 1993; ATSDR, 1999).

Exposure The principal route of exposure for people in the general population is food, and sources that produce excess exposure and toxic effects are usually environmental and presumably controllable. These sources include lead-based indoor paint in old dwellings, lead in dust from environmental sources, lead in contaminated drinking water, lead in air from combustion of lead-containing industrial emissions, hand-to-mouth activities of young children living in polluted environments, lead-glazed pottery, and—less commonly—lead dust brought home by industrial workers on their shoes and clothes. Dietary intake of lead has decreased since the 1940s, when estimates of intake were 400 to 500 μg/day for U.S. populations to present levels of under 20 μg/day. One factor reducing the lead content of food has been a reduction in the use of lead-soldered cans for food and beverages. Most municipal water supplies measured at the tap contain less than 0.05 μg/mL, so that daily intake from water is usually about 10 μg; it is unlikely to be more than 20 μg. Corrosive water (pH 6.4) will leach lead from soldered joints and lead-containing brass fittings (NRC, 1993). The introduction of lead-free gasoline and awareness of the hazards of indoor leaded paint has been credited with a decline in blood lead levels for persons ages 1 to 74 from 12.8 to 2.8 μg/day for 1988 to 1991 (Pirkle et al., 1994). Blood lead levels among people in the general population have continued to decline in the United States to <5 μg/dL (Pirkle, 1998). Nevertheless, the most current national survey (N-HANES IV) shows that nearly a million U.S. children are at risk from lead poisoning (blood lead levels >10 μg/dL) and that specific groups of children are at greatest risk (Fig. 23-5).

The geometric mean blood lead level of African-American children living in central portions of cities with more than 1 million people is 13.9 μg/dL, and about 35 percent of these children have blood lead levels greater than 10 μg/dL—that is, above the guideline recommended by the U.S. Centers for Disease Control (CDC, 1991). Major risk factors for these children are housing containing lead-based paint and exposure to urban dust (CDC, 1997).

[1]Atomic weight, 207.2; periodic table group, IVA; valence, +2 or + 4; discovery uncertain—known since early times.

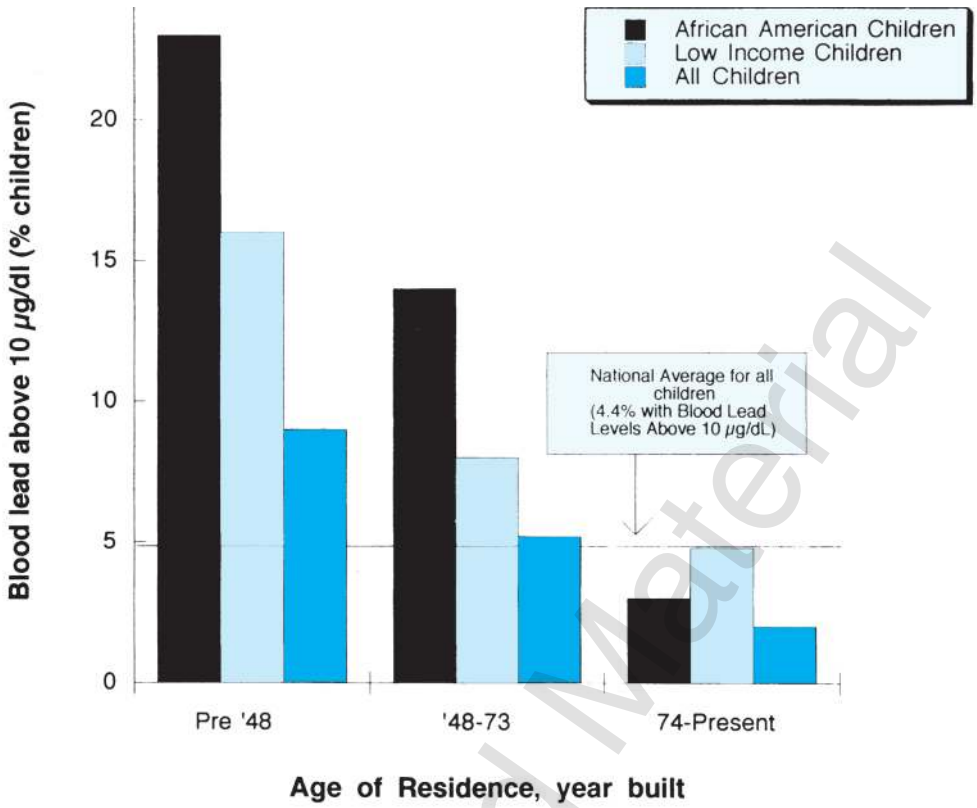

Figure 23-5. National blood lead levels. National Health and Nutrition Examination Survey. Phase 2, 1991–1994. [Adapted from CDC (2000).]

Utilizing radioisotope techniques, Manton et al. (2000) determined that major environmental sources of lead for infants and toddlers up to 4 years of age were hand-to-mouth transfer from floors, the lead being derived from dust sills and exterior surfaces. Seasonal influences, or increases in childhood lead exposure during the hot summer months, were previously thought to be due to effect of sunlight and mobilization of lead from bone. It has now been shown that seasonal variation in blood lead levels in children is related to dust lead levels in the home (Yin et al., 2000).

Other potential sources of exposure to lead are recreational shooting on indoor ranges, hand-loading of ammunition, soldering, jewelry making, pottery making, gunsmithing, glass polishing, painting, and stained glass crafting, all of which involve some exposure to lead. Workplace exposure is gradually being reduced. Overt or clinical lead poisoning among workers in lead industries was common in the 1930s, 1940s, and even in the early 1950s, but it is far less frequently observed today (Wegman and Fine, 1990). Nevertheless, lead continues to be one of the metals presenting a hazardous occupational exposure. Children of workers with occupational exposure to lead may have higher blood lead levels than children in the general population (Whelan et al., 1997). In addition, there are several nutritional and dietary factors that influence lead toxicity (Mahaffey, 1985). In a study of effects of lifestyle factors on blood lead levels, alcohol consumption has been shown to account for the large proportion of variability in blood lead levels, followed by age and smoking (Weyermann and Brenner, 1997). Wine had a greater effect on blood lead levels than beer. Other significant contributing factors were gender, hematocrit, calcium intake, and consumption of milk products.

Toxicokinetics Toxicokinetics of lead are reviewed in reports by the NRC (1993), and ATSDR (1999). Adults absorb 5 to 15 percent of ingested lead and usually retain less than 5 percent of what is absorbed. Children are known to have a greater absorption of lead than adults; one study found an average net absorption of 41.5 percent and 31.8 percent net retention in infants on regular diets. Lead absorption in children is related to age and development of the gastrointestinal tract (Ziegler et al., 1978). Nutritional problems—such as low dietary iron and calcium—enhance lead absorption (Wassermann et al., 1994; Bruening et al., 1999). Lead in water and other beverages is absorbed to a greater degree than lead in food. Lead ingested between meals is absorbed more than lead with meals, and increasing frequency of food intake minimizes lead absorption.

Concentrations of lead in air vary due to point-source emissions but are now usually less than 1.0 $\mu g/m^3$. Since the introduction of lead-free gasoline in the United States, airborne lead is only a minor component of total daily lead exposure. Lead in the atmosphere exists either in solid forms, dust or particulates of lead dioxide, or in the form of vapors. Lead absorption by the lungs also depends on a number of factors in addition to concentration. These include volume of air respired per day, whether the lead is in particle or vapor form, and size distribution of lead-containing particles. Only a very minor fraction of particles over 0.5 μm in mean maximal external diameter are retained in the lung, but they are then cleared from the respiratory track and swallowed. However, the percentage of particles less than 0.5 μm retained in the lung increases with reduction in particle size. About 90 percent of lead particles in ambient air that are deposited in the lungs are small enough to be retained. Absorption of retained lead through alveoli is relatively efficient and complete.

More than 90 percent of the lead in blood is in red blood cells. There seem to be at least two major compartments for lead in the red blood cell, one associated with the membrane and the other with hemoglobin and other blood cell components. Blood lead is in equilibrium between plasma and erythrocytes with 1 percent or less in the plasma, for blood lead levels up to 100 μg/dL. The relationship between blood and plasma lead is stable and nearly linear for blood lead levels up to 50 μg/dL. Above this level the relationship becomes curvilinear, with rapid increase in plasma levels (Manton et al., 1984). Because of analytic difficulties in the accurate measurement of the low levels of lead in plasma and the complicating potential of lead from hemolysis, measurement of plasma lead seems to be of limited usefulness for monitoring persons with occupational exposure.

The total body burden of lead may be divided into at least two kinetic pools, which have different rates of turnover (O'Flaherty, 1998). The largest and kinetically slowest pool is the skeleton, with a half-life of more than 20 years; the soft tissue pool is much more labile. Lead in trabecular bone is more labile than that in cortical bone, and trabecular bone has a shorter turnover time. Lead in bone may contribute as much as 50 percent of blood lead, so that it may be a significant source of internal exposure to lead. Lead in maternal bone is of particular concern during pregnancy and lactation, and it may be mobilized in later years in persons with osteoporosis (Silbergeld et al., 1988). The fraction of lead in bone increases with age from about 70 percent of body lead in childhood to as much as 95 percent of the body burden with advancing years. The total lifetime accumulation of lead may be as much as 200 mg to over 500 mg for a worker with heavy occupational exposure. The largest soft tissue accumulations of lead are in liver and kidney, but lead is present in most tissues of the body. Animal studies have shown that lead in the central nervous system tends to concentrate in gray matter and certain nuclei.

The major route of excretion of absorbed lead is the kidney. Renal excretion of lead is usually with glomerular filtrate with some renal tubular absorption. With elevated blood lead levels, excretion may be augmented by transtubular transport. Lead is also excreted to a lesser degree with other body fluids, including milk during lactation (Gulson et al., 1998). Lead crosses the placenta, so that cord blood lead levels generally correlate with maternal blood lead levels but are slightly lower. Maternal blood lead decreases slightly during pregnancy, probably due to hemodilution. Lead accumulation in fetal tissues, including brain, is proportional to maternal blood lead levels (Goyer, 1996).

Toxicity The toxic effects from exposures to inorganic lead form a continuum from subtle or biochemical effects to clinical or overt effects (Goyer, 1990). These effects involve several organ systems and biochemical activities. The critical effects or most sensitive effects in infants and children involve the nervous system (NRC, 1993; ATSDR, 1999). For adults with excess occupational exposure or even accidental exposure, the concerns are peripheral neuropathy and/or chronic nephropathy. However, the critical effect or most sensitive effect for adults in the general population may be hypertension. Effects on the heme system provide biochemical indicators of lead exposure in the absence of chemically detectable effects, but anemia due to lead exposure is uncommon without other detectable effects or other synergistic factors. Other target organs are the gastrointestinal, reproductive, and skeletal systems.

Neurologic, Neurobehavioral, and Developmental Effects in Children Clinically overt lead encephalopathy may occur in children with high exposure to lead, probably at blood lead levels of 80 μg/dL or higher. Symptoms of lead encephalopathy begin with lethargy, vomiting, irritability, loss of appetite, and dizziness progressing to obvious ataxia and a reduced level of consciousness, which may progress to coma and death. The pathologic findings at autopsy are severe edema of the brain due to extravasation of fluid from capillaries in the brain. This is accompanied by the loss of neuronal cells and an increase in glial cells. Recovery is often accompanied by sequelae including epilepsy, mental retardation, and, in some cases, optic neuropathy and blindness (Perlstein and Attala, 1966).

Over the past 20 or more years there have been a number of cross-sectional and prospective epidemiologic studies relating blood lead levels at the time of birth, during infancy, and through early childhood with measures of psychomoter, cognitive, and behavioral outcomes. These studies have been summarized by NRC (1993) and ATSDR (1999). Despite differences in the ranges of blood lead represented in a cohort, most studies report a 2- to 4-point IQ deficit for each 10 microgram-per-deciliter increase in blood lead within the range of 5 to 35 μg/dL. A threshold is not evident from these studies.

It has been difficult to discern whether there are specific neuropsychological deficits associated with increased lead exposures. To date there are no specific indicators of the neurologic effects of lead. The most sensitive indicators of adverse neurologic outcomes are psychomotor tests or mental development indices, such as the Bayley Scales for infants, and broad measures of IQ, such as full-scale WISC-R IQ scores for older children. Blood lead levels at 2 years of age are more predictive of a longer-term adverse neurologic outcome than umbilical cord blood lead concentration. Children in the lower socioeconomic strata may begin to manifest language deficits by the second year of life, which may be prevented in children with greater academic advantages. Increased blood lead levels in infancy and early childhood may be manifest in older children and adolescents as decreased attention span, reading disabilities, and failure to graduate from high school (Needleman et al., 1990).

The public health significance of small deficits in IQ may be considerable. When the actual cumulative frequency distribution of IQ between high- and low-lead subjects are plotted and compared, there is an increase in the number of children with a severe deficit, that is, IQ scores below 80. Also, the same shift truncates the upper end of the curve, where there is a 5 percent reduction in children with superior function (IQ 125 or greater). There is presently no estimate of the cost of this effect at the high end of the curve, but it may be of considerable importance to both society and to the individual. Small changes in IQ have been associated with differences in measures of socioeconomic status, such as income and educational achievement (Needleman, 1989).

An association between hearing thresholds and blood lead greater than 20 μg/dL has been found in teenagers (Schwartz et al., 1991).

Adults with occupational exposure may demonstrate abnormalities in a number of measures in neurobehavior, with cumulative exposures resulting from blood lead levels <40 μg/dL (Lindgren et al. 1996). Payton et al. (1998) performed a number of cognitive tests and measured tibial lead concentration on a cohort of men with mean age of 66.8 years and mean blood lead level of 55 μg/dL. They found those men with higher blood lead levels performed less

well than men with lower blood lead levels. They also found that men with higher blood lead and tibeal lead showed a slower response for pattern memory.

Mechanisms of Effects on the Developing Nervous System Studies to date suggest that the primary anatomic site for lead effect on the brain is the endothelial cell of the blood-brain barrier leading to entry of lead into the brain, followed by morphologic and pharmacologic effects (summarized by Goyer, 1996). Possible mechanisms for lead effects on the nervous system are summarized in Table 23-3.

A highly significant morphologic effect during development is the result of lead impairment of timed programming of cell:cell connections, resulting in modification of neuronal circuitry. Lead also induces precocious differentiation of the glia, whereby cells migrate to their eventual positions during structuring of the central nervous system. Within the catecholaminergic nervous system, lead exposure causes alterations in the concentrations of the transmitters noradrenaline and dopamine in addition to changes in the activities of the enzymes tyrosine hydroxylase and phenylethanolamine-*N*-methyl transferase. The activity of the cholinergic biosynthetic enzyme choline acetyltransferase is also affected (McIntosh et al., 1987).

Calcium is a critical component of numerous biochemical and metabolic functions in the brain, and lead may act as a surrogate for calcium, resulting in subtle disruptions of essential functions. Lead impairs normal calcium homeostasis and uptake by calcium membrane channels and substitutes for calcium in calcium-sodium ATP pumps. Lead also blocks entry of calcium into nerve terminals; it inhibits calcium uptake in brain mitochondria, with a decrease in energy production to perform brain functions. Probably the most critical interaction between lead and calcium is in cells where lead interferes with calcium receptors that are coupled with second-messenger functions. Intracellular calcium signals are received by a variety of calcium receptor proteins. The two that have received the most attention are calmodulin and protein kinase C. Calmodulin serves as a sensor for the concentration of calcium within cells. Lead acts by displacing calcium ions bound to calmodulin. Protein kinase C–mediated responses include cell division and proliferation, cell-cell communications, and organization of the cytoskeleton. Markovac and Goldstein (1988) found that lead activates protein kinase C in microvessels which may be a factor in altering the normally tight blood-brain barrier.

Table 23-3
Mechanisms for Lead Effects on the Nervous System

Morphologic effects (neurodevelopmental)
Impairment of timed programming of cell–cell connections
Interference with neural cell adhesion molecules
Altered migration of neurons during development
Pharmacologic effects (functional)
Interferes with neurotransmitter function
Disrupts calcium metabolism
Blocks voltage-dependent calcium membrane channels
Substitutes for calcium in calcium–sodium ATP pump
Competes for uptake by mitochondria
Binds to second messenger calcium receptors (e.g., calmodulin, protein kinase C)

SOURCE: Modified from Goyer (1996).

Peripheral Neuropathy Peripheral neuropathy is a classic manifestation of lead toxicity, particularly the footdrop and wristdrop that characterized the house painter and other workers with excessive occupational exposure to lead more than a half-century ago. Segmental demyelination and possibly axonal degeneration follow lead-induced Schwann cell degeneration. Wallerian degeneration of the posterior roots of sciatic and tibial nerves is possible, but sensory nerves are less sensitive to lead than motor nerve structure and function. Motor nerve dysfunction, assessed clinically by electrophysiologic measurement of nerve conduction velocities, has been shown to occur with blood lead levels as low as 40 μg/dL (ATSDR, 1999).

Hematologic Effects Lead has multiple hematologic effects. In lead-induced anemia, the red blood cells are microcytic and hypochromic, as in iron deficiency, and there are usually increased numbers of reticulocytes with basophilic stippling. The anemia results from two basic defects: shortened erythrocyte life span and impairment of heme synthesis. Shortened life span of the red blood cell is thought to be due to increased mechanical fragility of the cell membrane. The biochemical basis for this effect is not known, but the effect is accompanied by inhibition of sodium- and potassium-dependent ATPases.

A schematic presentation of the effects of lead on heme synthesis is shown in Fig. 23-6.

Probably the most sensitive effect is inhibition of δ-aminolevulinic acid dehydratase (ALA-D), resulting in a negative exponential relationship between ALA-D and blood lead. There is also depression of coproporphyrinogen oxidase, resulting in increased coproporphyrin activity. Lead also decreases ferrochelatase activity. This enzyme catalyzes the incorporation of the ferrous ion into the porphyrin ring structure. Failure to insert iron into protoporphyrin results in depressed heme formation. The excess protoporphyrin takes the place of heme in the hemoglobin molecule and, as the red blood cells containing protoporphyrin circulate, zinc is chelated at the center of the molecule at the site usually occupied by iron. Red blood cells containing zinc-protoporphyrin are intensely fluorescent and may be used to diagnose lead toxicity. Depressed heme synthesis is thought to be the stimulus for increasing the rate of activity of the first step in the heme synthetic pathway. Delta-aminolevulinic acid synthetase is subject to negative feedback control. As a consequence, the increased production of δ-aminolevulinic acid (ALA) and decreased activity of ALA-D result in a marked increase in circulating blood levels and urinary excretion of ALA. Prefeeding of lead to experimental animals also raises heme oxygenase activity, resulting in some increase in bilirubin formation. The change in rates of activity of these enzymes by lead produces a dose-related alteration in the activity of the affected enzymes, but anemia only occurs in very marked lead toxicity. The changes in enzyme activities, particularly ALA-D in peripheral blood and excretion of ALA in urine, correlate very closely with actual blood lead levels and serve as early biochemical indices of lead exposure (ATSDR, 1999).

A genetic polymorphism for the heme pathway enzyme was identified by Granick et al. in 1973, but the molecular characteristics and potential clinical implications have received attention only

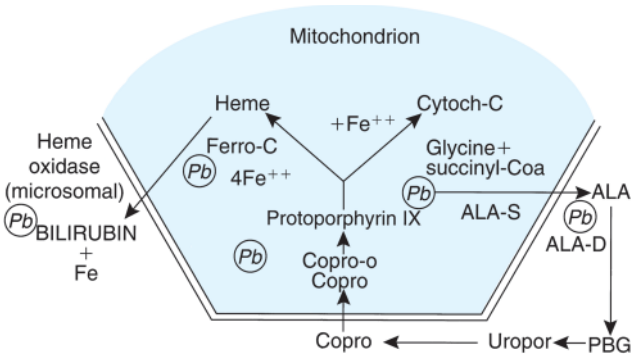

Figure 23-6. Scheme of heme synthesis showing sites where lead has an effect.

CoA, coenzyme A; *ALA-S*, aminolevulinic acid synthetase; *ALA,* δ-aminolevulinic acid; *ALA-D,* aminolevulinic acid dehydratase; *PBG,* porphobilinogen; *Uropor,* urorporphyrinogen; *Copro,* coproporphyrinogen; *Copro-O*, coproporphyrinogen oxidase; *Ferro-C,* ferrochelatase; *Cytoch-C,* cytoachrome-*C*; *Pb,* site for lead effect.

recently. Battistuzzi et al. (1981) identified two common alleles, ALAD-1 and ALAD-2, with frequencies of 0.9 and 0.1 in European-based populations, giving rise to three phenotypes, 1-1, 1-2, and 2-2. Heterozygotes have ALAD-2 activity that is 50 percent normal, whereas severely deficient homozygous (2-2) people have ALA-D activity that is approximately 2 percent of homozygous normal. Doss et al. (1982) reported that those workers with moderate workplace exposure to lead and high free erythrocyte protoporphyrin (FEP) concentrations were heterozygous for ALAD deficiency. Fleming and coworkers (1998) found that lead workers with the ALAD-2 allele had higher blood serum levels than ALAD-1 homozygotes and that the cumulative blood lead index based on blood lead histories and in vivo x-ray fluorescent (XRF) measurements of bone lead was greater in workers homozygous for ALAD-1. This finding suggested a greater transfer of blood lead to bone in this group than in workers with the ALAD-1/2 genotype. It is suggested, therefore, that the ALAD-2 allele affects the metabolism of lead, possibly leaving workers with this genotype more susceptible to soft tissue accumulation of lead. Smith et al. (1998) suggests a potential link between the ALAD variant and the subclinical indices of renal function (elevated BUN, uric acid, and creatinine).

Renal Toxicity Lead nephropathy is one of the oldest recognized health effects of lead (Oliver, 1902). It has been a major hazard from industrial exposure. However, with progressive reduction of exposure in the workplace and more sensitive biological indicators of renal toxicity, lead nephropathy should be a vanishing disease. The pathogenesis of lead nephropathy is described in stages, or as acute (reversible) or chronic (irreversible). Lead is a renal carcinogen in rodents, but whether it is carcinogenic to people is unclear. Acute lead nephrotoxicity is limited to functional and morphologic changes in proximal tubular cells (Goyer and Rhyne, 1973). It is manifest clinically by decrease in energy-dependent transport functions, including aminoaciduria, glycosuria, and ion transport. The functional changes are thought to be related to a lead effect on mitochondrial respiration and phosphorylation. In experimental models and biopsies from children with lead toxicity, there are ultrastructural changes in mitochondria consisting of swelling with distorted cristae. Mitochondria isolated from lead-poisoned rats show decreased state III respiration. These changes are reversible by treatment with a chelating agent.

A characteristic microscopic change is the formation of a lead–protein complex which appears in renal tubular cells as inclusion bodies. By light microscopy the inclusions are dense, homogeneous eosinophilic bodies. The bodies are composed of a lead–protein complex. The protein is acidic and contains large amounts of aspartic and glutamic acids and little cystine. It is suggested that lead binds loosely to the carboxyl groups of the acidic amino acids (Moore et al., 1973). Lead will form inclusion bodies in the cytoplasm of kidney cells grown in culture and tends to migrate into nuclei secondarily (McLaughlin et al., 1980). Renal biopsies from a group of shipwreckers with heavy exposure to lead have shown that the histologic features of early and chronic exposure to lead are similar in experimental animals and humans, suggesting similar pathogenetic mechanisms. Nuclear inclusion bodies become less common as renal tubules atrophy and as interstitial fibrosis increases in severity.

Proximal tubular dysfunction is usually not demonstrable in the chronic phase of lead nephropathy, but interstitial fibrosis is usually associated with asymptomatic renal azotemia and reduced glomerular filtration rate. In workers without azotemia but with decreased inulin clearance, there is decreased maximum reabsorption of glucose. Although progression from acute reversible to chronic irreversible lead nephropathy has not been clearly shown to occur in humans, this progression has been demonstrated in rodent models.

There is no specific biomarker for lead-induced renal disease. Lead may produce a chronic interstitial nephropathy, most commonly with prolonged exposure to blood lead levels greater than 60 μg/dL, but biochemical indicators may respond as low as 40 μg/dL. In a mortality study of 4519 battery plant workers and 2300 lead production workers by Cooper and coworkers (1985), there was excess mortality from chronic nephritis. The mean blood concentration of 1326 of the battery workers in this study with three or more analyses was 62.7 μg/100 g. Gennart and colleagues (1992), found that none of the indicators of renal function, including red blood plasma (RBP), β_2-microglobulin, albumin and NAG in urine, and creatinine differed from controls and did not correlate with blood lead levels (mean 51 μg/dL, range 40 to 75) or duration of exposure. This finding is consistent with the observation of Buchet and coworkers (1980) that workers who do not have recorded blood lead levels over 62 or 63 μg/dL for up to 12 years do not have lead nephropathy. However, depressed glomerular filtration rates have been reported in a group of lead-exposed workers whose blood lead levels were as low as 40 μg/dL. Some studies report correlations of blood lead levels as low as 30 μg/dL with urinary levels of NAG and urinary and serum β_2-microglobulin, but these findings are not confirmed by others (Buchet et al., 1980; Gennart et al., 1992). Increase in urinary β_2-microglobulin is not a characteristic finding in lead-induced nephropathy and there is no meaningful correlation with blood lead levels (Bernard and Lauwerys, 1989). Also, Ong et al. (1987) were not able to find a dose–response relationship between blood lead levels and urinary excretion of NAG. Urinary excretion of NAG might occur at an early stage of lead nephropathy, perhaps reflecting increased urinary leakage from damaged renal tubular epithelium. There is evidence that lead impairs heme-containing enzyme systems in the kidney that are involved in vitamin D metabolism. Vitamin D synthesis requires a heme-containing hydroxylase enzyme in the kidney for the hydroxylation of 25-hydroxyvitamin D to 1,25-dehydroxy-vitamin D, which is important in the gastrointestinal absorption of calcium. These effects may occur with lead levels as

low as 30 μg/dL, below the levels of lead that alters other biomarkers for nephrotoxicity (Rosen et al., 1985).

Lead and Gout The relationship between chronic lead exposure and gouty nephropathy was suggested more than a hundred years ago. The tubular or metabolic mechanism for the elevated blood uric acid levels is not known. However, patients with gout and renal disease have a greater chelate-provoked lead excretion than do renal patients without gout (Batuman et al., 1981).

Effects on Cardiovascular System There is considerable debate regarding the causal relationship between lead exposure and hypertension. Many of the studies are summarized in review literature (NRC, 1993; WHO, 1995; ATSDR, 1999). Epidemiologic studies on the effects of lead on blood pressure are inconclusive or contradictory and the WHO (1995) and ATSDR (1999) reviews conclude that the evidence to date is not sufficient to support causal relationship between blood lead levels and increases in blood pressure. Hu et al. (1996) related lead accumulation in bone with blood pressure in a cohort of 590 men, mean age 66.6 years, with hypertension (BP $>$160/90 mmHg). Results indicated an increase in odds ratio of 1.5 for hypertension for individuals with elevated bone lead.

The largest populations have been studied in the second National Health and Nutrition Examination Survey (NHANES II) for the U.S. population, performed during the years 1976 to 1980. These studies included blood lead levels and blood pressure measurements in a general population sample of 5803 men and women aged 12 to 74. Analysis of the data (Harlan et al., 1988) found a correlation between blood lead and blood pressure. Possible mechanisms for a lead effect on blood pressure include changes in plasma renin and in urinary kallikrein; alterations in calcium-activated functions of vascular smooth muscle cells, including contractility, by decreasing Na^+/K^+-ATPase activity and stimulation of the Na/Ca exchange pump; and changes in responsiveness to catecholamines (Victery, 1988; ATSDR, 1999).

Immunotoxicity Studies of workers with occupational exposures to lead suggest that lead is an immunosuppressive. McCabe and Lawrence (1991) suggest that decreases in immunoglobulins as well as other components of the immunologic system may be affected by lead. Changes in chemotaxis have been found in polymorphonuclear lymphocytes in workers with blood lead levels $<$ 33 μg/dL (Valentino et al., 1991). Also, numbers of peripheral B lymphocytes may be decreased (Jaremin, 1983).

Bone Effects The regulation of skeletal mass, including lead in bone, are determined by four different types of cells; osteoblasts, lining cells, osteoclasts, and osteocytes. These cells line and penetrate the mineralized matrix of bone and are responsible for matrix formation, mineralization, and bone resorption. Lead toxicity directly and indirectly alters many aspects of bone cell function. Retention and mobilization of lead in bone occur by the same mechanisms involved in regulating calcium influx and efflux, namely parathyroid hormone, calcitonin, vitamin D, and other hormones that influence calcium metabolism (Pounds et al., 1991). Lead also competes with calcium for gastrointestinal absorption (Fullmer et al., 1992). The interrelationship of vitamin D and calcium is complex and involves interactions with parathyroid hormone. Lead in bone readily exchanges with blood lead. Using stable isotope techniques, Gulson and coworkers (1995) have shown that lead in bone contributes between 45 and 70 percent of the lead in blood of women of childbearing age, and a similar percent of lead is identified in the fetus as being from mother's skeleton. Pregnancy and lactation further increase mobilization of lead from the maternal skeleton, with a proportionate increase in blood lead in the prenatal period (Gulson et al., 1998).

Reproductive Effects Overt or clinically apparent lead toxicity has long been associated with sterility and neonatal deaths in humans. Gametotoxic effects have been demonstrated in both male and female animals (Stowe and Goyer, 1971). A few clinical studies have found increased chromosomal defects in workers with blood lead levels above 60 μg/dL; reduction in sperm counts and abnormal sperm motility and morphology are found in lead battery workers with blood lead levels as low as 40 μg/dL (Assenato et al., 1986). Decreases in testicular endocrine function were found to be related to duration of lead exposure of smelter workers with mean blood lead level of 60 μg/dL (Rodamilans et al., 1988). An effect of chronic exposure to low levels of lead on female reproduction including abortion has not been demonstrated (Murphy et al., 1990).

Birth Outcomes The early literature on toxicology of lead focused on an increased incidence of spontaneous abortion and stillbirth, but these outcomes are rare today. Andrews et al. (1994) reviewed 25 epidemiologic studies to determine the relationship of prenatal lead exposure and birth outcomes. They concluded that prenatal lead exposure is unlikely to increase the risk of premature rupture of membranes but does appear to increase the risk of preterm delivery. An increase in the maternal blood lead level may also contribute to reducing gestational duration and birth weight (McMichael et al., 1988; Borschein et al., 1989).

Carcinogenicity Lead is classified as a 2B carcinogen by the IARC (1987). A study of workmen with occupational exposure to lead in England many years ago did not show an increased incidence of cancer (Dingwall-Fordyce and Lane, 1963). Causes of mortality in 7000 lead workers in the United States showed a slight excess of deaths from cancer (Cooper and Gaffey, 1975), but the statistical significance of these findings has been debated (Kang et al., 1980). The most common tumors found were of the respiratory and digestive systems, not the kidney. However, case reports of renal adenocarcinoma in workmen with prolonged occupational exposure to lead have appeared (Baker et al., 1980; Lilis, 1981).

Epidemiologic studies suggest a relationship between occupational lead exposure and cancer of the lung and brain. Anttila et al. (1995) correlated blood lead levels and mortality rates and cancer incidence for a cohort of 20,700 workers coexposed to lead and engine exhausts. Blood lead levels were monitored for over 10 years. A 1.4-fold increase in the overall cancer incidence was found, as well as a 1.8-fold increase in lung cancer among those who had ever a blood-lead level over 1.0 μmol/dL. Another epidemiologic study provides evidence for a potential link between occupational exposure to lead and brain cancer (Cocco et al., 1998). A job-exposure matrix for lead to occupation and industry codes was applied to information on death certificates of 27,060 brain cancer cases and 108,240 controls who died of nonmalignant disease in 24 U.S. states in 1984 to 1992. Brain cancer risk increased by probability of exposure to lead among Caucasian men and women with high-level exposure. Fu and Boffetta (1995) performed a meta-analysis of published data on cancer incidence among various industries. They focused the analysis on overall cancer, stom-

ach cancer, kidney cancer, and bladder cancer. The meta-analysis indicates a significant excess of cancer deaths from stomach cancer, lung cancer, and bladder cancer among workers exposed to lead. There was also a non-statistically-significant excess of deaths from kidney cancer. The investigators concluded that most of the studies lacked data on the level of cumulative exposure. Suggested relationships between high occupational exposure are from multimedia exposure, largely from inhalation, and often in association with potential toxins and/or cocarcinogens, so that the role of lead is generally nonconclusive.

Lead induction of renal adenocarcinoma in rats and mice is dose related and has not been reported at levels below that which produces nephrotoxicity. Lead-induced tumors may be a consequence of increased cellular proliferation (Calabrese, 1992). Lead compounds have been shown to stimulate the proliferation of renal tubular epithelial cells (Choie and Richter, 1980), and similar effects have been noted in the livers of rats (Columbano et al., 1983). Lead compounds induce cell transformation in Syrian hamster embryo cells (Zelikoff et al., 1988). Lead-related renal tumors may be a nonspecific response to epithelial hyperplasia, as has been noted in other experimental nephropathies and human diseases where renal tubular cysts and hyperplasia occur (Goyer, 1992).

Other Effects Lead lines (Burton's lines) or purple-blue discoloration of gingiva is a classic feature of severe lead toxicity in children with lead encephalopathy. However, this feature of lead toxicity, as well as the presence of lead lines at the epiphyses margins of long bones, is uncommon today.

Dose Response The toxic effects of lead and the minimum blood lead level at which the effect is likely to be observed are shown in Table 23-4. A detailed compilation of lowest observed effect levels in humans and animals from individual reports is available (ATSDR, 1999). Levels provided in this table are meant to be guidelines recognizing variation in susceptibility between individuals.

Table 23-4
Summary of Lowest Observed Effect Levels for Lead-Related Health Effects

EFFECT	*Blood Lead Levels, μg/dL* ADULT	CHILDREN
Neurologic		
Encephalopathy (overt)	80–100	100–120
Hearing deficits	20	—
IQ deficits	10–15	—
In utero effects	10–15	—
Nerve conduction velocity ↓	40	40
Hematologic		
Anemia	80–100	80–100
U-ALA ↑	40	40
B-EP ↑	15	15
ALA-D inhibition	10	10
Renal		
Nephropathy	40	40–60
Vitamin D metabolism	<30?	—
Blood pressure		30?
Reproduction		
Males		40
Females		?

SOURCE: Modified from NIOSH (1997) and ATSDR (1999).

Treatment Foremost in the treatment of increased blood lead levels and lead toxicity is removal of the subject from source(s) of exposure. The blood lead levels at which treatment with chelating drugs should begin are debatable. Certainly chelation usually has a role in the treatment of the symptomatic worker or child. Institution of chelation therapy is probably warranted in workers with blood lead levels over 60 μg/dL, but this determination must be made after an assessment of exposure factors, including biological estimates of clinical and biochemical parameters of toxicity. For children, criteria have been established that may serve as guidelines to assist in evaluating the individual case (CDC, 1991). For children with severe lead poisoning, including encephalopathy, chelation therapy is standard practice. Even then, the mortality rate may be 25 to 38 percent when EDTA or BAL is used singly, whereas combination therapy of EDTA and BAL has been shown to be effective in reducing mortality.

The decision to chelate children with blood lead levels above 45 μg/dL is a matter of clinical judgment. The oral chelating agent succimer [dimercaptosuccinic acid, (DMSA)] has been licensed by the U.S. Food and Drug Administration (FDA) for reduction of blood lead levels of 45 μg/dL or greater. DMSA has an advantage over EDTA in that it can be administered orally and is effective in temporarily reducing blood lead levels. Studies in rats suggest it may be effective in the treatment of acute lead poisoning (Kostial et al., 1999). However, DMSA does not seem to improve long-term blood lead levels in children with blood lead levels between 30 and 45 μg/dL. (O'Connor and Rich, 1999). Studies in monkeys suggest that DMSA does not reduce brain lead beyond the effect of cessation of exposure of lead alone (Cremin et al., 1999).

Organic Lead Compounds Tetraethyl lead (TEL) was used for many years as a gasoline additive, but production and use have now stopped in the United States. While the importance of TEL as a potential toxin for workers and the general population has lessened, it is still produced and used in some other countries. The potential use of gasoline as a recreational drug (gasoline sniffing) for a psychedelic high is an additional reason for concern about its potential toxicity.

Toxicokinetics Organic lead compounds have a special affinity for lipoid and nerve tissue, resulting in rapid metabolism and toxicity to the brain. Within 24 h of exposure, 50 percent of TEL is metabolized by P450 metabolizing enzymes to trimethyl lead (TML). The second metabolic product of TEL is inorganic lead, which is distributed to various tissues and excreted in urine. Most TEL is excreted from the body in about 20 days. Mechanisms of toxicity include damage to membranes, impairment of energy metabolism, and direct interference with neurotransmitter synthesis. Exposure to TEL is usually by inhalation, and about 60 to 80 percent is absorbed. The liquid is readily absorbed by the gastrointestinal tract and skin (Bolanowska et al., 1968; Bondy, 1991; Audesirk et al., 1995).

Toxicity Symptoms of acute intoxication include nausea, vomiting, and diarrhea associated with nervous system symptoms of irritability, headache, and restlessness. These symptoms progress rapidly to severe signs of central nervous system toxicity, including convulsions and coma. The mortality rate for acute intoxication is about 29 percent. Chronic exposure may result in milder symptoms. An immediate effect among recreational users may be

euphoria, followed by violent excitement and then coma. Chronic, heavy sniffing of leaded gasoline results in signs of dementia and encephalopathy, with cerebellar and corticospinal symptoms. Which aspects of these symptoms are due to TEL per se or other components of gasoline is unknown. Chelating agents are not thought to be a rational aspect of treatment and experience with gasoline sniffers has shown that chelation does not benefit these patients (Tenenbein, 1997). A case-control study of former workers in a TEL-producing plant found a strong association between exposure to the TEL manufacturing process and colorectal cancer (Fayerweather et al., 1997).

Mercury (Hg)

No other metal better illustrates the diversity of effects caused by different chemical species than does mercury.[1] There have been several major reviews (ATSDR, 1999; WHO, 1990; WHO, 1991; Goyer, 1996).

Mercury is unique as being the only metal that is in a liquid state at room temperature. The vapor from this liquid, usually referred to as *mercury vapor,* is much more hazardous than the liquid form. This element exists in three oxidation states. In the zero oxidation state (Hg^0) mercury exists in its metallic form or as the vapor. The mercurous and mercuric states are the two higher-oxidation states where the mercury atom has lost one (Hg^+) and two electrons (Hg^{2+}), respectively. In addition, mercuric mercury can form a number of stable organic mercury compounds by attaching to one or two carbon atoms. Methyl mercury (CH_3Hg^+) is the most important organic form from the point of view of human exposure. Each oxidation state and each organic species has characteristic toxicokinetics and health effects.

Exposure The major source of mercury (as mercury vapor) in the atmosphere is the natural degassing of the earth's crust. It is difficult to assess what quantities of mercury come from human activities, but these are believed to be approximately similar in magnitude to natural sources. Calculations based on the mercury content of the Greenland ice cap show an increase from the year 1900 to the present.

Mercury vapor in the atmosphere represents the major pathway of global transport of mercury. It resides there unchanged for periods of a year or so. Thus there is time for it to be distributed globally even from a point source of pollution. Eventually it is converted to a water-soluble form and returned to the earth's surface in rainwater.

At this stage, two important chemical changes may occur. The metal may be reduced back to mercury vapor and returned to the atmosphere, or it may be methylated by microorganisms present in sediments of bodies of fresh and ocean water. The main product of this natural biomethylation reaction is monomethyl mercury compounds, usually referred to generically as "methyl mercury." Some of the oldest organisms on an evolutionary scale, the methanogenic bacteria, carry out this methylation reaction.

Once produced, methyl mercury enters an aquatic food chain involving plankton, herbivorous fish, and finally carnivorous fish. In the tissues of fish consuming sea mammals, mercury can rise to levels a millionfold higher than those in the surrounding water. The sequence of biomethylation and bioconcentration can result in human dietary exposure to methyl mercury, whether the latter originated from natural or anthropogenic sources of inorganic mercury. Methyl mercury is found in most if not all fish tissues but most importantly in edible tissue, mainly muscle, in a water-soluble protein-bound form. Unlike the case of PCBs, which are deposited in fat, cooking the fish does not lower the methyl mercury content.

Inorganic compounds of mercury are also found in food. The source is unknown and the amount ingested is far below known toxic intakes.

Other sources of human exposure to mercury are occupational, where the main route is inhalation of mercury vapor from the working environment. Mercury has numerous uses, as in the chlor-alkali industry, where it is used as a cathode in the electrolysis of brine; in making a variety of scientific instruments and electrical control devices; in dentistry, as amalgam tooth filling; and in the extraction of gold. The last has now become a widespread activity in developing countries, where large quantities of metallic mercury are used to form an amalgam with gold. The amalgam is heated to drive off the mercury, resulting in a substantial release to the atmosphere.

Mercury vapor emitted from amalgam dental fillings is the major source of mercury vapor affecting the general public. Chewing increases the rate of release. Although the amount inhaled is low compared to known toxic levels, some individuals with a history of excessive chewing might attain levels that could pose a health risk.

Mercury levels in the general atmosphere and in drinking water are so low that they do not constitute an important source of exposure to the general population.

Disposition and Toxicokinetics Liquid metallic mercury, such as may be swallowed from a broken thermometer, is only slowly absorbed by the gastrointestinal tract (0.01 percent) at a rate related to the vaporization of the elemental mercury and is generally thought to be of no toxicologic consequence.

The vapor from metallic mercury is readily absorbed in the lungs, and, in mercury's dissolved form in the bloodstream, diffuses to all tissues in the body. Its high mobility is due to the fact that it is a monatomic gas, highly diffusible and lipid-soluble. It is rapidly oxidized to mercuric mercury, as discussed below.

Since human exposure to compounds of mercurous mercury now occurs rarely if at all, we have little information on its disposition in the body. Compounds of mercurous mercury, especially the chloride salt, have a low solubility in water and are poorly absorbed from the gastrointestinal tract. In the presence of protein, the mercurous ion disproportionates to one atom of metallic mercury (Hg^0) and one of mercuric mercury (Hg^{2+}). The latter will probably be absorbed into the bloodstream and distributed to tissues, as discussed below.

Gastrointestinal absorption of compounds of mercuric mercury from food is about 15 percent in a study of human volunteers, whereas absorption of methyl mercury is on the order of 90 to 95 percent. Distribution between red blood cells and plasma also differs. For inorganic mercury the cell-to-plasma ratio ranges from a high of 2 with high exposure to less than 1 but for methyl mercury it is about 10. The distribution ratio of the two forms of mercury between hair and blood also differs; much higher concentrations of methyl mercury are accumulated from blood.

Kidneys contain the greatest concentrations of mercury following exposure to inorganic salts of mercury and mercury vapor, whereas organic mercury has a greater affinity for the brain, particularly the posterior cortex. Mercury vapor also has a greater predilection for the central nervous system than do inorganic mercury salts.

[1]Atomic weight, 200.5; periodic table group, IIB; valence, +1 or +2; discovered before 1500 B.C.

Excretion of mercury from the body is by way of urine and feces, again differing with the form of mercury, size of the dose, and time after exposure. Exposure to mercury vapor is followed by exhalation of a small fraction, but fecal excretion is the major and predominant route of excretion initially after exposure to inorganic mercury. Renal excretion increases with time. About 90 percent of methyl mercury is excreted in feces after acute or chronic exposure, and this figure does not change with time (Miettinen, 1973).

All forms of mercury cross the placenta to the fetus, but most of what is known has been learned from experimental animals. Fetal uptake of elemental mercury in rats has been shown to be 10 to 40 times higher than uptake after exposure to inorganic salts. Concentrations of mercury in the fetus after exposure to alkylmercuric compounds are twice those found in maternal tissues, and levels of methyl mercury in fetal red blood cells are 30 percent higher than those in maternal red cells. Although maternal milk may contain only 5 percent of the mercury concentration of maternal blood, neonatal exposure to mercury may be increased by nursing (Grandjean et al., 1994).

Metabolic Transformation Elemental or metallic mercury is oxidized to divalent mercury after absorption to tissues in the body and is probably mediated by catalases. Inhaled mercury vapor absorbed into red blood cells is transformed to divalent mercury, but a portion is also transported as metallic mercury to more distal tissues, particularly the brain, where biotransformation may occur.

Methyl mercury undergoes biotransformation to divalent mercury compounds in tissues by cleavage of the carbon mercury bond. There is no evidence of formation of any organic form of mercury in mammalian tissues. The aryl (phenyl) compounds are converted to inorganic mercury more rapidly than the shorter-chain alkyl (methyl) compounds.

Biological half-lives are available for a limited number of mercury compounds. Elimination of methyl mercury from the body is adequately described by a single half-life. The most recent estimate is 44 days. More complex kinetics describe the elimination of mercury after inorganic salts or exposure to mercury vapor. The half-lives vary between tissues and sometimes more than one half-life is needed to characterize the kinetics of elimination. Generally, the half-lives are in the range of 20 to 90 days.

Cellular Metabolism Within cells, mercury may bind to a variety of enzyme systems including those of microsomes and mitochondria, producing nonspecific cell injury or cell death. It has a particular affinity for ligands containing sulfhydryl groups. In liver cells, methyl mercury forms soluble complexes of glutathione, which are secreted in bile and reabsorbed from the gastrointestinal tract. Inorganic mercury is also secreted in bile as a glutathione complex. The cysteine complex of methyl mercury enters the endothelial cells of the blood-brain barrier on the large neutral amino acid transporter.

Mercuric mercury, but not methyl mercury, induces synthesis of metallothionein in kidney cells; but unlike cadmium-metallothionein, it does not have a long biological half-life. Mercury within renal cells becomes localized in lysosomes (Madsen and Christensen, 1978).

Toxicology ***Mercury Vapor*** Inhalation of mercury vapor at extremely high concentrations may produce an acute, corrosive bronchitis and interstitial pneumonitis and, if not fatal, may be associated with symptoms of central nervous system effects such as tremor or increased excitability. With chronic exposure to mercury vapor, the major effects are on the central nervous system. Early signs are nonspecific, and this condition has been termed the *asthenic-vegetative syndrome* or *micromercurialism.* Identification of the syndrome requires neurasthenic symptoms and three or more of the following clinical findings: tremor, enlargement of the thyroid, increased uptake of radioiodine in the thyroid, labile pulse, tachycardia, dermographism, gingivitis, hematologic changes, or increased excretion of mercury in urine. With increasing exposure, the symptoms become more characteristic, beginning with tremors of muscles that perform fine-motor functions (highly innervated)—such as fingers, eyelids, and lips—and may progress to generalized trembling of the entire body and violent chronic spasms of the extremities. This is accompanied by changes in personality and behavior, with loss of memory, increased excitability (erethism), severe depression, and even delirium and hallucination. Another characteristic feature of mercury toxicity is severe salivation and gingivitis.

The triad of increased excitability, tremors, and gingivitis has been recognized historically as the major manifestation of mercury poisoning from inhalation of mercury vapor and exposure to mercury nitrate in the fur, felt, and hat industries (Goldwater, 1972).

Sporadic instances of proteinuria and even nephrotic syndrome may occur in persons with exposure to mercury vapor, particularly with chronic occupational exposure. The pathogenesis is probably immunologically similar to that which may occur following exposure to inorganic mercury.

There is growing concern that the toxic potential of mercury vapor released from dental amalgams may cause various health effects. Estimates of absorption of mercury by an adult with the average number of amalgams (8 per adult) is 30 to 40 percent of the total mercury exposure of 5 to 6 μg per day (Richardson et al., 1995). An increase in urinary mercury and accumulation in several organs, including the central nervous system and kidneys, has been related to the release of mercury from dental amalgams (Clarkson et al., 1988; Langworth et al., 1988). Aposhian and coworkers (1992) found a highly positive correlation between mercury excreted in urine following the administration of dimercapto-succinic acid (DMPS) and numbers of dental amalgams. However, this level of mercury exposure is believed to be below that which will produce any discernible health effect except for highly sensitive people.

Mercuric Salts Bichloride of mercury (corrosive sublimate) is the best-known mercuric salt of mercury from a toxicologic standpoint. Even the trivial name suggests its most apparent toxicologic effect when the salt is ingested in concentrations greater than 10 percent. A reference from the Middle Ages in Goldwater's book on mercury describes oral ingestion of mercury as causing severe abdominal cramps, bloody diarrhea, and suppression of urine (Goldwater, 1972). This is an accurate report of the effects following accidental or suicidal ingestion of mercuric chloride or other mercuric salts. Corrosive ulceration, bleeding, and necrosis of the gastrointestinal tract are usually accompanied by shock and circulatory collapse. If the patient survives the gastrointestinal damage, renal failure occurs within 24 h owing to necrosis of the proximal tubular epithelium, followed by oliguria, anuria, and uremia. If the patient can be maintained by dialysis, regeneration of the tubular lining cells is possible. These changes may be followed by ultrastructural changes consistent with irreversible cell injury, including actual disruption of mitochondria, release of lysosomal enzymes, and rupture of cell membranes.

Injection of mercuric chloride produces necrosis of the epithelium of the pars recta kidney (Gritzka and Trump, 1968). Cel-

lular changes include fragmentation and disruption of the plasma membrane and its appendages, vesiculation and disruption of the endoplasmic reticulum and other cytoplasmic membranes, dissociation of polysomes and loss of ribosomes, mitochondrial swelling with appearance of amorphous intramatrical deposits, and condensation of nuclear chromatin. These changes are common to renal cell necrosis due to various causes. Slight tubular cell injury, manifest by enzymuria and low-molecular-weight proteinuria may occur in workers with low-level exposure to metallic mercury vapor (Roels et al., 1985).

Although a high dose of mercuric chloride is directly toxic to renal tubular lining cells, chronic low-dose exposure to mercuric salts or even elemental mercury vapor levels may induce an immunologic glomerular disease. Exposed persons may develop a proteinuria that is reversible after workers are removed from exposure.

Experimental studies have shown that the pathogenesis has two phases: an early phase characterized by an anti–basement membrane glomerulonephritis, followed by a superimposed immune-complex glomerulonephritis with transiently raised concentrations of circulating immune complexes (Henry et al., 1988). The pathogenesis of the nephropathy in humans appears similar, although antigens have not been characterized. Also, the early glomerular nephritis may progress in humans to an interstitial immune-complex nephritis (Pelletier and Druet, 1995).

Mercurous Mercury Mercurous compounds of mercury are less corrosive and less toxic than mercuric salts, presumably because they are less soluble. Calomel, a powder containing mercurous chloride, has a long history of use in medicine. Perhaps the most notable modern usage has been in teething powder for children, and this powder is now known to be responsible for acrodynia or "pink disease." This is most likely a hypersensitivity response to the mercury salts in skin, producing vasodilation, hyperkeratosis, and hypersecretion of sweat. Children develop fever, a pink-colored rash, swelling of the spleen and lymph nodes, and hyperkeratosis and swelling of the fingers. The effects are thought to be a hypersensitivity reaction (Matheson et al., 1980).

Methyl Mercury Methyl mercury is the most important form of mercury in terms of toxicity and health effects from environmental exposures. Many of the effects produced by short-term alkyls are unique in terms of mercury toxicity but nonspecific in that they may be found in other disease states. Most of what is known about the clinical signs and symptoms and neuropathology of high-level or overt methyl mercury toxicity has been learned from studies of epidemics in Japan and Iraq (WHO, 1990; Berlin, 1986) and from published reports of occupational exposures (Hunter et al., 1940). Observations of changes in nonhuman primates studied experimentally are consistent with findings in humans and therefore provide additional information about the relationship between time, dose, and tissue burden, particularly for subclinical and subtle low-level effects (Mottet et al., 1985).

The major human health effects from exposure to methyl mercury are neurotoxic effects in adults (Bakir et al., 1973) and toxicity to the fetuses of mothers exposed to methyl mercury during pregnancy (Cox et al., 1989). The major source of exposure for people in the general population is from the consumption of fish, and in this instance the brain is the critical organ.

Clinical manifestations of neurotoxic effects are (1) paresthesia, a numbness and tingling sensation around the mouth, lips, and extremities, particularly the fingers and toes; (2) ataxia, a clumsy, stumbling gait, difficulty in swallowing and articulating words; (3) neurasthenia, a generalized sensation of weakness, fatigue, and inability to concentrate; (4) vision and hearing loss; (5) spasticity and tremor; and finally (6) coma and death.

Neuropathologic observations have shown that the cortex of the cerebrum and cerebellum are selectively involved with focal necrosis of neurons, lysis and phagocytosis, and replacement by supporting glial cells. These changes are most prominent in the deeper fissures (sulci), as in the visual cortex and insula. The overall acute effect is cerebral edema; but with prolonged destruction of gray matter and subsequent gliosis, cerebral atrophy results (Takeuchi, 1977).

The mechanisms of damage to the mature brain are not known. Inhibition of protein synthesis is among the earliest biochemical effects seen in animals. Syversen (1982) has proposed that all neuronal cells may be affected initially, but those cells having the least repair capacity eventually succumb whereas cells with more repair capacity survive. This mechanism may account for the highly localized focal pathology seen in the adult brain.

Experimental studies on the mechanisms of methyl mercury toxicity provide some insight into the basis for the clinical observations as well as the greater sensitivity of the developing brain (Clarkson, 1983). Exposure of the fetus in utero to high levels of mercury result in abnormal neuronal migration and deranged organization of brain nuclei (clusters of neurons) and layering of neurons in the cortex. Studies in mice have demonstrated an effect of methyl mercury on the microtubules of neurons. These observations may provide the cellular basis for the observed neuropathologic changes in the migration pattern of neurons during development, which is thought to be the basis for the developmental effects in the central nervous system. Male mice are more sensitive than females, consistent with the findings in humans (Sager et al., 1984; Choi et al., 1978).

Biological Indicators ***Inorganic Mercury*** The recommended standard (time-weight average) for permissible exposure limits for inorganic mercury in air in the workplace is 0.05 mg/m^3 (DHEW, 1977) and is equivalent to an ambient air level of 0.015 mg/m^3 for the general population (24-h exposure) (Table 23-5). The U.S. federal standard for alkyl mercury exposure in the workplace is 0.01 mg/m^3 as an 8-h time-weighted average with an acceptable ceiling of 0.04 mg/m^3. A study of the Iraq epidemic has provided estimates of the body burden of mercury and the onset and frequency of occurrence of symptoms (Fig. 23-7).

Table 23-5
The Time-Weighted Average Air Concentrations Associated with the Earliest Effects in the Most Sensitive Adults following Long-Term Exposure to Elemental Mercury Vapor

*Equivalent Concentrations**			
AIR, mg/m^3	BLOOD, μg/100 mL	URINE, μg/L	EARLIEST EFFECTS
0.05	3.5	150	Nonspecific symptoms
0.1–0.2	7–14	300–600	Tremor

*Blood and urine values may be used only on a group basis owing to gross individual variations. These average values reflect exposure for a year or more. After shorter periods of exposure, air concentrations would be associated with lower concentrations in blood and urine.
SOURCE: WHO (1976).

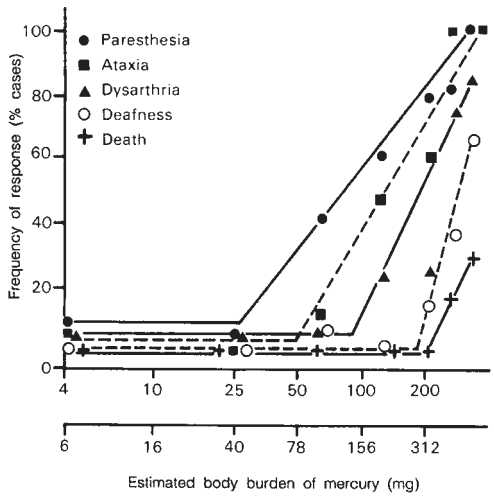

Figure 23-7. Dose–response relationships for methyl mercury.

The upper scale of estimated body burden of mercury was based on the author's actual estimate of intake. The lower scale is based on the body burden, which was calculated based on the concentration of mercury in the blood and its relationship to intake derived from radioisotopic studies of methyl mercury kinetics in human volunteers. [From Bakir et al. (1973).]

Methyl Mercury The relationship between health risks and intake of methyl mercury has been developed from toxicologic data obtained from studies of epidemics due to accidental poisoning in Minamata and Niigata, Japan, in the 1950s and 1960s and from studies of the episode in Iraq in 1972 (Berlin, 1986).

The critical or lowest level of observed adverse health effect in adults is paresthesia. By combining two relationships, body burden versus intake and effect versus body burden, a Swedish Expert Group (1971) was able to calculate the average long-term daily intake associated with health effects in the most susceptible individual. This was estimated to be about 300 μg/day for an adult or 4.3 μg/kg/day and would correspond to a steady-state blood level of 200 μg/L or a hair level of 50 μg/g.

Treatment Therapy for mercury poisoning should be directed toward lowering the concentration of mercury at the critical organ or site of injury. For the most severe cases, particularly with acute renal failure, hemodialysis may be the first measure, along with infusion of chelating agents for mercury, such as cysteine or penicillamine. For less severe cases of inorganic mercury poisoning, chelation with BAL may be effective.

However, chelation therapy is not very helpful for alkyl mercury exposure. Biliary excretion and reabsorption by the intestine and the enterohepatic cycling of mercury may be interrupted by surgically establishing gallbladder drainage or by the oral administration of a nonabsorbable thiol resin, which binds mercury and enhances intestinal excretion (Berlin, 1986).

Nickel (Ni)

Nickel[1] is a respiratory tract carcinogen in workers in the nickel-refining industry. Other serious consequences of long-term exposure to nickel are not apparent, but severe acute and sometimes fatal toxicity may follow exposure to nickel carbonyl. Allergic contact dermatitis is common among the general population.

Metallic nickel is produced from sulfide and silcate-oxide ores. In the United States approximately 200,000 metric tons of nickel (primary plus secondary use) are utilized per year. Nickel is included in various metal alloys, stainless steels, and electroplating. Major properties are strength, corrosion resistance, and good thermal and electrical conductivity (NIDI, 1997).

Exposure Nickel is ubiquitous in nature, occurring mainly in the form of sulfide, oxide, and silicate minerals. Very low levels of nickel can be found in ambient air as a result of industrial uses, combustion of fossil fuels, and sludge and waste incineration. Human exposure may be by inhalation, ingestion, and dermal contact. The main route of occupational exposure to nickel is through inhalation and to a lesser degree skin contact. Nickel refinery dust contains a mixture of many chemical species. Occupational exposures may contain elemental nickel, nickel compounds, complexes and alloys, and fumes from alloys used in welding and brazing. While there are no refineries in operation in the United States at present, there is still concern regarding effects on former workers from past exposures. Exposure to individuals in the general environment may result from contact with everyday items such as nickel-containing jewelry, cooking utensils, and clothing fasteners. Food is a major source of exposure for most people. The Environmental Protection Agency (EPA) estimates that an average adult consumes 100 to 300 μg of nickel per day. Drinking water contains very small amounts of nickel (ATSDR, 1997).

Toxicokinetics In the workplace, inhalation is the most serious toxicologic concern, followed by dermal exposure. Almost 35 percent of inhaled nickel is absorbed into the blood from the respiratory tract (WHO, 1991). Deposition, absorption, and elimination of nickel particles in the respiratory tract depend largely on the particle size and concentration of nickel. Only about half of particles larger than 30 μm are inhalable. Particles less than 10 μm may be deposited in the lower respiratory tract. Half-lives of 1 to 3 days for nickel sulfate, 5 days for nickel subsulfide, and more than 100 days for nickel oxide have been reported for inhaled or intratracheally instilled nickel compounds (Benson et al., 1987; Dunnick, 1989). Nickel has a half-life ranging from 30 to 53 h in the urine of workers exposed to insoluble nickel particles of small diameter (Raithel et al., 1982). Urinary nickel ranges from approximately 0.2 to 10 μg/L in unexposed individuals but from 2.6 μg/L in high nickel alloy production to 222 μg Ni/L in electrolyte refinery workers (Bernacki et al., 1978). In human volunteers exposed orally to soluble nickel sulfate hexahydrate, a half-life of 11 h was observed (Christensen and Lagesson, 1981). Nickel concentrations in the serum of unexposed individuals ranged from 0.05 to 1.1 μg/L (Sunderman et al., 1986). Urinary nickel has been shown to correlate closely with airborne levels of insoluble nickel compounds. It is not influenced by duration of exposure and may serve as a suitable measure of current nickel exposure (White and Boran, 1988).

The rate of dermal absorption depends on the rate of penetration of the epidermis, which differs for different chemical species of nickel. Nickel chloride penetrates in amounts ranging from 0.23 to 3.5 percent of the applied dose, whereas nickel sulfate may penetrate at rates 50 times lower (NIDI, 1997).

Nickel administered parenterally to animals is rapidly distributed to the kidneys, pituitary, lungs, skin, adrenals, ovaries, and

[1]Atomic weight, 58.69; periodic table group, VIII; valence, +0, +1, +2, +3; discovered in 1751.

testes (Sunderman, 1981). The intracellular distribution and binding of nickel is not well understood. Ultrafilterable ligands seem to be of major importance in the transport in serum and bile and urinary excretion as well as in intracellular binding. The ligands are not well characterized, but Sunderman (1981) suggests that cysteine, histidine, and aspartic acid form nickel complexes either singly or as nickel–ligand species. In vivo binding with metallothionein has been demonstrated, but nickel at best induces metallothionein synthesis in liver or kidney only slightly. A nickel-binding metalloprotein, called nickeloplasmin, has also been identified in plasma with properties suggesting that it is an α_1-glycoprotein complex and is important in the extracellular transport, intracellular binding, and urinary and biliary excretion of nickel (Niebor et al., 1988; Tabata et al., 1992).

Essentiality Evidence has accumulated over the past few years indicating that nickel is a nutritionally essential trace metal for some plant life, bacteria, and invertebrates (summarized by Nielson, 1996). Jackbean urease has been identified as a nickel metalloenzyme, and nickel is required for urea metabolism in cell cultures of soybean. However, a nickel-containing metalloenzyme has not yet been recovered from animal tissues. Nickel deficiency in rats is associated with retarded body growth and anemia, probably secondary to impaired absorption of iron from the gastrointestinal tract. In addition, there is a significant reduction in serum glucose concentration. An interaction of nickel with copper and zinc is also suspected because anemia-induced nickel deficiency is only partially corrected with nickel supplementation in rats receiving low dietary copper and zinc (Spears, 1978). A defined biochemical function in higher animals and humans has not been described, and human nutritional requirements have not been established (WHO, 1996).

Toxicity ***Carcinogenicity*** The IARC working group for consideration of nickel and nickel compounds concluded that nickel compounds are carcinogenic to humans (IARC, 1990). The respiratory tract is the main site of chronic effects reported in relation to nickel and its compounds. Risks were highest for lung and nasal cancers among workers heavily exposed to nickel sulfide, nickel oxide, and to metallic nickel. A cohort of 418 workers employed in a Finnish refinery reported a twofold increased incidence of lung cancer and a large increase in sinonasal cancers (Karjalainen et al., 1992). A follow-up of this study, including a total of 1155 workers, confirmed an elevated risk of lung and nasal cancers among refinery workers, with a greater risk among workers with a longer latency (greater than 20 years), (Anttila et al., 1998).

Because the refining of nickel in the plants that were studied involved the Mond process, with the formation of nickel carbonyl, it was believed for some time that nickel carbonyl was the principal carcinogen. However, additional epidemiologic studies of workers in refineries that do not use the Mond process also showed an increased risk of respiratory cancer, suggesting that the source of the increased risk is the mixture of nickel sulfides present in molten ore. Studies with experimental animals have shown that the nickel subsulfide (Ni_3S_2) produces local tumors at injection sites and by inhalation in rats, and in vitro mammalian cell tests demonstrate that Ni_3S_2 and $NiSO_4$ compounds give rise to mammalian cell transformation (IARC, 1990). Differences in the carcinogenic activities of nickel compounds may be attributable to variations in their capacities to provide nickel ion at critical sites within target cells (Sunderman, 1989; Costa, 1995). The order of lung toxicity corresponds to the water solubility of various compounds, with nickel sulfate being most toxic, followed by nickel subsulfide and nickel oxide (Dunick et al., 1989). However, nickel compounds lose their original chemical identity upon entering the blood, so that it is not possible to identify the original source of exposure (Grant and Mushak, 1989).

Mechanisms For Nickel Carcinogenesis The carcinogenicity of nickel is thought to be due to the ionic nickel species, but it has been difficult to explain the differences in carcinogenic potency between different nickel compounds. Some studies have suggested that water-insoluble crystalline nickel compounds were responsible for lung and nasal cancers seen in animal and human studies (IARC, 1990). However, not all water-insoluble crystalline nickel compounds induce tumors, so it was assumed that factors other than solubility were involved. More recently, Costa (1995) has proposed an epigenetic model suggesting that tumor induction is related to the ability of the cell to incorporate the crystalline compound into the cell by phagocytosis. Costa showed that Syrian hamster cells undergoing transformation selectively phagocytosed the negatively charged crystalline nickel sulfide compounds and not the positively charged amorphous nickel sulfide particles. When a negative charge was induced on the amorphous nickel sulfide particles, they too were phagocytosed and were able to exhibit transformation potency equivalent to that of crystalline nickel sulfide particles. Inside the cell, the particles dissolved in the intracellular space, a process enchanced by the acidic pH of the cytoplasm. Therefore, transformation appeared to directly relate to the ability of the particle to enter the cell and increase intracellular nickel concentrations. The model is based upon the known ability of nickel compounds to enhance DNA chromatin condensation. DNA found in heterochromatin is hypermethylated for direct protein binding for increased condensation. Another theory is that nickel damages DNA indirectly through reactive oxygen species (McCoy and Kenny, 1992). This proposal is supported by evidence that the antioxidant vitamin E inhibits some chromosomal condensation caused by nickel (Lin et al., 1991).

Sunderman and Barber (1988) proposed that nickel interacts with DNA by replacement of Zn^{2+} with Ni^{2+} on the Zn^{2+} binding sites of DNA-binding proteins. Ni^{2+} has a similar ionic radius to Zn^{2+}. DNA-binding proteins or "finger loop domains" have been identified on some proto-oncogenes and are thought to be likely targets for metal toxicity.

Nickel Carbonyl Poisoning Metallic nickel combines with carbon monoxide to form nickel carbonyl ($Ni[CO]_4$), which decomposes to pure nickel and carbon monoxide on heating to 200°C (the Mond process). This reaction provides a convenient and efficient method for the refinement of nickel. However, nickel carbonyl is extremely toxic, and many cases of acute toxicity have been reported. The illness begins with headache, nausea, vomiting, and epigastric or chest pain, followed by cough, hyperpnea, cyanosis, gastrointestinal symptoms, and weakness. The symptoms may be accompanied by fever and leukocytosis and the more severe cases progress to pneumonia, respiratory failure, and eventually to cerebral edema and death (WHO, 1991).

Dermatitis Nickel dermatitis is one of the most common forms of allergic dermatitis: 4 to 9 percent of persons with contact dermatitis react positively to nickels patch tests. Sensitization might occur from any of the metal products in common use, such as coins and jewelry. The notion that increased ingestion of nickel-

containing food increases the probability of external sensitization to nickel is supported by the finding that increased urinary nickel excretion is associated with episodes of acute nickel dermatitis (Liden et al., 1995).

Indicators of Nickel Toxicity Blood nickel levels immediately following exposure to nickel carbonyl provide a guideline as to the severity of exposure and indication for chelation therapy (Sunderman, 1979). Sodium diethyldithiocarbamate is the preferred drug, but other chelating agents, such as D-penicillamine and DMPS, provide some degree of protection from clinical effects.

ESSENTIAL METALS WITH POTENTIAL FOR TOXICITY

This group includes eight metals generally accepted as essential: cobalt, copper, iron, magnesium, manganese, molybdenum, selenium, and zinc. The traditional criteria for nutritionally essential metals is that deficiency produces either functional or structural abnormalities and that the abnormalities are related to or a consequence of specific biochemical changes that can be reversed by the presence of the essential metal (WHO, 1996). There are other metals in this chapter that may be nutritionally essential for vegetative life and may have beneficial health effects in humans but have not met the criteria for essentiality for human health. For essential trace elements, risk assessment requires consideration of both toxicity from excess exposures and health consequences as a result of deficiencies. There is increasing use of various standards that are designed to protect human health from excess exposure but provide risk for health effects from deficiency. Recognition of this problem prompted conferences in the United States and Scandinavia to address aspects of this problem (Mertz et al., 1994; Oskarsson et al., 1995). A methodology has been proposed to determine an acceptable level of oral intake for these metals (Nordberg et al., 1999).

Cobalt (Co)

Cobalt[1] is a relatively rare metal produced primarily as a by-product of other metals, chiefly copper. It is used in high-temperature alloys and in permanent magnets. Its salts are useful in paint dryers, as catalysts, and in the production of numerous pigments. Cobalt, in the form of cobalamin, is an essential component of vitamin B_{12} required for the production of red blood cells and prevention of pernicious anemia. Cobalamin is actually synthesized by intestinal flora, so that in actuality the nutritional requirement for cobalt in humans is as cobalamin produced by intestinal bacteria and not for colbalt ion per se. This consideration has led nutritionists not to regard cobalt as an essential element for humans. However, insufficient natural levels of cobalt in feed stock of sheep and cattle result in cobalt deficiency disease, characterized by anemia and loss of weight or retarded growth. If other requirements for cobalt exist, they are not well understood (WHO, 1996; Herbert, 1996).

The toxicokinetics and possible health effects of cobalt are summarized by Elinder and Friberg (1986), and Schrauzer (1995). Cobalt salts are generally well absorbed after oral ingestion, probably in the jejunum. Despite this fact, increased levels tend not to cause significant accumulation. About 80 percent of the ingested cobalt is excreted in the urine. Of the remaining portion, about 15 percent is excreted in the feces by an enterohepatic pathway, while the milk and sweat are other secondary routes of excretion. The total body burden has been estimated as 1.1 mg. Muscle contains the largest total fraction, but fat has the highest concentration. The liver, heart, and hair have significantly higher concentrations than other organs, but the concentration in these organs is relatively low. The normal levels in human urine and blood are about 1.0 and 0.18 μg/L, respectively. The blood level is largely associated with the concentration in red cells. Significant species differences have been observed in the excretion of radiocobalt. In rats and cattle, 80 percent is eliminated in the feces.

Cobalt has an erythropoietic effect when an excessive amount of cobalt is ingested by most mammals, including humans. High levels of chronic oral administration of cobalt for treatment of anemia may result in the production of goiter, and epidemiologic studies suggest that the incidence of goiter is higher in regions containing increased levels of cobalt in the water and soil. The goitrogenic effect has been elicited by the oral administration of 3 to 4 mg/kg to children in the course of treatment of sickle cell anemia. Toxicity resulting from overzealous therapeutic administration has been reported to produce vomiting, diarrhea, and a sensation of warmth. Intravenous administration leads to flushing of the face, increased blood pressure, slowed respiration, giddiness, tinnitus, and deafness due to nerve damage. Cardiomyopathy has been caused by an excessive intake of cobalt, >10 mg day, particularly from the drinking of beer to which cobalt was added to enhance its foaming qualities. The signs and symptoms were those of congestive heart failure. Autopsy findings have found a tenfold increase in the cardiac levels of cobalt.

Occupational inhalation of cobalt-containing dust in the cemented tungsten carbide industry may cause respiratory irritation at air concentrations of 0.002 to 0.01 mg/m^3. Higher concentrations (0.1 mg Co/m^3 or higher) may be a cause of "hard metal" pneumoconiosis, a progressive form of interstitial fibrosis. Skin contact is sometimes associated with an allergic dermatitis of an erythematous papular type. Affected persons may have positive skin tests.

Injection of cobalt in animal models produces myocardial degeneration. Also, hyperglycemia due to β-cell pancreatic damage has been reported after injection of cobalt into rats. Single and repeated subcutaneous or intramuscular injection of cobalt powder and salts in rats may cause sarcomas at the site of injection. Cobalt is only weakly mutagenic and there is no evidence of carcinogenicity from any other route of exposure.

Trivalent Chromium, Cr(III)

Chromium,[1] the most common form found in nature and chromium in biological materials, is probably always trivalent. There is no evidence that trivalent chromium is converted to hexavalent forms in biological systems. However, hexavalent chromium readily crosses cell membranes and is reduced intracellularly to trivalent chromium.

Essentiality Cr (III) is considered an essential trace nutrient serving as a component of the "glucose tolerance factor." Evidence for the physiologic role of chromium is summarized by Stoecker (1996). It is thought to be a cofactor for insulin action and to have a role in the peripheral activities of this hormone by forming a ter-

[1]Atomic weight, 58.93; periodic table group, VIII; valence, +2 or +3; discovered in 1735.

[1]Atomic weight, 52; periodic table group, VIB; valence, +3; discovered in 1797.

nary complex with insulin receptors, facilitating the attachment of insulin to these sites. The role for chromium in carbohydrate metabolism is based on epidemiologic studies showing that chromium supplementation improved the efficiency of insulin effects on blood lipid profiles. Of 15 controlled studies, only three found no effect on glucose, insulin, or lipids. Subjects with some degree of impaired glucose tolerance were more responsive to chromium supplementation than others. In studies of patients whose total parenteral nutrition solutions contained no chromium, chromium supplementation reduced insulin requirements and glucose intolerance. Other evidence for a physiologic role for chromium is from animal studies. Decreased weight gain has been reported for rats, mice, and guinea pigs whose diets were depleted of chromium. Also, chromium in mouse liver is concentrated in the nuclei 48 h after intraperitoneal injection. Also, Cr(III) bound to DNA in vitro, thus enhancing RNA synthesis. Chromium supplementation in diets of "travel-stressed cattle" significantly decreased serum cortisol and increased serum immunoglobulin. It is recognized, however, that further research is needed to resolve questions about the structure and function of the glucose tolerance factor and other possible physiologic functions of Cr(III). The Food and Nutrition Board of the United States Academy of Sciences has established that an estimated safe and adequate daily intake for chromium in adults ranges from 50 to 200 μg (NRC, 1989).

Copper (Cu)

Copper[1] is widely distributed in nature and is a nutritionally essential element. Ambient air levels are generally low in the United States; for the general population, food, beverages, and drinking water are potential sources of excess exposure. Daily intake of copper in adults varies between 0.9 and 2.2 mg. Intake in children has been estimated to be 0.6 to 0.8 mg/day (0.07 to 0.1 mg/kg body weight per day) (WHO, 1998). The EPA's maximum contaminant level for copper in drinking water is 1.3 mg/L, but this is under revision (EPA, 1994). The provisional WHO guideline for copper in drinking water is 2 mg/L (WHO, 1993). Copper exposures in industry are to particulates in miners or to metal fumes in smelting operations, welding, and related activities.

Toxicokinetics The metabolism and health effects of copper are reviewed by WHO (1996), Sheinberg and Sternlieb (1996), Chan et al. (1998), Harris (1997), and NRC (2000). An overview of copper metabolism is shown in Fig. 23-8.

Gastrointestinal absorption of copper is normally regulated by homeostatic mechanisms. It is transported in serum bound initially to albumin and later more firmly to ceruloplasmin and transcuprein. The normal serum level of copper is 120 to 145 μg/L. The bile is the normal excretory pathway and plays a primary role in copper homeostasis. Most copper is stored in liver and bone marrow, where it may be bound to metallothionein. Copper as Cu(II) entering into hepatocytes is initially reduced and complexed by glutathione prior to binding with metallothionein. Alternatively, copper entering the cell may be exported by a copper ATPase translocase. Copper is not an effective inducer of metallothionein relative to zinc or cadmium. Nevertheless, copper bound to metallothionein is thought to be a normal storage form of copper, particularly in infancy and childhood. Isolated hepatic cells are protected from copper toxicity by prior induction of metallothionein with zinc. Copper-metallothionein accumulates in lysosomes, facilitating the biliary excretion of copper.

The newborn is dependent on stored copper, which may not be adequate in premature infants. The amount of copper in milk is not enough to maintain adequate copper levels in the liver, lungs, and spleen of the newborn. Tissue levels gradually decline up to about 10 years of age, remaining relatively constant thereafter. Brain levels, on the other hand, tend to almost double from infancy to adulthood. The ratio of newborn to adult liver copper levels shows considerable species difference: human, 15:4; rat, 6:4, and rabbit, 1:6. Since urinary copper levels may be increased by soft water, concentrations of approximately 60 μg/L under these conditions are not uncommon.

Essentiality Copper is a component of all living cells and is associated with many oxidative processes. It is an essential component of several metalloenzymes, including type A oxidases and type b monamine oxidases. Of the type B oxidases, cytochrome *c*-oxidase is probably the most important because it catalyzes a key reaction in energy metabolism. Of the type A oxidases, lysyl oxidase plays a major role in elastin and collagen synthesis. There are two forms of superoxide dismutase. The copper/zinc superoxide dismutase is present in the cytosol of most cells, particularly brain, thyroid, liver, and erythrocytes. Both dismutases scavenger superoxide radical by reducing them to hydrogen peroxide. Impairment of the function of these enzymes is responsible for the various diseases associated with copper deficiency (Chan et al., 1998).

Deficiency Copper deficiency is uncommon in humans. The most susceptibile are low-birth-weight infants and infants who were malnourished after birth. Copper deficiency is manifest clinically by hypochromic, microcytic anemia refractory to iron as well as susceptibility to infections. This deficiency is sometimes accompanied by bone abnormalities. Less frequent manifestations are hypopigmentation of the hair and hypotonia. Molybdenum also influences tissue levels of copper. Biomarkers of copper deficiency include ceruloplasmin and serum copper levels, levels of low-density lipoproteins, and cytochrome oxidase activity.

Toxicity Experimental studies in humans suggest that ingestion of drinking water with >3 mg Cu/L will produce gastrointestinal symptoms including nausea, vomiting, and diarrhea (Pizzaro et al., 1999). Ingestion of large amounts of copper salts, most frequently copper sulfate, may produce hepatic necrosis and death. Epidemiologic studies have not found any relation between copper exposure and cancer (WHO, 1998). Individuals with glucose-6-phosphate deficiency may be at increased risk for the hematologic effects of copper, but there is uncertainty as to the magnitude of the risk (Goldstein et al., 1985).

Wilson's Disease Wilson's disease is characterized by the excessive accumulation of copper in liver, brain, kidneys, and cornea. Serum ceruloplasmin is low and serum copper that is not bound to ceruloplasmin is elevated. Urinary excretion of copper is high. Clinical abnormalities of the nervous system, liver, kidneys, and cornea are related to copper accumulation. The disorder is sometimes referred to as *hepatolenticular degeneration* in reference to effects of copper accumulation in the brain. Patients with Wilson's disease have impaired biliary excretion of copper, which is believed to be the fundamental cause of copper overload. Reversal of abnormal copper metabolism is achieved by liver transplantation, con-

[1]Atomic weight, 63.5; periodic table group, IB; valence, +1 or +2; discovered 5000 years ago.

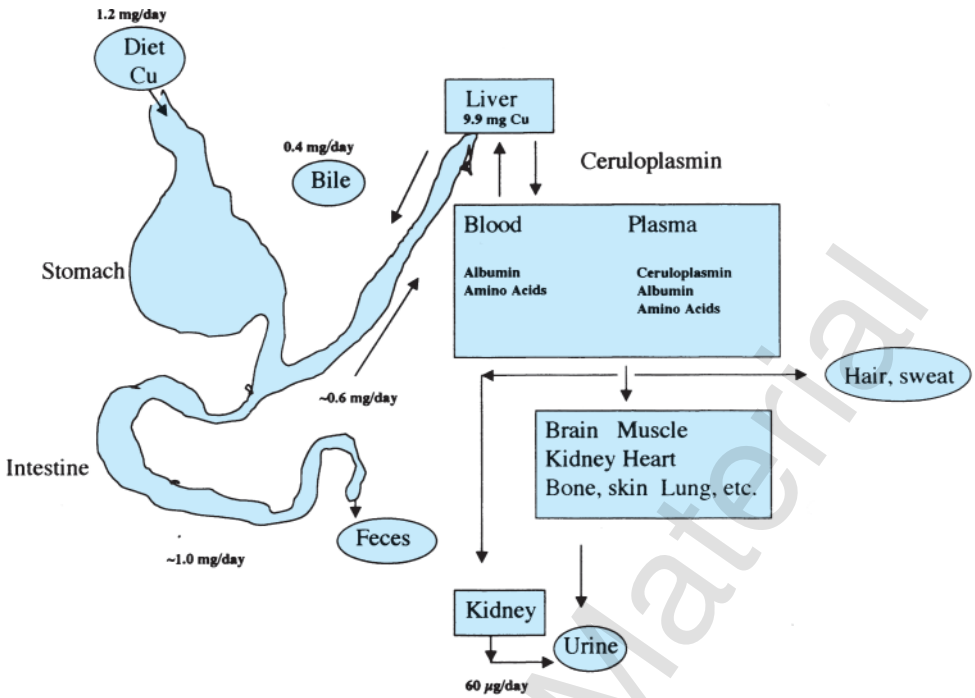

Figure 23-8. Overview of copper absorption, transport, and excretion.

The liver receives copper from the intestine via the portal circulation and redistributes the copper to the tissue via ceruloplasmin, albumin, and amino acids. Approximately half the copper consumed is not absorbed and passes into the feces. Another two-thirds of the daily intake is returned to the liver and released into the bile. Consequently fecal excretion accounts quantitatively for nearly all of the copper consumed as the systems endeavor to stay in balance. A small amount, 60 μg/day, is excreted by the kidney via the urine, and still lesser amounts appear in hair and sweat. This interplay among the various systems maintains homeostasis and balance throughout the organism. The values in the figure are based on a dietary input of 1.2 mg/day. [Adapted from Harris (1997).]

firming that the basic defect is in the liver. Genetic studies have identified a linkage between the Wilson's disease locus (WND) and the erythrocyte enzyme esterase D, establishing that the defect is on chromosome 13 (Frydman et al., 1985). The abnormal gene product, WND protein, converts the energy from ATP hydrolysis to cation transport and is responsible for copper secretion from the liver cell into the biliary canaliculus (Tanzi et al., 1993). However, there appears to be several polymorphisms of the defect, which may explain the clinical variability in the disorder. Diagnosis may be suspected with elevated serum copper but must be confirmed by liver biopsy and elevated liver copper (normal 15 to 55 μg/g; Wilson's disease, >250 μg/g to as high as 300 μg/g). Fibroblasts from persons with Wilson's disease have increased intracellular copper when cultured in Eagle's minimum essential medium with fetal bovine serum (Chan et al., 1983). Clinical improvement can be achieved by chelation of copper with penicillamine (Walshe, 1964). Trien [triethylene tetramine (2HCl)] is also effective and has been used in patients with Wilson's disease who have toxic reactions to penicillamine. The antagonistic effect of zinc on copper absorption may also be useful in the treatment of Wilson's disease (Brewer, 1993). An animal model of Wilson's disease, the Long-Evans cinnamon (LEC) rat, has excessive liver copper and diminished biliary excretion (Schilsky et al., 1994).

Menke's Disease Menke's disease, or Menke's "kinky-hair syndrome," is a sex-linked trait characterized by peculiar hair, failure to thrive, severe mental retardation, neurologic impairment, and death usually by 5 years of age. Bones are osteoporotic with flared metaphases of the long bones and bones of the skull. There is extensive degeneration of the cerebral cortex and of white matter. The symptoms result from copper deficiency and effects on copper-containing enzymes. The gene responsible for Menke's disease produces a cation transporting ATPase and has some homologies with the gene responsible for Wilson's disease (Mercer et al., 1993).

Indian Childhood Cirrhosis (ICC) ICC is a peculiar disorder occurring in young children; it is characterized by jaundice due to an insidious but progressive liver disease. Diagnosis is by liver biopsy. Two distinguishing features are a widespread brown orcein staining (copper) and intralobular fibrosis progressing to portal cirrhosis and inflammation (Pradham et al., 1983). Etiology is not known but suspected to be related to bottle feeding of copper contaminated from storage in brass vessels. However, epidemiologic studies suggest an autosomal recessive genetic component because of strong familial occurrence and high consanguinity among affected children (Sethi et al., 1993).

Idiopathic Copper Toxicosis or Non-Indian Childhood Cirrhosis There are scattered reports of a disorder in children similar to ICC occurring in some western countries (WHO, 1998). The largest non-Indian series of cases are reported by Muller et al. (1996) from the Tyrol region of Austria. This group also used copper vessels to store milk, and the incidence of the disorder has declined since replacement of the copper vessels. A number of other cases have been reported from other parts of the world, some with increased amounts of copper in drinking water (Fewtrell et al., 1996).

Iron (Fe)

The major scientific and medical interest in iron[1] is as an essential metal, but toxicologic considerations are important in terms of iron deficiency and accidental acute exposures and chronic iron overload due to idiopathic hemochromatosis or as a consequence of excess dietary iron or frequent blood transfusions. The complex metabolism of iron and mechanisms of toxicity are detailed by Spivey Fox and Rader (1988) and Yip and Dallman (1996).

Toxicokinetics The disposition of iron is regulated by a complex mechanism to maintain homeostasis, mainly involving intake, stores, and loss. Generally, about 2 to 15 percent is absorbed from the gastrointestinal tract, whereas elimination of absorbed iron, is only about 0.01 percent per day (percent body burden or amount absorbed). Iron absorption is influenced by quantity and bioavailability of dietary iron, amount of storage iron, and rate of erythrocyte production. The best-known enhancer is vitamin C (ascorbic acid). Dietary inhibitors of nonheme iron absorption include calcium phosphate, bran, phytic acid, and polyphenols present in some plants. During periods of increased iron need (childhood, pregnancy, or blood loss), absorption of iron is greatly increased. Absorption occurs in two steps: (1) absorption of ferrous ions from the intestinal lumen into the mucosal cells and (2) transfer from the mucosal cell to plasma, where it is bound to transferrin for transfer to storage sites. Transferrin is a β_1-globulin with a molecular weight of 75,000 and is produced in the liver. As ferrous ion is released into plasma, it becomes oxidized by oxygen in the presence of ferroxidase I, which is identical to ceruloplasmin. There are 3 to 5 g of iron in the body. About two-thirds is bound to hemoglobin, 10 percent in myoglobin and iron-containing enzymes, and the remainder is bound to the iron storage proteins ferritin and hemosiderin. Exposure to iron induces synthesis of apoferritin, which then binds ferrous ions. The ferrous ion becomes oxidized, probably by histidine and cysteine residues and carbonyl groups. Iron may be released from ferritin by reducing agents. Ascorbic acid, cysteine, and reduced glutathione release iron slowly. Normally, excess ingested iron is excreted, and some is contained within shed intestinal cells and in bile and urine and in even smaller amounts in sweat, nails, and hair. Total iron excretion is usually on the order of 0.5 mg/day.

Iron Deficiency Iron deficiency is the most common nutritional deficiency in the United States and worldwide, affecting older infants, young children, and women of childbearing age. The third National Health and Nutrition Examination Survey 1991–1994 identified about 5 percent of children 1 to 2 years of age as iron-deficient. Infants are born with stores of iron roughly proportional to birth weight. Low-birth-weight infants have less stores than full-term infants, so that iron stores are depleted earlier, often by 2 to 3 months of age. The critical period for iron deficiency is between the ages of 6 months and 2 years. The major manifestation of iron deficiency is anemia, diagnosed in the presence of microcytic hypochromic red blood cells and laboratory evidence of iron deficiency. Iron status is determined by measurement of parameters of iron metabolism. For example, low serum ferritin is evidence of iron deficiency. A rise in hemoglobin levels should occur promptly after iron administration. Other effects of iron deficiency include impaired intellectual development, decreased resistance to infection, and possibly increased susceptibility to lead and cadmium toxicity.

Iron Overload With excess exposure to iron or iron overload, there may be a further increase in ferritin synthesis in hepatic parenchymal cells. In fact, the ability of the liver to synthesize ferritin exceeds the rate at which lysosomes can process iron for excretion. Lysosomes convert the protein from ferritin to hemosiderin, which then remains in situ. The formation of hemosiderin from ferritin is not well understood, but it seems to involve denaturation of the apoferritin molecule. With increasing iron loading, ferritin concentration appears to reach a maximum, and a greater portion of iron is found in hemosiderin. Both ferritin and hemosiderin are, in fact, storage sites for intracellular metal and are protective in that they maintain intracellular iron in bound form. A portion of the iron taken up by cells of the reticuloendothelial system enters a labile iron pool available for erythropoiesis and becomes stored as ferritin.

Toxicity Acute iron poisoning from accidental ingestion of iron-containing medicines is the most common cause of acute iron toxicity. It most often occurs in children. A decrease in occurrences of this type followed the use of "childproof" lids on prescription medicines. Severe toxicity occurs after the ingestion of more than 0.5 g of iron or 2.5 g of ferrous sulfate. Toxicity becomes manifest with vomiting 1 to 6 h after ingestion. This is followed by signs of shock and metabolic acidosis, liver damage, and coagulation defects within the next couple of days. Late effects may include renal failure and hepatic cirrhosis. The mechanism of the toxicity is thought to begin with acute mucosal cell damage and absorption of ferrous ions directly into the circulation, which causes capillary endothelial cell damage in the liver.

Chronic iron toxicity or iron overload in adults is a more common problem. There are three basic ways in which excessive amounts of iron can accumulate in the body. The first circumstance is hereditary hemochromatosis due to abnormal absorption of iron from the intestinal tract. The frequency of homozygosity is approximately 3 to 4 per 1000 in populations of European extraction. The heterozygote (incidence about 1 in 10) may also have a lesser degree of increased iron absorption. A second possible cause of iron overload is excess dietary iron. The African Bantu who prepares their daily food and brew fermented beverages in iron pots are classic subjects for this form of iron overload. Sporadic other cases occur owing to excessive ingestion of iron-containing tonics or medicines. The third circumstance in which iron overload may occur is from the regular requirement for blood transfusion for some form of refractory anemia and is sometimes referred to as *transfusional siderosis.* The pathologic consequences of iron overload are similar regardless of basic cause. The body iron content is increased to between 20 and 40 g. Most of the extra iron is hemosiderin. The greatest concentrations are in the parenchymal cells of liver and pancreas as well as in endocrine organs and the heart. Iron in reticuloendothelial cells (in the spleen) is greatest in transfusional siderosis. Further clinical effects may include disturbances in liver function, diabetes mellitus, and even endocrine disturbances and cardiovascular effects. At the cellular level, increased lipid peroxidation occurs, with consequent membrane damage to mitochondria, microsomes, and other cellular organelles. There is epidemiologic evidence for a relationship between iron levels and cardiovascular disease (Sa-

[1]Atomic weight, 56; periodic table group, VIII; valence, +2, +3, +4, or +6; discovered in prehistoric times.

lomen et al., 1992). It has also been suggested that women who are heterozygous for hereditary hemochromatosis are at increased risk for cardiovascular disease (Roest et al., 1999). Experimental evidence suggests that iron may contribute to lipid peroxidation in an early step in the formation of atherosclerotic lesions. Macrophages and endothelial cells are involved, but the details of the mechanism are only speculative (de Valk et al., 1999). Iron loading in mice can alter and damage cellular organelles in heart muscle, including mitochondria, lysosomes, and endoplasmic reticulum (Bartfay et al., 1999).

Treatment of acute iron poisoning is directed toward removal of the ingested iron from the gastrointestinal tract by inducing vomiting or gastric lavage and providing corrective therapy for systemic effects such as acidosis and shock. Desferrioxamine is the chelating agent of choice for the treatment of iron overload absorbed from acute exposure as well as for removal of tissue iron in hemosiderosis. Repeated phlebotomy can remove as much as 20 g of iron per year. Inhalation of iron oxide fumes or dust by workers in metal industries may result in deposition of iron particles in lungs, producing an x-ray appearance resembling silicosis. These effects are seen in hematite miners, iron and steelworkers, and arc welders. Hematite is the most important iron ore (mainly Fe_2O_3).

Magnesium (Mg)

Magnesium[1] is a nutritionally essential metal that can be responsible for adverse health effects due to deficiency or excess (Birch, 1995; Shils, 1996). Nuts, cereals, seafoods, and meats are high dietary sources of magnesium. The drinking water content of magnesium increases with the hardness of the water. Magnesium citrate, oxide, sulfate, hydroxide, and carbonate are widely taken as antacids or cathartics. Magnesium hydroxide, or milk of magnesia, is one of the constituents of the universal antidote for poisoning. Topically, the sulfate also is used widely to relieve inflammation. Magnesium sulfate may be used as a parenterally administered central nervous system depressant. Its most frequent use for this purpose is in the treatment of seizures associated with eclampsia of pregnancy and acute nephritis.

Toxicokinetics Magnesium is a cofactor of many enzymes involved in intermediary metabolism. In the glycolytic cycle converting glucose to pyruvate, there are seven key enzymes that require Mg^{2+}. It is also involved in the citric acid cycle and in the beta oxidation of fatty acids. Magnesium salts are poorly absorbed from the intestine. In cases of overload, this may be due in part to their dehydrating action. Magnesium is absorbed mainly in the small intestine; the colon also absorbs some. Calcium and magnesium are competitive with respect to their absorptive sites, and excess calcium may partially inhibit the absorption of magnesium. Magnesium is excreted into the digestive tract by the bile and pancreatic and intestinal juices. A small amount of radiomagnesium given intravenously appears in the gastrointestinal tract. The serum levels are remarkably constant. There is an apparent obligatory urinary loss of magnesium, which amounts to about 12 mg/day, and the urine is the major route of excretion under normal conditions. Magnesium found in the stool is probably not absorbed. Magnesium is filtered by the glomeruli and reabsorbed by the renal tubules. In the blood plasma, about 65 percent is in the ionic form while the remainder is bound to protein. The former is that which appears in the glomerular filtrate. Excretion also occurs in the sweat and milk. As in the case of other essential elements, physiologic homeostatic mechanisms prevent large fluctuations in blood through changes in absorption and excretion. Approximately 70 percent of serum magnesium is ultrafilterable, and about 95 percent of filtered magnesium is reabsorbed, an important factor in maintaining magnesium homeostasis. Endocrine activity—particularly of the adrenocortical hormones, aldosterone, and parathyroid hormone—also has an effect on magnesium levels, although this may be related to the interaction of calcium and magnesium. Tissue distribution studies indicate that of the 20-g body burden, the majority is intracellular in the bone and muscle including the myocardium, but some magnesium is present in every cell of the body. Bone concentration of magnesium decreases as calcium increases.

Deficiency Deficiency may occur and, in humans, is usually a complication of various disease states that cause intake of magnesium to be impaired (malabsorption syndromes), renal dysfunction with excessive losses, and endocrine disorders. Deficiency in humans causes neuromuscular irritability, frank tetany, and even convulsions. There is a decrease in the magnesium content of ischemic hearts, but the cause and significance are not known.

Deficiency in animals may result from ingestion of grasses grown in magnesium-poor soil. The deficiency is called *grass staggers* in cattle and *magnesium tetany* in calves.

Toxicity Magnesium toxicity can occur when magnesium-containing drugs, usually antacids, are ingested chronically by individuals with serious renal insufficiency. The toxic effects may progress from nausea and vomiting to hypotension, electrocardiograph abnormalities, and secondary central nervous system effects. Magnesium toxicity can be counteracted with calcium infusion.

With industrial exposures, increases of serum magnesium up to twice the normal levels have failed to produce ill effects but were accompanied by calcium increases. Freshly generated magnesium oxide can cause metal fume fever if inhaled in sufficient amounts, analogous to the effect caused by zinc oxide. Both zinc and magnesium exposure of animals produced similar effects.

Manganese (Mn)

Manganese[1] is a transitional metal and can exist in 11 oxidation states, from −3 to +7. The most common valences are +2, +4, and +7. The most common valence in biological systems is +2; +4 is present as MnO_2. Mn^{3+} is also important in biological systems. It is the oxidative state of manganese in superoxide dismutase and is probably the form that interacts with Fe^{3+}. Cycling between Mn^{2+} and Mn^{3+} may be potentially deleterious to biological systems because it can involve the generation of free radicals. Manganese is an essential element and is a cofactor for a number of enzymatic reactions, particularly those involved in phosphorylation, cholesterol, and fatty acids synthesis. Manganese is present in all living organisms. The principal source of intake is food. Veg-

[1]Atomic weight, 55; periodic table group, IIA; valence, +2; discovered in 1831.

[1]Atomic weight, 55; periodic table group, VIIB; valence, +1, +4, +6, or +7; isolated in 1774.

etables, the germinal portions of grains, fruits, nuts, tea, and some spices are rich in manganese (Keen and Zidenberg-Cherr, 1996). Daily manganese intake ranges from 2 to 9 mg. There is current interest in the toxicology of manganese because of potential exposure from the use of the manganese-containing fuel additive MMT (methylcyclopentadienyl Mn tricarbonyl) as a replacement for lead containing additives in gasoline.

The industrial use of manganese has also expanded in recent years as a ferroalloy in the iron industry and as a component of alloys used in welding (Apostoli et al., 2000).

Toxicokinetics Gastrointestinal absorption is less than 5 percent and occurs throughout the length of the small intestine. Manganese is transported in plasma bound to a β_1-globulin, thought to be transferrin, and is widely distributed in the body. Manganese concentrates in mitochondria, so that tissues rich in these organelles—including the pancreas, liver, kidneys, and intestines—have the highest concentrations of manganese. The biological half-life in the body is 37 days. Manganese readily crosses the blood-brain barrier and its half-life in the brain is longer than in the whole body. Manganese is eliminated in the bile and is reabsorbed in the intestine, but the principal route of excretion is with feces.

Deficiency Manganese deficiency has been produced in many species of animals, but so far there are questions about whether deficiency has actually been demonstrated in humans (WHO, 1996). Deficiency in animals results in impaired growth, skeletal abnormalities, and disturbed reproductive function.

Toxicity There are few reported cases of manganese toxicity from oral ingestion. Homeostatic mechanisms involving the liver and biliary excretion, gastrointestinal mechanisms for excreting excess manganese, and perhaps the adrenal cortex, plus the tendency for extremely large doses of manganese salts to cause gastrointestinal irritation, account for the lack of systemic toxicity following oral administration or dermal application. The most common form of manganese toxicity is the result of chronic inhalation of airborne manganese in mines, steel mills, and some chemical industries (ATSDR, 1997). Industrial toxicity from inhalation exposure, generally to manganese dioxide in mining or manufacturing, is of two types: The first, manganese pneumonitis, is the result of acute exposure. Men working in plants with high concentrations of manganese dust show an incidence of respiratory disease 30 times greater than normal. Pathologic changes include epithelial necrosis followed by mononuclear proliferation.

The second and more serious type of disease resulting from chronic inhalation exposure to manganese dioxide, generally over a period of more than 2 years, involves the central nervous system. Chronic manganese poisoning (manganism) produces a neuropsychiatric disorder characterized by irritability, difficulty in walking, speech disturbances, and compulsive behavior that may include running, fighting, and singing. If the condition persists, a mask-like face, retropulsion or propulsion, and a Parkinson-like syndrome develop. The outstanding feature of manganese encephalopathy has been classified as severe selective damage to the subthalamic nucleus and pallidum. These symptoms and the pathologic lesions—degenerative changes in the basal ganglia—make the analogy to Parkinson's disease feasible. In addition to the central nervous system changes, liver cirrhosis is frequently observed. Victims of chronic manganese poisoning tend to recover slowly, even when removed from the excessive exposure. Metal-sequestering agents have not produced remarkable recovery; L-dopa, which is used in the treatment of Parkinson's disease, has been more consistently effective in the treatment of chronic manganese poisoning than in Parkinson's disease (Cotzias et al., 1971).

The oral absorption of manganese is increased by iron deficiency, which may contribute to variations in individual susceptibility. The syndrome of chronic nervous system effects has been duplicated only in squirrel monkeys by inhalation or intraperitoneal injection.

Molybdenum (Mo)

Molybdenum[1] is an essential element and may exist in multiple oxidation states, +3, +4, +5, and +6, facilitating electron transfer. Molybdenum concentration of food varies considerably, depending on the environment in which the food was grown. Molybdenum is added in trace amounts to fertilizers to stimulate plant growth. The average daily human intake in food ranges from 120 to 240 μg/day. The human requirement for molybdenum is low and easily provided by a common U.S. diet; the provisional recommended range for the dietary intake of molybdenum is based on average reported intakes. The concentration of molybdenum in urban air is minimal. Most public water supplies contribute between 2 and 8 μg/day. Excess exposure can result in toxicity to animals and humans (NRC, 1989).

The most important mineral source of molybdenum is molybdenite (MoS_2). The United States is the major world producer of molybdenum. The industrial uses of this metal include the manufacture of high temperature–resistant steel alloys for use in gas turbines and jet aircraft engines and in the production of catalysts, lubricants, and dyes.

Toxicokinetics The soluble hexavalent compounds are well absorbed from the gastrointestinal tract into the liver (Nielson, 1996). It is a component of xanthine oxidase, which has a role in purine metabolism and has been shown to be a component of aldehyde oxidase and sulfite oxidase. In plants, it is necessary for the fixing of atmospheric nitrogen by bacteria at the start of protein synthesis. Increased molybdenum intake in experimental animals has been shown to increase tissue levels of xanthine oxidase. In humans, molybdenum is contained principally in the liver, kidneys, fat, and blood. Of the approximate total of 9 mg in the body, most is concentrated in the liver, kidneys, adrenal, and omentum. More than 50 percent of molybdenum in the liver is contained in a nonprotein cofactor bound to the mitochondrial outer membrane and can be transferred to an apoenzyme, transforming it into an active enzyme molecule. The molybdenum level is relatively low in the newborn and increases until age 20, declining in concentration thereafter. More than half of the molybdenum excreted is in the urine. The blood level is in association with the level in red blood cells. The excretion of molybdenum is rapid, mainly as molybdate. Excesses may be excreted also by the bile, particularly the hexavalent forms.

Deficiency Molybdenum deficiency has been described in various animal species and consists of disturbances in uric acid metabolism and sulfite metabolism, but the clinical manifestation of molybdenum deficiency in humans is still evolving. Molybdenum is a component of sulfite oxidase, which converts sulfite to sulfates.

[1]Atomic weight, 96; periodic table group, VIB; valence, +2, +3, +4, +5(?), or +6.

Molybdenum deficiency resulting from parenteral methionine therapy has been described and is characterized by mouth and gum disorders as well as hypouricemia, hyperoxypurinemia, mental disturbances, and coma. The symptoms are indicative of a defect in sulfur-containing amino acid metabolism; supplementation with ammonium molybdate improved the clinical condition, reversed the sulfur handling defect, and normalized uric acid production. A rare genetic disease characterized by a deficiency of sulfite oxidase has been identified in humans and is characterized by severe brain damage; mental retardation; dislocation of the ocular lenses; increased output of sulfite, *S*-sulfocysteine, and thiosulfate; and decreased output of sulfate (Nielson, 1996).

Toxicity Chronic exposure to excess molybdenum in humans is characterized by high uric acid levels in serum and urine, loss of appetite, diarrhea, anemia, and slow growth. A gout-like disease has been observed in inhabitants of a high-molybdenum area of a province of Russia (Chan et al., 1998). Experimental studies have revealed differences in toxicity of molybdenum salts. In nonruminants, intake of 100 to 5000 mg/kg in food and water was required to produce clinical toxicity. In rats, molybdenum trioxide at a dose of 100 mg/kg/day by inhalation was irritating to the eyes and mucous membranes and subsequently lethal. After repeated oral administration at sufficient levels, fatty degeneration of the liver and kidney was induced (Nielson, 1996).

Selenium (Se)

The availability as well as the toxic potential of selenium[1] and selenium compounds is related to their chemical form and, most importantly, to solubility. Selenium occurs in nature and biological systems as selenate (Se^{6+}), selenite (Se^{4+}), elemental selenium (Se^{0}), and selenide (Se^{22}); deficiency leads to a cardiomyopathy in mammals, including humans (WHO, 1987; Levander and Burk, 1996).

Foodstuffs are a daily source of selenium. Seafoods, especially shrimp, and meat, milk products, and grains provide the largest amounts in the diet. Levels of selenium in river water vary, depending on environmental and geological factors; 0.02 ppm has been reported as a representative estimate. Selenium has also been detected in urban air, presumably from sulfur-containing materials.

Toxicokinetics Absorption of selenium does not appear to be regulated and appears to be very high, above 50 percent, whereas selenites and elemental selenium are virtually insoluble. Because of their insolubility, these forms may be regarded as a form of inert selenium sink. Elemental selenium is probably not absorbed from the gastrointestinal tract. Absorption of selenite is from the duodenum. Monogastric animals have a higher intestinal absorption than ruminants, probably because selenite is reduced to an insoluble form in rumen. Over 90 percent of milligram doses of sodium selenite may be absorbed by humans and widely distributed in organs, with the highest accumulation initially in the liver and kidneys, but appreciable levels remain in the blood, brain, myocardium, skeletal muscle, and testes. Selenium is transferred through the placenta to the fetus, and it also appears in milk. Levels in milk are dependent on dietary intake. Selenium in red cells is associated with glutathione peroxidase and is about three times more concentrated than in plasma. The excretion pattern of a single exposure to selenite appears to have at least two phases, the first being rapid, with as much as 15 to 40 percent of the absorbed dose excreted in the urine the first week. During the second phase there is an exponential excretion of the remainder of the dose, with a half-life of 103 days. The half-life of Se-methionine is 234 days. In the steady state, urine contains about twice as much as feces, and increased urinary levels provide a measure of exposure. Urinary selenium is usually less than 100 μg/L. Excretory products appear in sweat and expired air. The latter may have a garlicky odor due to dimethyl selenide (WHO, 1987).

Essentiality Selenates are relatively soluble compounds, similar to sulfates, and are readily taken up by biological systems. Selenium metabolism is regulated to meet several metabolic needs and is outlined in Fig. 23-9.

Selenophosphate is an anabolic form of selenium involved in the synthesis of selenoproteins and seleno-tRNAs. Selenoprotein synthesis is regulated transcriptionally by tissue specificity, cell development, and environmental factors. Most selenium in animal tissues is present in two forms, selenomethionein, which is incorporated in place of methionine in a variety of proteins, and selenocysteine, a cofactor for both glutathione peroxidase, an enzyme of the antioxidant defense system and type 1 iodothyronine deiodinase, and selenoprotein P. Both enzymes contain one unit of selenocysteine at each of four catalytic sites. Glutathione peroxidase uses glutathione to reduce peroxides in cells and, in this way, protects membrane lipids and possibly proteins and nucleic acids from damage by oxidants or free radicals. It is present in many tissues and in high concentrations in liver, lung, stomach mucosa, erythrocytes and skeletal muscle and has both extracellular and intracellular forms. Type 1 iodothyronine is present in liver, kidney, and skeletal muscle and catalyzes the conversion of thyroxine (T_4) to triodothyronine (T_3). Deficiency of the cofactor may lead to hypothyroidism in the elderly. Selenoprotein P is an abundant extracellular selenoprotein that contains multiple selenocysteine residues and may have an antioxidant functioning in the extracellular space. Biologically active selenium can be assessed by measuring glutathione peroxidase and selenoprotein P concentration. The requirement for selenium is related to the degree of oxidant activity and the supply of nutrients such as zinc, copper, manganese, iron, and vitamin E, so that increased amounts of these elements increase the need for selenium.

Selenium Deficiency The most extensively documented deficiency of selenium in humans is Keshan disease. This is an endemic cardiomyopathy first discovered in Keshan county in the People's Republic of China in 1935. It occurs most frequently in children under 15 years of age and in women of childbearing age. The disease is characterized clinically by various degrees of cardiomegaly and cardiac decompensation, and the histopathology of the myocardium consists of the degeneration and necrosis of myocardial fibers and their replacement by fibrosis and scar formation (Chen et al., 1980). Occurrence of the disease was invariably associated with a lower content of selenium in the diet of maize and rice than that in grain grown in unaffected areas. The average selenium concentration in the hair of residents of affected areas was 0.122 ± 0.010 ppm versus 0.270 ± 0.066 ppm in the hair of people in unaffected areas. Also, low glutathione peroxidase activities of whole blood in the affected population coincided with low blood selenium levels in affected areas. It was suggested that

[1]Atomic weight, 79; periodic table group, VIA; valence, −2, +4, or +6; discovered in 1817.

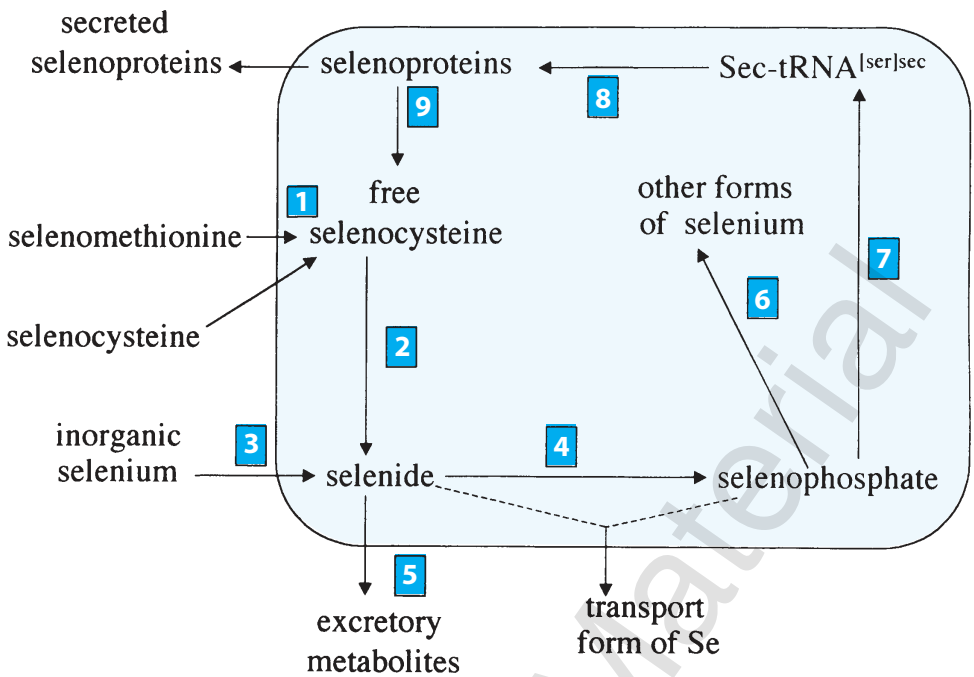

Figure 23-9. Regulated selenium metabolism.

The box represents the cell. The numbers in the squares indicate (1) the transulfuration pathway, (2) selenocysteine β-lyase, (3) reduction by glutathione, (4) selenophosphate synthetase, (5) methylation, (6) replacement of sulfur in tRNA by selenium, (7) replacement of oxygen in serine with selenium to produce selenocysteine, (8) decoding of UGA in mRNA with insertion of selenocysteine into primary structure of protein, and (9) proteolytic breakdown of proteins. The origin and identity of the transport form of selenium is unknown. It might arise from selenide or selenophosphate, as indicated by the broken lines. [Adapted from Levander and Burk

the low blood selenium content and low blood glutathione peroxidase activity might play a role in the myocardial lesions. Administration of sodium selenite greatly reduced the incidence of the disease—a fact that provides additional support for the role of selenium deficiency in the etiology of the disorder.

Deficiency of selenium in lambs and calves produces congenital "white muscle disease," a form of nutritionally induced muscular dystrophy. Deficiency of selenium produces liver necrosis in rats, a bleeding disorder in poultry, and cellular necrosis in the liver, kidneys, and skeletal and heart muscle in mice, resulting in cardiac failure and death. In each of these entities the health effect is prevented by adding selenium to the diet, so that now there are well-defined dietary requirements for selenium for livestock and poultry (WHO, 1987).

Toxicity Selenium toxicity occurs when the intake exceeds the excretory capacity. The potential toxicity of selenium was first suspected over 50 years ago and, through the years, well-defined syndromes of toxicity have been described in animals and humans living in seminiferous areas where the soil content is relatively rich in selenium, contributing to relatively high selenium in vegetation. Plants vary in their ability to accumulate selenium. Grasses, grains, and most weeds do not accumulate selenium even when grown in high-selenium areas, so that these plants add very little to the selenium content of livestock feed. But there are several plant species that are classified as "selenium accumulators" and they may contain selenium levels of 100 to 10,000 mg/kg. These plants, however, usually grow in nonagricultural areas and when consumed by livestock may, within a few weeks, cause a disease syndrome described as the *blind staggers.* Early symptoms are impaired vision, depressed appetite, and a tendency to wander in circles. This may progress to various degrees of paralysis and death from respiratory failure (Alexander et al., 1987). A more chronic syndrome described in livestock and horses is *alkali disease,* characterized by the loss of vitality, emaciation, deformity and shedding of hoofs, loss of long hair, and erosion of joints of long bones. Similar syndromes have been described in sheep and dogs. The areas of the world where human toxicity has been noted include several areas of China, areas of Venezuela, and parts of the state of South Dakota in the United States. A study of 70 families living in three counties of South Dakota and in one county of northern Nebraska, from farms where alkali disease in cattle had been recognized, found bad teeth, a yellowish discoloration of the skin, skin eruptions, and diseased nails of the fingers and toes in various family members. A syndrome now believed to be the result of selenium intoxication was discovered in 1961 to affect about 50 percent of 248 inhabitants of five villages in the Hubei province of China (Yang et al., 1983). There are similarities between this syndrome and the chronic effects in livestock and horses. The main symptoms were brittle hair with intact follicles, brittle nails with spots and streaks, and skin lesions on the backs of hands and feet and on the forearms, legs, and the back of the neck. These areas were red and swollen and contained blisters. In addition, 13 of 22 people in one village had neurologic symptoms, including peripheral anesthesia, pain, and hyperreflexia. In some individuals, these symptoms progressed to numbness, convulsions, paralysis, and altered motor function. Selenium has produced loss of fertility and congenital defects and is considered embryotoxic and teratogenic on the basis of animal experiments (WHO, 1987).

Biological Interactions Selenium has various biological interactions, which may affect the toxicity or deficiency of selenium as well as toxicity of another metal. If the intake of vitamin E is low, susceptibility to selenium toxicity is increased in experimental animals, whereas resistance is increased if vitamin E intake is increased. Selenium also forms insoluble complexes with silver, copper, cadmium, and mercury. Feeding silver to experimental animals results in tissue accumulations of both metals and symptoms of selenium deficiency may occur. Selenium forms complexes with copper, and toxicity to either selenium or copper is influenced by the intake of both metals. Selenium may prevent the toxic effects of cadmium on rat testicular tissue and dietary selenium can reduce the toxic effects of methyl mercury. Workers in a mercury mine and local inhabitants accumulate equimolar amounts of mercury and selenium in the pituitary and thyroid glands and in the brain. And finally, arsenite increases the biliary excretion of selenium, enhancing selenium excretion in urine. The mechanisms for these interactions are only partially understood, but their occurrence certainly influences the determination of safe and toxic levels of selenium for persons in the general population (WHO, 1987, 1996).

Anticarcinogenicity Selenium has been suspected of being a human carcinogen, but further studies have shown that it has anticarcinogenic properties (WHO, 1987).

Epidemiologic investigations have indicated a decrease in human cancer death rates (age- and sex-adjusted) correlated with an increasing selenium content of forage crops. In addition, experimental evidence supports the antineoplastic effect of selenium with regard to benzo[a]pyrene- and benzanthracene-induced skin tumors in mice, *N*-2-fluorenylacetamide- and diethylaminoazobenzene-induced hepatic tumors in rats, and spontaneous mammary tumors in mice. A possible mechanism of the protective effects of selenium has been postulated to involve inhibition of the formation of malonaldehyde, a product of peroxidative tissue damage, which is carcinogenic. In addition to the apparent protective effect against some carcinogenic agents, selenium is an antidote to the toxic effects of other metals, particularly arsenic, cadmium, mercury, copper, and thallium. The mechanism underlying these interactions is unknown.

Dose Effect in Humans Because of the potential for producing adverse health effects from both selenium excess and from deficiency, risk assessment must include both possible effects. The National Research Council's Food and Nutrition Board (NAS, 1980) recommends 200 μg/day as the maximum safe upper limit for an adult human's intake. Metabolic balance studies on North American adults showed that 70 μg/day for the standard human (70 kg body weight) appears to be required to maintain selenium balance and presumably to satisfy selenium requirements in these subjects. Chinese data indicate that daily intake of less than 20 μg can cause Keshan disease. Countries such as New Zealand have areas where daily intake is around 30 μg, but there is no evidence that this has a significant effect on the health of the people living in these areas. The critical level for prevention of deficiency, therefore, is 20 μg/day.

Zinc (Zn)

Zinc[1] is a nutritionally essential metal, and a deficiency results in severe health consequences. At the other extreme, excessive exposure to zinc is relatively uncommon and occurs only at very high levels. Zinc is ubiquitous in the environment, so that it is present in most foodstuffs, water, and air. The zinc content of substances in contact with galvanized copper or plastic pipes may be increased. Seafoods, meats, whole grains, dairy products, nuts, and legumes are high in zinc, while vegetables are lower, although zinc applied to soil is taken up by growing vegetables. Atmospheric zinc levels are higher in industrial areas (NRC, 2000).

Essentiality and Metabolism More than 200 metalloenzymes belonging to six major categories—including oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases—require zinc as a cofactor (Cousins, 1996). Zinc induces the synthesis of metallothionein, which is a factor in regulating the metabolism of zinc, including absorption and storage (Nordberg, 1998; Miles et al., 2000). Zinc is a functional component of several proteins that contribute to gene expression and regulation of genetic activity. Zinc chelates with cysteine and/or histidine in a tetrahedral configuration forming looped structures, called "zinc fingers," which bind to specific DNA regions and are bound in various transcription factors such as steroid hormone receptors and polymerase (Berg and Shi, 1996; Wang et al., 1997). Zinc has a normal physiologic role in membrane stabilization by binding ligands in membranes for maintenance of the normal structural geometry of the protein and lipid components (Cousins, 1996). Zinc is essential for the development and normal function of the nervous system.

Zinc has a role in immune function and the cytokines, primarily interleukin-1 (IL-1) and IL-6, influence zinc metabolism (Cousins, 1996). Zinc is required for optimal vitamin A metabolism. Although the mechanisms for intestinal absorption of iron and zinc differ, they appear to be inverse. There is a reciprocal relationship between plasma levels of zinc and copper, to the degree that massive zinc ingestion may produce copper deficiency and large doses of elemental zinc result in negative copper balance in patients with Wilson's disease. The metabolisms of zinc and calcium are interrelated in that zinc is required for normal calcification of bone (Leek et al., 1988).

Toxicokinetics The average daily intake for Americans is approximately 12 to 15 mg, mostly from food. Gastrointestinal absorption of zinc is homeostatically controlled and is probably a carrier-mediated process (Cousins, 1996; WHO, 1996). It is influenced by prostaglandins E_2 and F_2 and is chelated by picolinic acid, a tryptophan derivative. A deficiency of pyridoxine or tryptophan depresses zinc absorption. Within the mucosal cell, zinc induces metallothionein synthesis and, when the cell is saturated, this may depress zinc absorption. In the blood, about two-thirds of the zinc is bound to albumin and most of the remainder is complexed with β_2-macroglobulin. Zinc enters the gastrointestinal tract as a component of metallothionein secreted by the salivary glands, intestinal mucosa, pancreas, and liver. The normal basic physiologic requirement for absorbed zinc is 1.4 mg/day. Assuming 20 percent absorption, a daily diet of 7 mg will meet the basic requirement for males, but the requirement for females is greater during pregnancy and lactation. Adaptation to low dietary zinc will increase gastrointestinal absorption to as much as 50 percent. Bile is the major route of zinc excretion. Homeostatic control of zinc is maintained primarily by fecal excretion of endogenous zinc. Urinary excretion of zinc is low and not significantly influenced by dietary zinc. Zinc concentration in tissues varies widely. The liver receives up to about 40 percent of a tracer dose, declining to about 25 dto

[1]Atomic weight, 65; periodic table group, IIB; valence, +2; discovered in the thirteeth century.

cent within 5 days. Liver concentration is influenced by humoral factors, including adrenocorticotropic hormone, parathyroid hormone, and endotoxin. In the liver as well as in other tissues, zinc is bound to metallothionein. The greatest concentration of zinc in the body is in the prostate, probably related to the rich content of zinc-containing enzyme acid phosphatase.

Assessment of Zinc Status The concentration of zinc in the plasma is not a sensitive indicator of zinc status and does not reflect the dose-response relationship between zinc levels in the body and effects at various target sites. Other approaches include measurement of zinc levels in hair and nails and in urine and zinc in shed teeth from children. The most reliable index of zinc status is the determination of zinc balance—that is, the relationship between intake and excretion—but these measurements require the facilities of a metabolic research unit in order to control dietary zinc intake while measuring excretion. An alternative approach is to identify a biomarker sensitive to changes in zinc status, such as metallothionein, serum alkaline phosphatase, and erythrocyte superoxide dismutase. The thymic hormone thymulin, which is involved in the differentiation of T cells, is zinc-dependent (Prasad et al., 1988). Reduced activity of this hormone may provide an early indication of mild zinc deficiency.

Deficiency Zinc deficiency results in a wide spectrum of clinical effects depending on age, stage of development, and deficiencies of related metals. Zinc deficiency in humans was first characterized by Prasad (1983) in adolescent Egyptian boys with growth failure and delayed sexual maturation accompanied by protein-calorie malnutrition, pellegra, and iron and folate deficiency. Zinc deficiency in the newborn may be manifest by dermatitis, loss of hair, impaired healing, susceptibility to infections, and neuropsychological abnormalities. Dietary inadequacies coupled with liver disease from chronic alcoholism may be associated with dermatitis, night blindness, testicular atrophy, impotence, and poor wound healing. Other chronic clinical disorders— such as ulcerative colitis and the malabsorption syndromes, chronic renal disease, and hemolytic anemia — are also associated with zinc deficiency. Many drugs affect zinc homeostasis, particularly metal-chelating agents and some antibiotics, such as penicillin and isoniazid. Less common zinc deficiency may occur with myocardial infarction, arthritis, and even hypertension (Walshe et al., 1994). Latent zinc deficiency is the most common zinc deficiency syndrome, implying marginally adequate zinc status. This may be the result of zinc-deficient dietary habits, particularly among young children or the elderly, or may occur as a consequence of a disease state (USDA, 1986). Zinc deficiency in growing children may result in poor growth performance, which has been shown to be improved with zinc supplementation (Prentice, 1997).

Zinc in Neurologic Disorders Because of its requirement as a cofactor for numerous enzymes and proteins, zinc has been implicated in various degenerative diseases of the nervous system (Prasad, 1995). It has been suggested that zinc modulates the solubility of β-amyloid in the brain and contributes to the formation of degenerative plaques in brains of patients with Alzheimer's disease. Also, zinc deficiency may alter activity of the antioxidant enzyme Cu-Zn-superoxide dismutase (SOD), resulting in excess free radicals that are damaging to cell membranes (Cuajungco and Lees, 1997). A genetic abnormality of one of the forms of Cu-Zn SOD may be the basis of a familial form of amyotrophic lateral sclerosis (Lyons, 1996).

Toxicity Acute zinc toxicity from excessive ingestion is uncommon, but gastrointestinal distress and diarrhea have been reported following ingestion of beverages standing in galvanized cans or from the use of galvanized utensils. However, evidence of hematologic, hepatic, or renal toxicity has not been observed in individuals ingesting as much as 12 g of elemental zinc over a 2-day period.

With regard to industrial exposure, metal fume fever resulting from inhalation of freshly formed fumes of zinc presents the most significant effect. This disorder has been most commonly associated with inhalation of zinc oxide fumes, but it may be seen after inhalation of the fumes of other metals, particularly magnesium, iron, and copper. Attacks usually begin after 4 to 8 h of exposure—chills and fever, profuse sweating, and weakness. Attacks usually last only 24 to 48 h and are most common on Mondays or after holidays. The pathogenesis is not known, but it is thought to result from endogenous pyrogen release due to cell lysis. Extracts prepared from tracheal mucosa and from the lungs of animals with experimentally induced metal fume fever produce similar symptoms when injected into other animals. Exposure of guinea pigs for 3 h/day for 6 consecutive days to 5 mg/m^3 of freshly formed ultrafine zinc oxide (the recommended threshold limit value) produced decrements in lung volumes and carbon monoxide diffusing capacity that persisted for 72 h after exposure. These functional changes were correlated with microscopic evidence of interstitial thickening and cellular infiltrate in alveolar ducts and alveoli (Lam et al., 1985).

Carcinogenicity Epidemiologic studies of workers in lead industries have not found any evidence of a relationship between zinc and cancer (Logue et al., 1982). Testicular tumors have been produced by direct injection in rats and chickens. This effect is probably related to the concentration of zinc normally in the gonads and may be hormonally dependent (Walshe et al., 1994).

METALS RELATED TO MEDICAL THERAPY

Metals considered in this group include aluminum, bismuth, gold, lithium, and platinum. Metals at one time were used to treat a number of human ills, particularly heavy metals like mercury and arsenic. Gold salts are still useful for the treatment of forms of rheumatism, and organic bismuth compounds are used to treat gastrointestinal disturbances. Lithium has become an important aid in the treatment of depression. The toxicologic hazards from aluminum are not from its use as an antacid but rather from the accumulations that occur in bone and from neurotoxicity in patients with chronic renal failure receiving hemodialysis therapy. A more recent concern regarding the potential neurotoxicity of aluminum involves its relationship to Alzheimer's dementia and its increase in bioavailability from changes in soil and water pH from acid rain. Platinum is receiving attention as an antitumor agent. Barium and gallium are used as radiopaque and radiotracer materials, respectively, and gallium is used for treating hypercalcemia.

Aluminum (Al)

Aluminum[1] is the most abundant metal and the third most abundant element in the earth's crust. Due to its high reactivity, aluminum is not found in the free state in nature. All the chemical

[1]Atomic weight, 26.98; periodic table group, III; valence, +3; first isolated in 1825.

compounds involve aluminum in the +3 valence state (Al^{3+}). As a hard trivalent ion, Al^{3+} binds strongly to oxygen-donor ligands such as citrate and phosphate. The chemistry of aluminum compounds is complicated by a tendency to hydrolyze and form polynuclear species, many of which are sparingly soluble (Harris et al., 1996).

Aluminum has, until recently, existed predominantly in forms that are not available to humans and most other species. Acid rain, however, has dramatically increased the amount of aluminum appearing in biological ecosystems, resulting in well-described destructive effects on fish and plant species. However, it is not bioaccumulated to any significant extent except in the tea plant.

Aluminum has many uses, mainly in the form of alloys in packaging, building, construction, transportation, and electrical applications. Over 95 percent of beer and carbonated drinks are packaged in two-piece aluminum cans. Cooking in aluminum utensils results in the transfer of aluminum to food. Human exposure to aluminum comes from food and drinking water as well as from pharmaceuticals. The normal average daily intake is 1 to 10 mg for adults (Greger, 1992).

Toxicokinetics Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Inhalation of particulate aluminum may result in direct transfer to brain tissue via the olfactory system (Roberts 1986; Perl and Good, 1987). Approximately 0.1 percent of aluminum in the diet is absorbed, but this figure may rise to 1 percent depending on speciation. Absorption from the gut depends largely on pH and the presence of complexing ligands, particularly carboxylic acids, which are absorbable. For example, intestinal absorption is enhanced in the presence of citrate. However, the citrate complex is not itself absorbed. Apparently citrate makes aluminum available to other transport pathways across the gastrointestinal (GI) tract (Jouhanneau et al., 1997). Silicon is a potent inhibitor of GI absorption of aluminum and may also accelerate urinary excretion (Flaten et al, 1993). It probably interacts with aluminum to form poorly absorbed hydroxyalumino-silicates.

Biological speciation is also of major importance in distribution, and excretion of aluminum in mammals. In plasma, 80 to 90 percent of aluminum binds to transferrin, an iron-transport protein for which there are receptors in many body tissues. Based on potentiometric and nuclear magnetic resonance studies, it is predicted that the remainder of aluminum in plasma is in the form of small-molecule hydroxy species and small complexes with carboxylic acids, phosphate, and, to a lesser degree, amino acids (DeVoto and Yokel, 1994).

Bone and lung have the highest concentrations of aluminum, suggesting that bone may be a sink for aluminum. It does not normally accumulate in blood to any great extent (Ganrote, 1986). It is removed from blood by the kidneys and excreted in urine. Uremic animals and humans have higher-than-normal levels of aluminum in spite of increased urinary clearance.

Aluminum compounds can affect absorption of other elements in the gastrointestinal tract and alter intestinal function. Aluminum inhibits fluoride absorption and may decrease the absorption of calcium and iron compounds and salicylic acid, which, in turn, may affect the absorption of aluminum (Exley et al., 1996). The absorption of cholesterol may be inhibited by forming an aluminum pectin complex that binds fats to nondigestible vegetable fibers (Nagyvary and Bradbury, 1977). The binding of phosphorus in the intestinal tract can lead to phosphate depletion and osteomalacia. Aluminum may alter gastrointestinal tract motility by inhibition of acetylcholine-induced contractions and may be the explanation of why aluminum-containing antacids often produce constipation.

Toxicity In cases of human toxicity, the target organs are the lung, bone, or central nervous system. Aluminum affects the same target organs in animals as well as producing developmental effects. In addition, aluminum released into bodies of fresh water via the action of acid rain kills fish by damaging the gills (Flaten et al., 1993).

Lung and Bone Toxicity Occupational exposure to aluminum dusts can produce lung fibrosis in humans. The effects are probably due to lung overload caused by excessive deposits of dust (Morrow, 1992). Osteomalacia has been associated with excessive intake of aluminum-containing antacids in otherwise healthy individuals; this is assumed to be due to interference with intestinal phosphate absorption. Osteomalacia also can occur in uremic patients exposed to aluminum in the dialysis fluid. In these patients, osteomalacia may be a direct effect of aluminum on bone mineralization as bone levels are high.

Neurotoxicity Aluminum has markedly different effects on animals at different points in their life span and in different species. The normal concentration of aluminum in the mammalian brain is approximately 1 to 2 μg/g. In certain aluminum-sensitive species, such as cats and rabbits, increased aluminum by intrathecal infusion so that brain concentration is greater than 4 μg/g induces a characteristic clinical and pathologic response. Initially, animals show subtle behavioral changes, including learning and memory deficits and poor motor function. These changes progress to tremor, incoordination, weakness, and ataxia. This is followed by focal seizures and death within 3 or 4 weeks of initial exposure. With lesser doses, there is longer survival but no recovery (DeBoni et al., 1976).

The most prominent early pathologic change is an accumulation of neurofibrillary tangles (NFT) in cell body, proximal axons, and dendrites of neurons of many brain regions. This is associated with loss of synapses and atrophy of the dendritic tree. Not all species show this reaction to aluminum, however. The rat fails to develop NFTs or encephalopathy and the monkey develops these only after more than a year following aluminum infusion. NFTs are found primarily in large neurons such as Purkinje cells of the cerebellum and large neurons of the cerebral cortex. There is marked reduction in the numbers of neurotubules and the rate of cytoplasmic transport with impairment of intracellular transport. Aluminum also interacts with neuronal chromatin or DNA and is associated with a decreased rate of DNA synthesis. RNA polymerase activity is also reduced.

Aluminum competes with or alters calcium metabolism in several organ systems including the brain. Brain tissue calcium rises following aluminum exposure. Aluminum also binds to calmodulin and induces changes in its structure, leading to the suggestion that aluminum impairs the function of calmodulin as a calcium regulator. While these studies in animals have provided some insights into the mechanisms of the neurotoxicity of aluminum in experimental models, the relationship to human disease is presently uncertain (Siegel and Hagu, 1983; Bizzi and Gambetti, 1986; Birchall and Chappel, 1988).

Human Dementia Syndromes ***Dialysis Dementia*** A progressive, fatal neurologic syndrome has also been reported in patients on long-term intermittent hemodialysis treatment for chronic renal

failure (Alfrey, 1993). The first symptom in these patients is a speech disorder followed by dementia, convulsions, and myoclonus. The disorder, which typically arises after 3 to 7 years of dialysis treatment, may be due to aluminum intoxication. The aluminum content of brain, muscle, and bone tissues increases in these patients. Sources of the excess aluminum may be from oral aluminum hydroxide commonly given to these patients or from aluminum in dialysis fluid derived from the tap water used to prepare the dialysate fluid. The high serum and aluminum concentrations may be related to increased parathyroid hormone, which is due to the low blood calcium and osteodystrophy common in patients with chronic renal disease. The syndrome may be prevented by avoidance of the use of aluminum-containing oral phosphate binders and by monitoring of aluminum in the dialysate. Chelation of aluminum may be achieved with use of desferrioxamine, and progression of the dementia may be arrested or slowed (Wills and Savory, 1983).

Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Syndromes of Guam (Guam ALS-PD Complex) The Chamorro peoples of the Marina Islands in the western Pacific Ocean, particularly Guam and Rota, have an unusually high incidence of neurodegenerative diseases associated with nerve cell loss and neurofibrillary degeneration of the Alzheimer's type. Garruto et al. (1984) noted that the volcanic soils of the regions of Guam with a high incidence of ALS-PD contained high concentrations of aluminum and manganese and were low in calcium and magnesium. They postulated that a low intake of calcium and magnesium induced secondary hyperparathyroidism, resulting in an increase in calcium, aluminum, and other toxic metals, resulting in neuronal injury and death. How and why aluminum enters the brain of these people is unclear. A recent study of mineral content of food did not indicate high exposure to aluminum or low dietary calcium (Crapper-McLachlan et al., 1989). These authors suggest that the diet of the inhabitants of Guam may be the source of the aluminum, particularly through the respiratory tract. Perl and Good (1987) have shown that aluminum may be taken up through nasal-olfactory pathways. On the other hand, the consumption of the neurotoxic seed of the false sago palm tree may also play a role in the prevalence of ALS in these areas.

Alzheimer's Disease A possible relationship between aluminum and Alzheimer's disease has been a matter of speculation for many decades. The basis for this relationship is the finding of increased aluminum levels in Alzheimer brains, neurofibrillary lesions in experimental animals, and the fact that aluminum is associated with various components of the pathologic lesions in Alzheimer brain tissue. However, elevated aluminum levels in Alzheimer brains may be a consequence and not a cause of the disease. The reduced blood-brain barrier in Alzheimer's might allow more aluminum into the brain (Banks et al., 1988; Liss and Thornton, 1986; Shore and Wyatt, 1983). Also, recent studies have raised the possibility that the staining methods in earlier studies may have lead to aluminum contamination (Makjanic et al., 1998). Furthermore, the neurofibrillary tangles seen in aluminum encephalopathy differ structurally and chemically from those in Alzheimer's (Goyer, 1996).

Epidemiologic and case-control studies examining the role of aluminum exposure in Alzheimer's disease arrive at conflicting conclusions. Some studies have found significant associations (Martyn et al., 1989; McLachlan et al., 1996; Michel et al., 1990) whereas other studies did not find a significant relationship (Forster et al., 1995; Martyn et al., 1997; Wettstein et al., 1991).

In conclusion, whereas a causative role for aluminum in the etiology of Alzheimer's and other neurodegenerative diseases has not been established, observations on dialyzed patients provide convincing evidence that aluminum is the causative agent of "dialysis dementia."

Bismuth (Bi)

Bismuth[1] has a long history of use in pharmaceuticals in Europe and North America. Both inorganic and organic salts have been used, depending on the specific application. Trivalent insoluble bismuth salts are used medicinally to control diarrhea and other types of GI distress. Various bismuth salts have been used externally for their astringent and slight antiseptic properties. Bismuth salts have also been used as radiocontrast agents. Further potential for exposure comes from the use of insoluble bismuth salts in cosmetics. Injections of soluble and insoluble salts, suspended in oil to maintain adequate blood levels, have been used to treat syphilis. Bismuth sodium thioglycollate, a water-soluble salt, was injected intramuscularly for malaria (*Plasmodium vivax*). Bismuth glycolyarsanilate is one of the few pentavalent salts that have been used medicinally. This material was formerly used for treatment of amebiasis (Fowler and Vouk, 1986). Exposure to various bismuth salts for medicinal use has decreased with the advent of newer therapeutic agents.

Recently there has been an increased interest in bismuth to treat peptic ulcer disease. This interest was prompted by the discovery in 1982 of a gram-negative bacterium from the gastric mucosa of patients suffering from gastritis. The bacterium, *Helicobacter pylori,* is now thought to predispose patients with chronic gastritis to peptic ulcer formation and duodenal ulceration. Antacids containing bismuth compounds have been effective in promoting healing of peptic ulcers, which is now thought to be due to the antibacterial action of bismuth.

Toxicokinetics Most bismuth compounds are insoluble and poorly absorbed from the GI tract or when applied to the skin, even if the skin is abraded or burned. The three compounds used clinically, colloidal tripotassium dicitrato bismuthate, bismuth subsalicylate (Pepto Bismol) and bismuth citrate are also poorly absorbed (less than 1 percent of an oral dose) (Tillman et al., 1996). Binding in blood is thought to be due largely to a plasma protein with a molecular weight greater than 50,000. In vitro studies have shown the Bi^{3+} binds to serum transferrin (Li et al., 1996). Tissue distribution, omitting injection depots, reveals the kidney as the site of the highest concentration (Zidenberg et al., 1989), probably due to its capacity to induce metallothionein (Tanaka-Kagawa et al., 1993). Passage of bismuth into the amniotic fluid and into the fetus has been demonstrated. The urine is the major route of excretion. It is also secreted in bile in association with glutathione (Gyurasics et al., 1992). Traces of bismuth can be found in milk and saliva. The elimination half-life is reported to be about 21 days (Froomes et al., 1989); but after injection, elimination of total bismuth may be slow, depending on its mobilization from the injection site.

Toxicity Acute renal failure can occur following oral administration of such compounds as bismuth sodium triglycocollamate or thioglycollate, particularly in children (Urizar and Vernier, 1966). The tubular epithelium is the primary site of toxicity, producing degeneration of renal tubular cells and nuclear inclusion bodies

[1]Atomic weight, 209; periodic table group, VA; valence, +3 or +5; discovered in 1753.

composed of a bismuth-protein complex analogous to those found in lead toxicity (Fowler and Goyer, 1975).

The symptoms of chronic toxicity in humans consist of decreased appetite, weakness, rheumatic pain, diarrhea, fever, metal lines on the gums, foul breath, gingivitis, and dermatitis. Jaundice and conjunctival hemorrhage are rare but have been reported. Bismuth nephropathy with proteinuria may occur. In the 1970s reports appeared from France and Australia of a unique encephalopathy occurring in colostomy and ileostomy patients using bismuth subgallate, subnitrate, and subcarbonate for control of fecal odor and consistency (Slikkerveer and de Wolff, 1989). The symptoms included progressive mental confusion, irregular myoclonic jerks, a distinctive pattern of disordered gait, and a variable degree of dysarthria. The disorder was fatal to patients who continued use of the bismuth compounds, but full recovery was rapid in those in whom therapy was discontinued. The severity of the disorder seemed to be independent of dose and duration of therapy (Thomas et al., 1977). Bismuth-containing paste dressings have produced encephalopathy when applied to brain tissues after neurosurgery (Sharma et al., 1994).

Chelation therapy using dimercaprol (BAL) is said to be helpful in the removal of bismuth from children with acute toxicity (Arena, 1974).

Gallium (Ga)

The main valence state of gallium[1] is +3 (gallic), but the +2 (gallous) also can form stable compounds. Gallium is of interest because of the use of radiogallium as a diagnostic tool for the localization of bone lesions and the use of nonradioactive gallium nitrate, $Ga(NO_3)_3$ as an antitumor agent. Also, it has recently been approved in the United States for the treatment of hypercalcemia. Gallium is obtained as a by-product of copper, zinc, lead, and aluminum refining and is used in high-temperature thermometers, as a substitute for mercury in arc lamps, as a component of metal alloys, and as a seal for vacuum equipment. It is the only metal other than mercury that is liquid at or near room temperature.

Toxicokinetics Gallium is sparsely absorbed from the GI tract, but concentrations of less than 1 ppm can be localized radiographically in bone lesions. Higher doses will allow one to visualize the liver, spleen, and kidney as well (Hayes, 1988). Gallium binds to plasma transferrin and enters cells on iron (Fe^{3+}) transport mechanisms. Urine is the major route of excretion. The half-life in the body is about 4 to 5 days.

Toxicity Clinical studies on $Ga(NO_3)_3$ as an antitumor agent, reveal that it accumulates in metabolically active regions of bone and increases the calcium and phosphate content. It inhibits osteoclastic bone resorption without poisoning the osteoclast cells (Bockman, 1991). Therapeutic trials with intravenous doses indicate that nephrotoxicity is dose-limiting. Other effects include nausea, vomiting, and anemia with mild leukopenia. Less frequent are neurologic, pulmonary, and dermatologic effects. It can elicit a variety of biochemical and hormonal changes. The mechanism of bone uptake and inhibition of bone resorption is not known, but the gallate anion, $Ga(OH)_4^-$, may be the active species. Uptake by and effects on other cells may be explained by Ga^{3+} competition with Fe^{3+} for transferrin and other iron-binding proteins leading the depletion of intracellular iron and apoptosis. [For a detailed review, see Bernstein (1998).]

Administration of gallium arsenide to experimental animals results in arsenic intoxication (Webb et al., 1984). There are no reported adverse effects of gallium following industrial exposure.

Gold (Au)

Gold[1] is widely distributed in small quantities, but economically usable deposits occur as the free metal in quartz veins or alluvial gravel. Gold is almost always found in association with silver. Seawater contains 3 or 4 mg/ton and small amounts, 0.03 to 1 percent, have been reported in many foods. Gold has a number of industrial uses because of its electrical and thermal conductivity. While gold and its salts have been used for a wide variety of medicinal purposes, their present uses are limited to the treatment of rheumatoid arthritis and rare skin diseases such as discoid lupus.

Toxicokinetics Gold salts are poorly absorbed from the gastrointestinal tract. The upper limit of normal levels can be considered to be 0.5 μg/L for both whole blood and urine (Perelli and Piolotto, 1992). After injection of most of the soluble salts, gold is excreted via the urine, while the feces account for the major portion of insoluble compounds. Gold seems to have a long biological half-life, and detectable blood levels can be demonstrated for 10 months after cessation of treatment. Trivalent gold binds strongly to metallothionein (Saito and Kuraski, 1996).

Toxicity Dermatitis is the most frequently reported toxic reaction to gold and is sometimes accompanied by stomatitis probably involving allergic mechanisms (Hostynek, 1997). The use of gold in the form of organic salts to treat rheumatoid arthritis may be complicated by the development of proteinuria and the nephrotic syndrome, which morphologically consists of an immune-complex glomerulonephritis, with granular deposits along the glomerular basement membrane and in the mesangium (Bigazzi, 1994). The pathogenesis of the immune-complex disease is not certain, but gold may behave as a hapten and generate the production of antibodies with subsequent disposition of gold protein-antibody complexes in the glomerular subepithelium. Another hypothesis is that antibodies are formed against damaged tubular structures, particularly mitochondria, providing immune complexes for the glomerular deposits (Voil et al., 1977).

The pathogenesis of the renal lesions induced by gold therapy also has a direct toxicity to renal tubular cell components. From experimental studies it appears that gold salts have an affinity for mitochondria of proximal tubular lining cells, which is followed by autophagocytosis and accumulation of gold in amorphous phagolysosomes (Stuve and Galle, 1970). Gold particles can be identified in degenerating mitochondria in tubular lining cells and in glomerular epithelial cell by x-ray microanalysis (Ainsworth et al., 1981).

[1]Atomic weight, 69.72; periodic table group, IIIA; valence, +2 or +3; discovered in 1875.

[1]Atomic weight, 197; periodic table group, IB; valence, +1 or +3; discovered in earliest times.

Lithium (Li)

Lithium[1] (carbonate) is used in the treatment of depression. There must be careful monitoring of usage to provide optimal therapeutic value and to avoid toxicity. The therapeutic index is narrow (0.6 to 1.5 meq/L). Lithium is present in many plant and animal tissues. It has some industrial uses, in alloys, as a catalytic agent, and as a lubricant. Lithium hydride produces hydrogen on contact with water and is used in manufacturing electronic tubes, in ceramics, and in chemical synthesis.

Toxicokinetics The physiology, pharmacology, and toxicology of lithium compounds have been reviewed in detail by Timer and Sands (1999). Daily intake is about 2 mg. It is readily absorbed from the GI tract. Distribution is to total body water with higher levels in kidney, thyroid, and bone as compared to other tissues. Excretion is chiefly through the kidneys with 80 percent of the filtered load reabsorbed. The usual elimination half-life is 12 to 27 h, but it may rise to nearly 60 h if renal excretion is compromised. Lithium can substitute for sodium or potassium on several transport proteins. It enters cells via the amiloride-sensitive sodium channel or the Na/H^+ exchanger. The greater part of lithium is contained in the cells, perhaps at the expense of potassium. In general it may be competing with sodium at certain sites—for example, in renal tubular reabsorption.

Toxicity From the industrial point of view, except for lithium hydride, none of the other salts is hazardous, nor is the metal itself. Lithium hydride is intensely corrosive and may produce burns on the skin because of the formation of hydroxides (Cox and Singer, 1981). The therapeutic use of lithium carbonate may produce unusual toxic responses. These include neuromuscular changes (tremor, muscle hyperirritability, and ataxia), central nervous system changes (blackout spells, epileptic seizures, slurred speech, coma, psychosomatic retardation, and increased thirst), cardiovascular changes (cardiac arrhythmia, hypertension, and circulatory collapse), GI changes (anorexia, nausea, and vomiting), and renal damage (albuminuria and glycosuria). The last is believed to be due to temporary hypokalemic nephritis. Long-term sequelae from acute lithium poisoning include cognitive losses such as impaired memory, attention and executive functions, and visuospatial deficits (Brumm et al., 1998).

Chronic lithium nephrotoxicity and interstitial nephritis can occur with long-term exposure even when lithium levels remain within the therapeutic range (Singer, 1981). Animal studies have shown a similarity between lithium and sodium handling and that lithium may cause an antidiuretic hormone (ADH)–resistant polyuria and secondary polydipsia. This abnormality appears to be mediated by a central pituitary effect that reduces ADH release (Carney et al., 1996). Treatment with lithium salts has also been associated with nephrotic syndrome with minimal glomerular changes. The cardiovascular and nervous system changes may be due to the competitive relationship between lithium and potassium and may thus produce a disturbance in intracellular metabolism. The effects of lithium on neurotransmitter, neuropeptide, and signal transduction systems have been reviewed by Lenox et al. (1998).

Thyrotoxic reactions, including goiter formation, have also been suggested (Davis and Fann, 1971). While there has been some indication of adverse effects on fetuses following lithium treatment, none was observed in rats (4.05 meq/kg), rabbits (1.08 meq/kg), or primates (0.67 meq/kg). This dose to rats was sufficient to produce maternal toxicity and effects on the pups of treated, lactating dams.

Lithium overdosage and toxicity may be treated by the administration of diuretics (amiloride) and lowering of blood levels (via hemodialysis). Treatment with diuretics must be accompanied by replacement of water and electrolytes (Steele, 1977).

[1]Atomic weight, 6.94; periodic table group, 1; valence, +1; discovered in 1817.

Platinum (Pt) and Related Metals

Platinum-group metals include a relatively light triad of ruthenium, rhodium, and palladium, and the heavy metals osmium, iridium, and platinum.[1] They are found together in sparsely distributed mineral deposits or as a by-product of refining other metals, chiefly nickel and copper. Osmium and iridium are not important toxicologically. Osmium tetroxide, however, is a powerful eye irritant. The other metals are generally nontoxic in their metallic states but have been noted to have toxic effects in particular circumstances. Toxicologic information for ruthenium is limited to references in the literature indicating that fumes may be injurious to eyes and lungs (Browning, 1969). Palladium chloride is not readily absorbed from subcutaneous injection, and no adverse effects have been reported from industrial exposure. Colloid palladium ($Pd[OH]_2$) is reported to increase body temperature, produce discoloration and necrosis at the site of injection, decrease body weight, and cause slight hemolysis.

Allergenic Effects of Platinum Salts Platinum is interesting because of its extensive industrial applications and because of the use of certain complexes as antitumor agents. Higher platinum levels are found in roadside dust where traffic density is high because of its use in catalytic converters. Mean levels of platinum in whole blood and urine in nonoccupationally exposed adults are reported as 0.13 μg/L of blood and 0.11 μg/g of creatinine, respectively (Farago et al., 1998). Platinum metal itself is generally harmless, but an allergic dermatitis can be produced in susceptible individuals (Hunter, 1969). Skin changes are most common between the fingers and in the antecubital fossae. Symptoms of respiratory distress, ranging from irritation to an asthmatic syndrome—with coughing, wheezing, and shortness of breath—have been reported following exposure to platinum dust. The skin and respiratory changes are termed *platinosis*. They are mainly confined to persons with a history of industrial exposure to soluble compounds such as sodium chloroplatinate, although cases resulting from the wearing of platinum jewelry have been reported (WHO, 1991). The complex salts of platinum may act as powerful allergens, particularly ammonium hexachloroplatinate and hexachloroplatinic acid. Platinum salt sensitization may persist for years after cessation of exposure (Brooks et al., 1990). In general, platinum allergy is confined to a small group of charged compounds that contain reactive ligands, the most effective of which are chloride ligands (Farago et al., 1998).

Antitumor Effects of Platinum Complexes Major consideration for this group of metals are the potential antitumor and carcinogenic effects of certain neutral complexes such as *cis*-dichlorodiammine platinum (II) (or cisplatin), and various analogs

[1]Atomic weight, 195.08; periodic table group, VIII; valence, +1?, +2, +3, or +4; discovered in 1735.

(Kazantzis, 1981). Other metals in the group give complexes that are inactive or less active than the platinum analog. They can inhibit cell division and have antibacterial properties as well. These compounds can react selectively with specific chemical sites in proteins such as disulfide bonds and terminal NH_2 groups, with functional groups in amino acids and, in particular, with receptor sites in nucleic acids. These compounds also exhibit neuromuscular toxicity and nephrotoxicity. Platinum complexes, particularly cisplatin, are effective antitumor agents and are used clinically for the treatment of cancers of the head and neck, certain lymphomas, and testicular and ovarian tumors. For antitumor activity, the complexes should be neutral and should have a pair of *cis*-leaving groups. At dosages that are therapeutically effective (antitumor), these complexes produce severe and persistent inhibition of DNA synthesis and little inhibition of RNA and protein synthesis. DNA polymerase activity and transport of DNA precursors through plasma membranes are not inhibited. The complexes are thought to react directly with DNA in regions that are rich in guanosine and cytosine (Abrams and Murrer, 1993).

Mutagenic and Carcinogenic Effects of Platinum Complexes Cisplatin is a strong mutagen in bacterial systems and has been shown to form both intrastrand and interstrand cross-links. There is also a correlation between antitumor activity of cisplatin and its ability to bind DNA and induce phage from bacterial cells. It also causes chromosomal aberrations in cultured hamster cells and a dose-dependent increase in sister chromosome exchanges. Although cisplatin has antitumorigenic activity, it also seems to increase the frequency of lung adenomas and give rise to skin papillomas and carcinomas in mice. These observations are consistent with the activity of other alkylating agents used in cancer chemotherapy. There are no reports of increased risk of cancer from occupational exposure to platinum compounds.

Nephrotoxicity Cisplatin is also a nephrotoxin, which compromises its usefulness as a therapeutic agent. Platinum compounds with antitumor activity produce proximal and distal tubular cell injury, mainly in the corticomedullary region, where the concentration of platinum is highest (Madias and Harrington, 1978). Although 90 percent of administered cisplatin becomes tightly bound to plasma proteins, only unbound platinum is rapidly filtered by the glomerulus and has a half-life of only 48 min. Within tissues, platinum is protein-bound, with the largest concentrations in kidney, liver, and spleen, and it has a half-life of 2 or 3 days. Tubular cell toxicity seems to be directly related to dose, and prolonged weekly injection in rats causes atrophy of the cortical portions of nephrons, cystic dilatation of inner cortical or medullary tubules, and chronic renal failure due to tubulointerstitial nephritis (Choie et al., 1981). Experimental studies suggest that the preadministration of bismuth subnitrate, a potent inducer of metallothionein in the kidney, reduces the nephrotoxicity of cisplatin without interfering with its anticancer effect (Kondo et al., 1992).

MINOR TOXIC METALS

Antimony (Sb)

Antimony[1] belongs to the same periodic group as arsenic and has the same oxidation states. Most compounds of antimony involve the tri- and pentavalent states. Antimony is included in alloys in the metals industry and is used for producing fireproofing chemicals, ceramics, glassware, and pigments. Antimony has been used medicinally in the treatment of schistosomiasis and leishmaniasis. Antimony is a common air pollutant from industrial emissions, but exposure for the general population is largely from food. The average daily intake from food and water is about 5 μg (ATSDR, 1992).

The disposition of antimony in the body resembles that of arsenic. Most antimony compounds can be absorbed from the lung and GI tract, but no quantitative data are available on humans. Clearance from the lung is estimated to be on the order of days to weeks and GI absorption from most compounds has been estimated to be about 1 percent (ICRP, 1981). Many antimony compounds are GI irritants. Trivalent antimony is concentrated in red blood cells and liver, whereas the pentavalent form is mostly in plasma. The pentavalent form is predominantly excreted in urine, whereas the trivalent is found mainly in feces after injection into animals. [For detailed review, see ATSDR (1992).]

Most information about antimony toxicity has been obtained from industrial experiences. Occupational exposures are usually by inhalation of dust containing antimony compounds, such as the pentachloride and trichloride, trioxide, and trisulfide. Effects may be acute, particularly from the pentachloride and trichloride exposures, producing a rhinitis and even acute pulmonary edema. Chronic exposures by inhalation of other antimony compounds result in rhinitis, pharyngitis, tracheitis, and, over the longer term, bronchitis and eventually pneumoconiosis with obstructive lung disease and emphysema. Transient skin eruptions (antimony spots) may occur in workers with chronic exposure (Elinder and Friberg, 1986). Antimony-containing compounds may also produce alterations in cardiac function, and autopsy studies have shown that cardiac toxicity was the cause of death in patients treated with antimonial drugs (Winship, 1987).

A recent review by Léonard and Garber (1996) concluded that evidence that antimony compounds have mutagenic properties is insufficient. In most studies claiming to find carcinogenic properties, exposure to antimony compounds has been accompanied by other proven or likely carcinogens. Two exceptions are antimony trioxide and trisulfide, for which evidence for carcinogenicity was described as sufficient and limited respectively by the IARC (1989). In general, the mutagenic, carcinogenic, and teratogenic risks of antimony compounds, if they exist at all, are not very important in relation to such metals as arsenic, chromium, and nickel.

The metal hydride of antimony, stibine (H_3Sb), is a highly toxic gas that can be generated when antimony is exposed to reducing acids or when batteries are overcharged. High-purity stibine is also used in the production of semiconductors. Stibine, like arsine, causes hemolysis.

Barium (Ba)

Barium[1] is used in various alloys; in paints, soap, paper, and rubber; and in the manufacture of ceramics and glass. Barium fluorosilicate and carbonate have been used in pesticides. Barium sulfate, an insoluble compound, is used as a radiopaque aid to x-ray diagnosis. Barium is relatively abundant in nature and is found in plants and animal tissue. Brazil nuts have very high concentrations

[1]Atomic weight, 121.75; periodic table group, VA; valence; −2, +3, or +5; discovered in about 1450.

[1]Atomic weight, 137.33; periodic table group, II; valence, +2; discovered in 1808.

(3000 to 4000 ppm). Barium from natural sources may exceed federal safety standards in some bodies of freshwater. Daily intake is about 750 μg coming mainly from the diet.

The toxicity of barium compounds depends on their solubility. Aerosols of soluble barium compounds are well absorbed in the lung. Ingested soluble compounds are absorbed similarly to calcium to the extent of about 8 percent of the dose. Bone and teeth are the major sites of deposition, up to 90 percent of the body burden. The lung has an average concentration of 1 ppm (dry weight). The kidney, spleen, muscle, heart, brain, and liver concentrations are 0.10, 0.08, 0.05, and 0.03 ppm, respectively. Barium is reabsorbed by the renal tubules with only minor amounts appearing in the urine. The major route of excretion is the feces. The elimination half-life is about 3 to 4 days.

Occupational poisoning to barium is uncommon, but a benign pneumoconiosis (baritosis) may result from inhalation of barium sulfate (barite) dust and barium carbonate. It is not incapacitating and is usually reversible with cessation of exposure. Accidental poisoning from ingestion of an acute toxic dose (over 200 mg) of soluble barium salt results first in perioral paresthesia, intractable vomiting, and severe diarrhea. Hypertension and cardiac dysrhythmias may ensue. Profound hypokalemia and weakness progressing to flaccid paralysis are the hallmarks of barium poisoning (Johnson and VanTassell, 1991). Experimental studies indicate that barium directly stimulates muscle cells. Its basic mechanism of action probably involves the blocking of calcium activated potassium channels responsible for the cellular efflux of potassium. As a result, intracellular potassium rises and extra cellular levels fall leading to hypokalemia. Treatment with intravenous potassium appears beneficial. The lethal dose is between 1 to 15 g as barium carbonate. [For more detailed reviews, see Reeves (1986), ATSDR (1992).]

Germanium (Ge)

The chemical and physical properties of germanium[1] are intermediate between a metal and a nonmetal. It has two stable oxidation states, divalent and tetravalent. It forms organometallic compounds such as dimethyl germanium and a hydride (GeH_4). It was widely used in the semiconductor industry up to the mid-1970s, when it was replaced by silicon. Its current uses are in infrared lenses, optic fibers, as a catalyst, and in alloys with other metals. Some organogermanium compounds such as spirogermanium have antineoplastic properties but so far have not achieved therapeutic applications.

The diet is the dominant source of exposure to the general population. Germanium concentrations in most foods are similar to the natural abundance level of about 0.6 to 1.0 ppm in soils. But some canned foods are higher (tuna 2.2; baked beans 5.8 ppm). The daily intake from food is reported in the range of 370 to 3700 μg. Intake from drinking water and ambient air (except for occupational exposures) is negligible.

Inorganic germanium compounds are well absorbed from the diet. It is widely distributed throughout the body with the highest concentrations occurring in the spleen. Germanium is excreted mainly via the kidneys. The whole-body half-lives are between 1 and 4 days. Hair and nails may be useful media for biological monitoring.

[1]Atomic weight, 72.59; periodic table group, IVA; valence, +2 and +4; discovered in 1886.

The gas germane (GeH_4) is highly toxic to the cardiovascular system, liver and kidneys. It causes hemolysis of red cells and probably acts in the same way as stibine (SbH_3). The inorganic compounds exhibit low toxicity when taken orally. The LD_{50} values in animals are above 100 mg/kg body weight of germane. Ingestion of germanium dioxide (GeO_2) in an elixir, according to a case report on 18 people, resulted in renal damage that did not completely disappear after cessation of exposure. Approximately 16 to 328 g of germanium were ingested over a period of 4 to 36 months.

Germanium is not carcinogenic and may even inhibit carcinogenesis. The organo derivative, spirogermanium, selectively kills cancer cells. It is not mutagenic and can inhibit the action of other mutagens. High doses can cause embryonic resorption and the organo derivative, dimethyl germanium oxide, can produce fetal malformations in animal tests. [For references and details see the review by Gerber and Leonard (1997).]

Indium (In)

Indium[1] is a rare metal whose principal valence state is +3. In its metallic form, it is used in alloys, solders, and as a hardening agent for bearings. Its compounds such as indium phosphide (InP) are widely used in the electronics industry for production of semiconductors and photovoltaic. It is currently being used in medicine for the scanning of organs and the treatment of tumors. The average human intake of indium has been estimated in the range of 8 to 10 μg/day (Smith et al., 1978).

Indium compounds, specially InP, are poorly absorbed from the gastrointestinal tract or after intratracheal instillation (Zheng et al., 1994). It is excreted in the urine and feces. Its tissue distribution is relatively uniform.

There are no meaningful reports of human toxicity to indium. From animal experiments it is apparent that toxicity is related to the chemical form. Indium chloride given intravenously to mice produces renal toxicity and liver necrosis. Intratracheal instillation of the trichloride can produce severe pulmonary damage with fibrosis (Blazka et al., 1994). The phosphide appears less toxic (Oda, 1997). No evidence could be found for reproductive toxicity of $InCl_3$ in animal tests (Chapin et al., 1995) and teratogenic effects were found only when maternal toxicity occurred (Ungvary et al., 2000).

Silver (Ag)

Silver[2] forms only a +1 valence state, Ag^+, from which all its chemical compounds are formed. It occurs naturally as a silver ore often in association with gold and copper deposits. Silver mines are known to have been worked in Asia Minor before 2500 BC. Its principal industrial use is as silver halide in the manufacture of photographic plates. Other uses are for jewelry, coins, and eating utensils. Silver nitrate is used for making indelible inks and for medicinal purposes. The use of silver nitrate for prophylaxis of ophthalmia neonatorum is a legal requirement in some states. Other medicinal uses of silver salts are as an antiseptic and astringent.

[1]Atomic weight, 114.82; periodic table group, IIIA; valence, +1, +2, or +3; discovered in 1863.

[2]Atomic weight, 107.86; periodic table group, IB; valence, +2; discovered in ancient times.

Silver sulfadiazine is widely used in the treatment of burn injuries. Dietary intake including fluids is in the range of 70 to 90 μg/day.

Silver compounds can be absorbed orally, by inhalation, and through damaged skin. In the unexposed general population, average blood levels of silver are about 2.4 μg/L, urinary excretion is 2 μg/day, and tissue levels are about 0.05 μg/g (Wan et al., 1991). Dental amalgam fillings lead to higher tissue levels (Drasch et al., 1995). Complexes with serum albumin accumulate in the liver, from which a fractional amount is excreted. In animals parenterally dosed with silver salts, silver is widely distributed to most tissues. It can cross the blood-brain barrier and produce long-lasting deposits in many structures of the nervous system (Rungby, 1990). It is located exclusively in lysosomes of neuronal cells (Stoltenberg et al., 1994). A specific transporter protein may be involved (Havelaar et al., 1998). Autopsy findings after treatment of burn injuries indicated highest levels in skin, gingiva, cornea, liver, and kidneys (Wan et al., 1991). Excretion is via the GI tract and kidneys. Specific transport proteins are responsible for secretion of silver from liver cells to bile (Dijkstra et al., 1996).

The major effect of excessive absorption of silver is local or generalized impregnation of the tissues, where it remains as silver sulfide, which forms an insoluble complex in elastic fibers, resulting in argyria. The complexes also contain selenium (Matsumura et al., 1992). Industrial argyria, a chronic occupational disease, has two forms, local and generalized. The local form involves the formation of gray-blue patches on the skin or may manifest itself in the conjunctiva of the eye. In generalized argyria, the skin shows widespread pigmentation, often spreading from the face to most uncovered parts of the body. In some cases the skin may become black, with a metallic luster. The eyes may be affected to such a point that the lens and vision are disturbed. The respiratory tract may also be affected in severe cases. Large oral doses of silver nitrate cause severe gastrointestinal irritation due to its caustic action. Lesions of the kidneys and lungs and the possibility of arteriosclerosis have been attributed to both industrial and medicinal exposures. Chronic bronchitis has also been reported to result from medicinal use of colloidal silver (Browning, 1969). Animal experiments indicate that silver disturbs copper metabolism (Hirasawa et al., 1994) and that metallothionein may protect against the toxic action of silver (Shinogi and Maeizumi, 1993).

Tellurium (Te)

Tellurium[1] is a semimetallic element in the sulfur and selenium family. It is found in various sulfide ores along with selenium and is produced as a by-product of metal refineries. Its industrial uses include applications in the refining of copper and in the manufacture of rubber. Tellurium vapor is used in "daylight" lamps and in various alloys as a catalyst and as a semiconductor frequently in combination with other metals.

Tellurium in food is probably in the form of tellurates. Condiments, dairy products, nuts, and fish have high concentrations of tellurium. Food packaging contains some tellurium; higher concentrations are found in aluminum cans than in tin cans. Some plants, such as garlic, accumulate tellurium from the soil. Potassium tellurate has been used to reduce sweating. The average body burden in humans is about 600 mg, mainly in bone.

The biochemistry and toxicity of the metal has been reviewed recently by Taylor (1996). Soluble tetravalent tellurates, absorbed into the body after oral administration, are reduced to tellurides, partly methylated, and then exhaled as dimethyl telluride. The latter is responsible for the garlic odor in persons exposed to tellurium compounds. The kidney has the highest content among the soft tissues. Tellurium may also accumulate in the liver (Schroeder and Mitchener, 1972). The urine and bile are the principal routes of excretion. Sweat and milk are secondary routes of excretion.

Tellurates and tellurium are of low toxicity, but tellurites are generally more toxic. Acute inhalation exposure results in sweating, nausea, a metallic taste, and sleeplessness. A typical garlic breath is an indicator of exposure to tellurium by the dermal, inhalation, or oral route. Serious cases of tellurium intoxication from industrial exposure have not been reported. One of the few serious recorded cases of tellurium toxicity resulted from accidental poisoning by injection of tellurium into the ureters during retrograde pyelography. Two of the three victims died. Garlic breath, renal pain, cyanosis, vomiting, stupor, and loss of consciousness were observed in this unlikely incident. The amount of sodium telluride used was about 2 g (Hunter, 1969).

In rats, chronic exposure to high doses of tellurium dioxide has produced decreased growth and necrosis of the liver and kidney (Cerwenka and Cooper, 1961; Browning, 1969). Rats fed 1 percent of metallic tellurium in the diet developed demyelination of peripheral nerve (Goddrum, 1998), probably due to the inhibition of squalene monooxygenase, a key enzyme in cholesterol biosynthesis (Laden et al., 2000). Cadmium telluride is a novel compound used in semiconductors. On inhalation this compound was shown to cause severe pulmonary inflammation and fibrosis in rats (Morgan et al., 1997). Tellurium compounds can produce hydrocephalus in experimental animals. Dimercaprol treatment for tellurium toxicity increases the renal damage. While ascorbic acid decreases the characteristic garlic odor, it may also adversely affect the kidneys in the presence of increased amounts of tellurium (Fishbein, 1977).

Thallium (Tl)

Thallium[1] is one of the more toxic metals. The thallium ion, Tl^+, has a similar charge and ionic radius as the potassium ion. Some of its toxic effects (see below) may result from interference with the biological functions of potassium. It is obtained as a by-product of the refining of iron, cadmium, and zinc. It is used as a catalyst in certain alloys, optical lenses, jewelry, low-temperature thermometers, semiconductors, dyes and pigments, and scintillation counters. Industrial poisoning is a special risk in the manufacture of fused halides for the production of lenses and windows. It has been used medicinally as a depilatory. Thallium compounds, chiefly thallous sulfate, have been used as rat poison and insecticides. This is one of the commonest sources of human thallium poisoning.

Thallium is absorbed through the skin and gastrointestinal tract. The highest concentrations after poisoning are in the kidney. Following the initial exposure, large amounts are excreted in urine during the first 24 h, but after that period excretion is slow and the feces may be an important route of excretion. The half-life in humans has been reported in the range of 1 to 30 days and may be dose-dependent. Thallium undergoes enterohepatic circulation.

[1]Atomic weight, 127.6; periodic table group, VIA; valence, +2, +4, or +6; discovered in 1792.

[1]Atomic weight, 204; periodic table group, IIIA; valence, +1 or +3; discovered in 1861.

Prussian blue, the most commonly used antidote, is given orally to break the enterohepatic cycle by trapping thallium secreted in bile and carrying it into the feces. For major reviews, see Malkey and Oehme (1993), Galván-Arzate and Santamaría (1998).

There are numerous clinical reports of acute thallium poisoning in humans characterized by GI irritation, acute ascending paralysis, psychic disturbances, and alopecia. The estimated acute lethal dose in humans is 8 to 12 mg/kg. Epilation begins about 10 days after ingestion and complete hair loss in about 1 month. Thallium targets the epithelial cells of the hair papillae. The turnover of these cells allows complete restoration of the hair in about 2 to 3 months. The growth of fingernails is impaired and transverse white stripes appear in the nails.

The acute cardiovascular effects of thallium ions probably result from competition with potassium for membrane transport systems, inhibition of mitochondrial oxidative phosphorylation, and disruption of protein synthesis. It also alters heme metabolism.

In humans, fatty infiltration and necrosis of the liver, nephritis, gastroenteritis, pulmonary edema, degenerative changes in the adrenals, degeneration of the peripheral and central nervous system, alopecia, and in some cases death have been reported as a result of long-term systemic thallium intake. These cases usually are caused by the contamination of food or the use of thallium as a depilatory. Loss of vision plus the other signs of thallium poisoning have been related to industrial exposures (Browning, 1969).

Studies on animals suggest that the mitochondrion is an important intracellular target. Thallium, besides competing with potassium, may combine with the sulfhydryl groups in the mitochondria and thereby interfere with oxidative phosphorylation. Its affinity for sulfydryl groups may also explain its ability to induce lipid peroxidation and deplete intracellular glutathione levels.

Evidence is scanty that thallium is mutagenic or carcinogenic (Leonard and Gerber, 1997). On the other hand, it may be teratogenic, especially with regard to cartilage and bone formation, but most of the evidence comes from chicks, not mammals. A teratogenic response to thallium salts characterized as achondroplasia (dwarfism) has been described in rats (Nogami and Terashima, 1973). Prenatal exposure of humans has resulted in skin and nail dystrophy, alopecia, and low body weight in newborns.

Tin (Sn)

Tin[1] has two higher valence states: stannous, Sn^{2+} and stannic, Sn^{4+}, tin. Both form stable inorganic compounds. In addition, stannic tin can form a volatile hydride, SnH_4 and a number of toxicologically important organometallic compounds in which the stannic atom form is covalently attached to one or more carbon atoms. Tin has a long history of use dating back to ancient Egypt. Currently it is used in the manufacture of tinplate, in food packaging, and in solder, bronze, and brass. Stannous and stannic chlorides are used in dyeing textiles. Organic tin compounds have been used in fungicides, bactericides, and slimicides, as well as in plastics as stabilizers. The daily intake is about 3.5 mg of tin, considerably lower than the 17 mg estimated in previous decades thanks to better food packaging methods. [The disposition and possible health effects of inorganic and organic tin compounds have been summarized in a number of reviews (WHO (1980), Alessio and Dell'Orto (1998), and Winship (1988).]

[1]Atomic weight, 118.7; periodic table group, IVA; valence, +2, +4; discovered in ancient times.

There is only limited absorption of even soluble inorganic compounds after oral administration. Ninety percent of the tin administered in this manner is recovered in the feces. The small amounts absorbed are reflected by increases in the liver and kidneys. Injected tin is excreted by the kidneys, with smaller amounts in bile. A mean normal urine level of 16.6 μg/L or 23.4 μg/day has been reported. The majority of inhaled tin remains in the lungs, most extracellularly, with some in the macrophages, in the form of SnO_2.

The organic tins, particularly the trimethyltin and triethyltin compounds, are better absorbed than inorganic species of tin. The tissue distribution of tin from these compounds shows the highest concentrations in the blood and liver, with smaller amounts in the muscle, spleen, heart, or brain. Tetraethyltin is converted to triethyltin in vivo.

Chronic inhalation of tin in the form of dust or fumes leads to benign pneumoconiosis. Tin hydride (SnH_4) is more toxic to mice and guinea pigs than is arsine; however, its effects appear mainly in the central nervous system and no hemolysis is produced. Orally, tin or its inorganic compounds require relatively large doses (500 mg/kg for 14 months) to produce toxicity. Inorganic tin salts given by injection produce diarrhea, muscle paralysis, and twitching. Studies on animals reveal that administration of inorganic tin compounds disturbs copper, zinc, and iron metabolism [Yu and Beynen (1995), Reicks and Rader (1990)]. The stannous ion also interacts with N-type calcium channels enhancing calcium transport into neurons (Hattori and Maehashi, 1991, 1992). Stannous is a more potent inducer than stannic tin of hemeoxygenase (HO-1), the rate determining enzyme in the catabolism of the heme ring (Neil et al., 1995). Tin also inhibits aminolevulinic dehydratase, a key enzyme in the synthesis of the heme ring, but not as potently as lead (Zareba and Chmielnicka, 1992). This action may be another example of tin displacing an essential metal cofactor, in this case zinc (Chmielnicka et al., 1992). Experimental studies have failed to find any evidence of mutagenicity, carcinogenicity, or teratogenicity of inorganic tin compounds. In fact some anticarcinogenic properties have been detected (Winship, 1988).

Some organic tin compounds are highly toxic, particularly triethyltin. Trimethyltin and triethyltin cause encephalopathy and cerebral edema. Toxicity declines as the number of carbon atoms in the chain increases. An outbreak of almost epidemic nature took place in France due to the oral ingestion of a preparation (Stalinon) containing diethyltin diodide for the treatment of skin disorders. Excessive industrial exposure to triethyltin has been reported to produce headaches, visual defects, and electroencephalographic (EEG) changes that were very slowly reversed (Prull and Rompel, 1970). Experimentally, triethyltin produces depression and cerebral edema. The resulting hyperglycemia may be related to the centrally mediated depletion of catecholamines from the adrenals. Acute burns or subacute dermal irritation has been reported among workers as a result of tributyltin. Triphenyltin has been shown to be a potent immunosuppressant (Verschuuren et al., 1970). Inhibition on the hydrolysis of adenosine triphosphate and an uncoupling of the oxidative phosphorylation taking place in the mitochondria have been suggested as the cellular mechanisms of tin toxicity (WHO, 1980).

Some butyl and methyl compounds of tin were positive in the Ames mutagenicity test (Hamasaki et al., 1993). Tributyl tin can suppress natural killer cells in mice. This inhibition may predispose animals to malignancy (Ghoneum et al., 1990).

Titanium (Ti)

Most titanium compounds are in the oxidation state +4 (titanic), but oxidation state +3 (titanous) and oxidation state +2 compounds as well as several organometallic compounds do occur. Because of its resistance to corrosion and inertness, metallic titanium[1] has many metallurgic applications, particularly as a component of surgical implants and prostheses. Titanium dioxide, the most widely used compound, is a white pigment used in paints and plastics; as a food additive to whiten flour, dairy products, and confections; and as a whitener in cosmetic products. It occurs widely in the environment; in urban air, rivers, and drinking water and is detectable in many foods. Titanium in feces is sometimes used as a measure of soil ingestion.

Approximately 3 percent of an oral dose of titanium is absorbed. The majority of that absorbed is excreted in the urine. The normal urinary concentration has been estimated at 10 μg/L (Schroeder et al., 1963; Kazantzis, 1981). The estimated body burden of titanium is about 15 mg. Most of it is in the lungs, probably as a result of inhalation exposure, as it tends to remain in the lungs for long periods. Lung burdens increase with age and vary according to geographic location. Mean concentrations of 8 and 6 ppm for the liver and kidney, respectively, were reported in the United States. Titanium IV may circulate in plasma bound to transferrin (Messori et al., 1999). Newborns have little titanium.

Occupational exposure to titanium, usually in the form of titanium dioxide, (TiO_2) may be heavy, and concentrations in air up to 50 mg/m^3 have been recorded. TiO_2 has been classified as a nuisance particulate with a TLV of 10 mg/m^3. Nevertheless, slight fibrosis of lung tissue has been reported following inhalation exposure to titanium dioxide pigment, but the injury was not disabling. Ultrafine particles of TiO_2 are more likely to produce pulmonary inflammation than larger particles (Baggs et al., 1997). Excessive deposits in the lung will cause pulmonary overload, impairing the clearance mechanism (Warheit et al., 1997). Otherwise, titanium dioxide has been considered physiologically inert by all routes (ingestion, inhalation, dermal, and subcutaneous). Titanium dioxide was found not to be carcinogenic in a bioassay study in rats and mice (NCI, 1979).

The metal and other salts are also relatively nontoxic except for titanic acid, which, as might be expected, will produce irritation (Berlin and Nordberg, 1986). A titanium coordination complex, titanocene, suspended in trioctanoin and administered by intramuscular injection to rats and mice produced fibrosarcomas at the site of injection and hepatomas and malignant lymphomas (Furst and Haro, 1969). A titanocene is a sandwich arrangement of titanium between two cyclopentadiene molecules.

Uranium (U)

The chief raw material of uranium[2] is pitchblende or carnotite ore. This element is largely limited to use as a nuclear fuel and, as a spent fuel in military ordinance. It is present naturally in air, water, food, and soil. The average daily intake from food is 1 to 2 μg and about 1.5 μg from 1 L of drinking water. This metal has five oxidation states but only the +4 and +6 forms are stable enough to be of practical importance. The +6 forms the uranyl ion (UO_2^{2+}), which forms water-soluble compounds and is an important species of uranium in body fluids.

The uranyl ion is rapidly absorbed from the GI tract. About 60 percent is carried as a soluble bicarbonate complex, while the remainder is bound to plasma protein. Sixty percent is excreted in the urine within 24 h. About 25 percent may be fixed in the bone (Chen et al., 1961).

Naturally occurring depleted uranium, although radioactive, presents predominantly a toxicologic rather than radiologic health risk. Following inhalation of the insoluble salts, retention by the lungs is prolonged. Uranium tetrafluoride and uranyl fluoride can produce toxicity because of hydrolysis to hafnium. For example, they will burn skin on contact.

The soluble uranium present in plasma as the uranyl ion complexed with bicarbonate produces systemic toxicity in the form of acute renal damage and renal failure, which may be fatal. However, if exposure is not severe enough, the renal tubular epithelium is regenerated and recovery occurs. Renal toxicity with the classic signs of impairment—including albuminuria, elevated blood urea nitrogen, and loss of weight—is brought about by filtration of the bicarbonate complex through the glomerulus, bicarbonate reabsorption by the proximal tubule, liberation of uranyl ion, and subsequent damage to the proximal tubular cells. Uranyl ion is most likely concentrated intracellularly in lysosomes (Ghadially et al., 1982). A study of uranium mill workers suggested that workers' long-term low level exposure is associated with β_2-microglobulinuria and amino aciduria (Thun et al., 1985).

In those studies where a higher incidence of lung cancer has been found in uranium miners, the cancer is probably due to radon and its daughter products, not to uranium itself (ATSDR, 1999). In fact, there is no convincing evidence that uranium is carcinogenic.

The threshold limit for uranium in the workroom (TWA) is 200 μg/m^3 and the EPA-established limit in drinking water is 100 μg/L. [For a detailed review of uranium, see ATSDR (1999).]

Vanadium (V)

Vanadium[1] may be an essential trace element, but a deficiency disease has not yet been defined in humans. It has several oxidation states, the most common being +3, +4, and +5. It is a byproduct of petroleum refining, and vanadium pentoxide is used as a catalyst in the reactions of various chemicals including sulfuric acid. It is used in the hardening of steel, in the manufacture of pigments, in photography, and in the formulation of insecticides. Food is the major source of human exposure. Significant amounts are found in milk, seafood, cereals, and vegetables. The daily intake in the U.S. population ranges from 10 to 60 μg. The normal blood and urine levels are estimated to be around 1 and 10 nmol/L respectively (Sabbioni et al., 1996).

Metallic vanadium does not occur in nature, but human tissues come into long-term contact in medical implants. The lungs absorb soluble vanadium compounds well, but the absorption of vanadium salts from the gastrointestinal tract is poor. In the body, the pentavalent form (VO_3^-) is the predominant species in extracellular fluid whereas quadrivalent form (VO^{2+}) is most common inside the cell. The largest single compartment is the fat. Bone and teeth stores contribute to the body burden. The principal route of

[1]Atomic weight, 47.9; periodic table group, IVB; valence, +2, +3, or +4; discovered in 1791.

[2]Atomic weight, 238; periodic table group, V; valence, +2, +3, +4, and +6; discovered in 1841.

[1]Atomic weight, 50.93; periodic table group, VA; valence, +2, +3, +4, or +5; discovered in 1801.

excretion of vanadium is the urine with a biological half-life of 20 to 40 h.

The pentavalent compounds are the most toxic. The toxicity of vanadium compounds usually increases as the valence increases. The toxic action of vanadium is largely confined to the respiratory tract. Bronchitis and bronchopneumonia are more frequent in workers exposed to vanadium compounds. In industrial exposures to vanadium pentoxide dust, a greenish-black discoloration of the tongue is characteristic. Irritant activity with respect to skin and eyes has also been ascribed to industrial exposure. Gastrointestinal distress, nausea, vomiting, abdominal pain, cardiac palpitation, tremor, nervous depression, and kidney damage, too, have been linked with industrial vanadium exposure (Waters, 1977; Wennig and Kirsch, 1988; Goyer, 1996; Barceloux, 1999).

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