CHAPTER 8

The Marriage Bed

(The Physiological Relationship Between Lead and Humanity)

Had she affections and warm youthful blood
She would be as swift in motion as a ball'
My words would bandy her to my sweetlove,
And his to me
But old folks, many feign as they were dead
Unwieldy, slow, heavy, and pale as lead

Romeo and Juliet, Act 2, 5.17, Shakespeare

Life evolved on an earth surface that was by and large devoid of lead (Chapters 1 and 2). As a result there is no known biological use for lead, nor any mechanism by which lead is specifically targeted for detoxification. Lead, once in the body, is an intruder. In order to assess the impact of lead on human health we need to understand the trajectory of lead through a living organism as governed by chemical principles. There are five routes by which lead can enter a person: 1) through the skin (subcutaneously), 2) gunshot wound, 3) inhalation, 4) through the digestive track; and 5) direct injection into the blood stream. The toxicity of lead will depend upon the mode of entry and the chemical and physical form of the ingested lead and its mode of transfer from the three main phases in the body: water, organic (cell membranes), and solid (bones) (Figure 8.3).

Once within the body inorganic lead masquerades as calcium, as well as interrupts enzyme functions through binding with sulfur. We examine the main symptoms of lead poisoning and speculate as to the molecular chemistry causing those symptoms. We also examine alleviation

Figure 8.1. Alchemists' image of the marriage between silver and gold. Herbsrandst Jamstahler's *Viatorium Spayricum*, Frankfort, 1602. From Gareth Roberts' *The Mirror of Alchemy*, 1994.

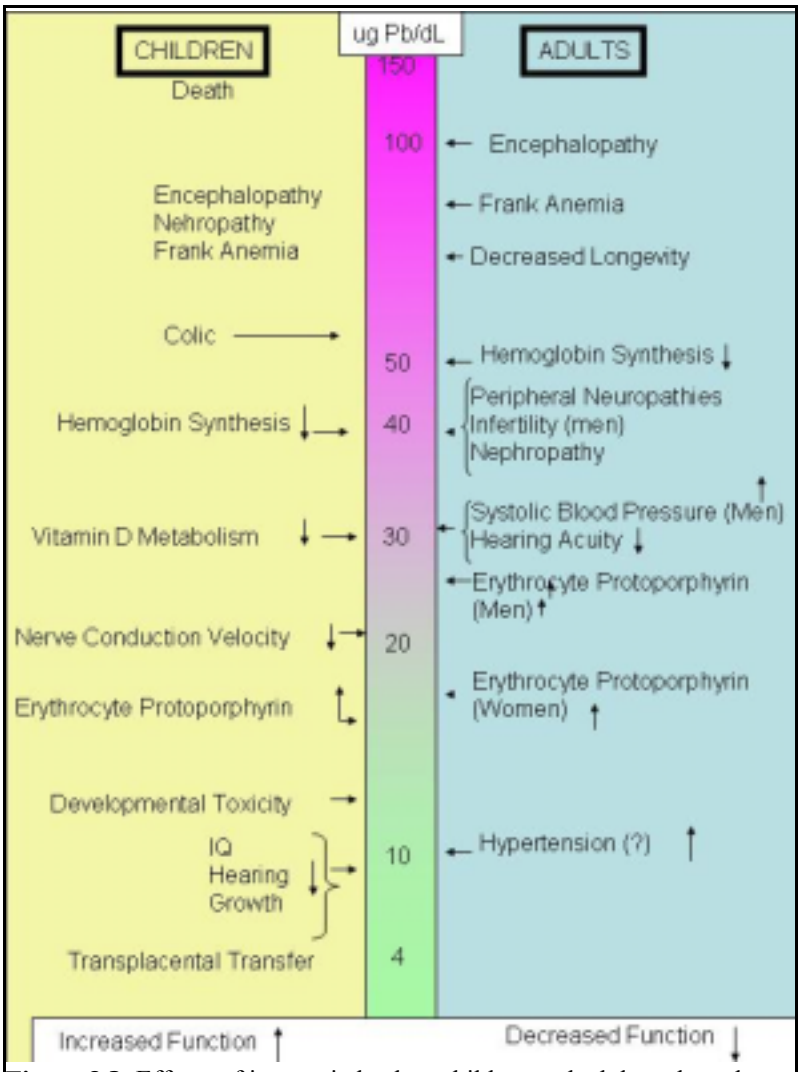

Figure 8.2: Effects of inorganic lead on children and adults, adapted from ATSDR, *Toxicological Profile for Lead (1989)*

of acute clinical symptoms of lead poisoning is through chelation therapy. We end with a cursory review of the veterinary literature.

The general symptoms of lead poisoning are shown in Figure 8.2. The Figure is adapted from ATSDR Toxicological Profile for Lead (1989).

MODES OF ENTRY

Organo-Lead Inhalation

Transport In

Organo-lead ($(CH_3CH_2)_4Pb$) inhalation arises primarily from leaded gasoline which, although banned in many countries (USA), is still prevalent in others. Organo-lead vapors are particularly toxic. It was because of this toxicity that the addition of organo-lead to gasoline was vehemently opposed by public health officials (see Chap. 10). The opposition was fueled by early incidents in industrial production in which several fatalities occurred. Production workers within several facilities called those facilities a "House of Butterflies" because of the propensity of workers to randomly stop, stare into space, and grab at hallucinogenic butterflies (Rosner and Markowitz 1985).

Why should organo-lead be so particularly toxic? The sp^3 structure of lead, consistent with tetravalent organo-lead compounds has been mentioned (Chap.2, 4, & 7). Pb^{4+} with an sp^3 hybridization should yield four equivalent orbitals. The only way to place these equivalent lobes in a sphere is with 120° bond angles. Thus we expect the overall compound to have the metal encased spherically in four organic or "oil-like" chains. The lead is well "hidden" in this oil-like environment. This species can relatively easily be accommodated within the oil-like (lipid) membranes that constitute the protective barriers in our bodies (blood cell membranes, skin, etc.).

The membrane, which is itself organic, is unable to accommodate the high charge on "bare" lead, Pb^{2+} or Pb^{4+}. Great structural rearrangement of the lipid membrane is required to allow water associated with the lead ion to traverse through the membrane. In contrast, lead, as organic lead, can easily move across the membrane from a region of high concentration (lung air) to a region of low concentration of lead (blood).

Organo Lead Action on the Proton Pump

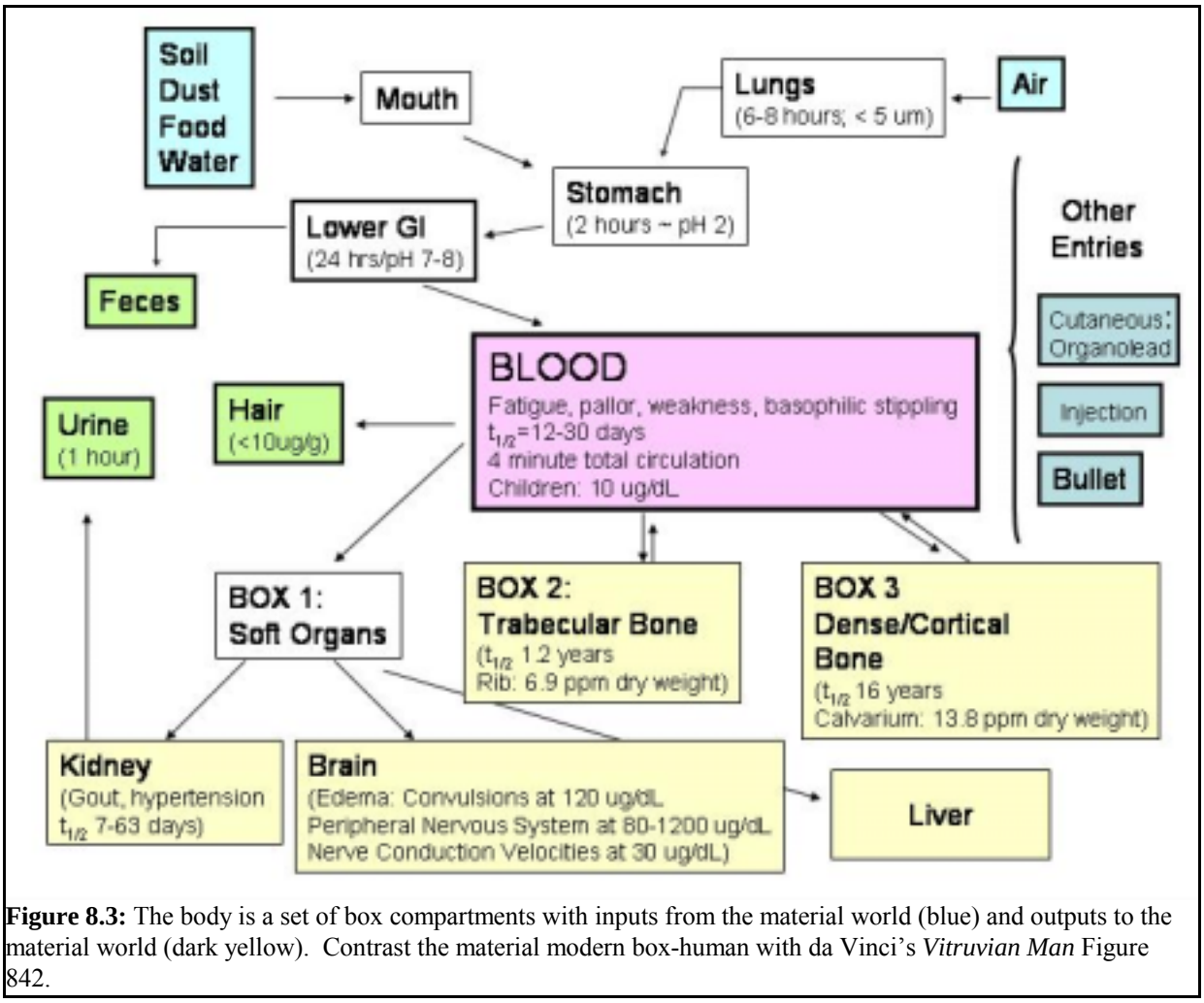

Figure 8.3: The body is a set of box compartments with inputs from the material world (blue) and outputs to the material world (dark yellow). Contrast the material modern box-human with da Vinci's *Vitruvian Man* Figure 842.

Is this the sole reason that organo-leads are the only lead compounds known in recent years (last 100) to induce death in adults? No. These compounds exercise a double whammy for precisely the same chemical reasons that made the compounds beneficial in the gasoline industry. Lead bonded to four carbons (organo lead) is unstable. As a consequence one of the four bonds breaks easily leaving a free radical, charge unsatisfied, lead compound. The compound rapidly picks up a compensating negatively charged chloride ion.

How fast is the tetraorgano-lead converted to the chloride species? Very rapidly. In mice injected with R_4Pb and killed within a few hours, little R_4Pb remains in the tissue or blood (Bolanowska 1968; Bolanowska and Garczynski 1968).

Neurological information, as well as cell regulation is accomplished by exquisite control of the distribution of simple cations and anions across the lipid layer of the membrane (see Figure 8.5) (Selwyn and others 1970). The amount (concentration) of ions distributed across a membrane imparts an electrical voltage (voltage =separation of charge in space). This voltage is the source of rapid communication from one portion of the body to another through the nerve cells. How are ion concentrations controlled physiologically? They are controlled by a "gating" process. Channels within the organo- (lipid barrier) open and close in response to molecular stimuli. While open, the channel will allow ion flow. Alternatively, the entire energy storage process of ATP to ADP involves a net chemical reaction with proton release. The enzyme responsible for this energy production is localized within the lipid membrane of the mitochondria. The enzyme has a configuration suitable for the transfer of H^+ across the membrane. Once this proton is transferred it needs to

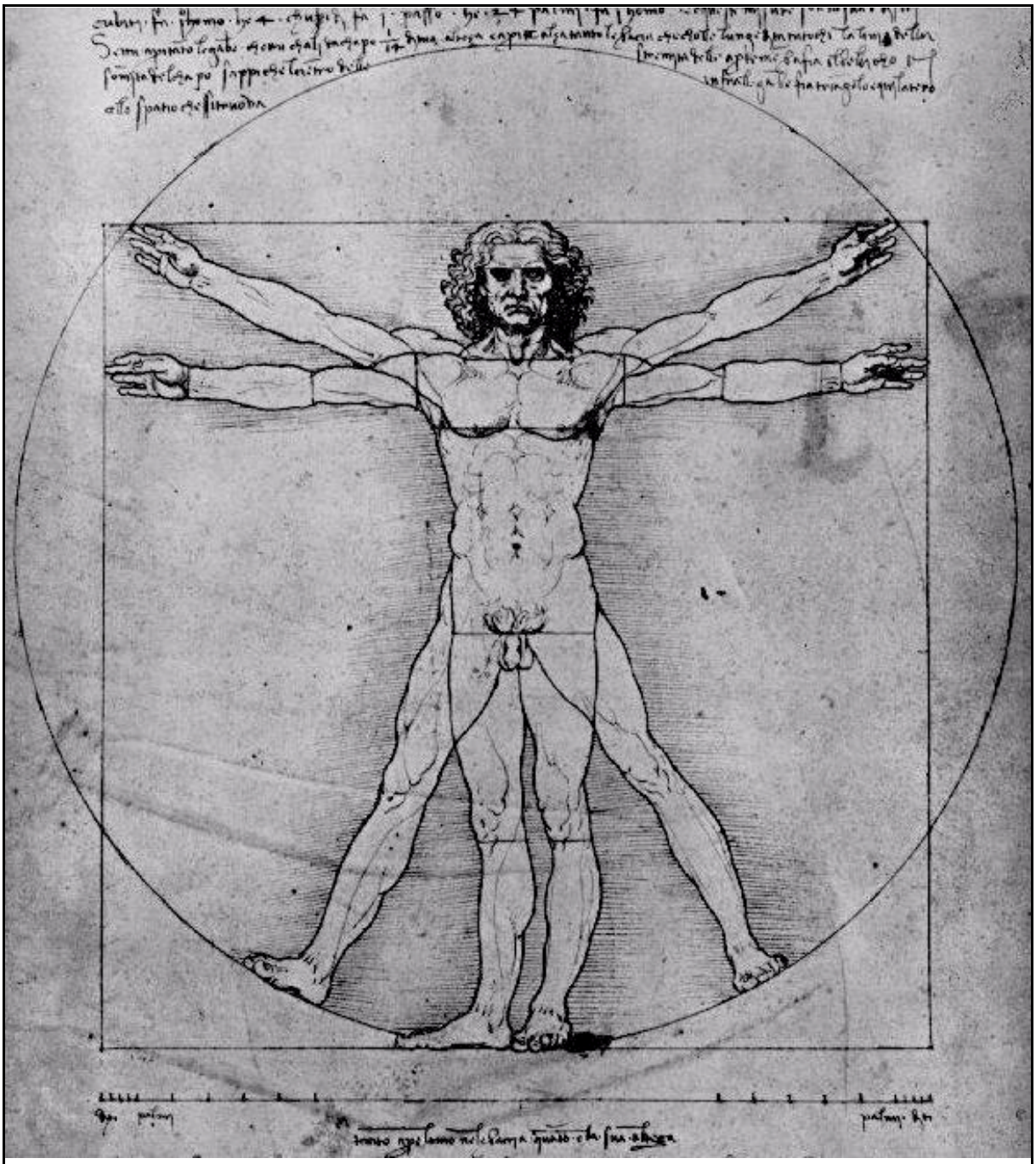

Figure 8.4. Leonardo da Vinci's *Vitruvian man* is centered in the material universe. Contrast this image with the material world for man and lead in Figure 8.3

be charge stabilized (with chloride). If the chloride concentration external to the cell membrane is perturbed the entire process is perturbed. The protons can not be charge stabilized which shuts down the ATP process.

R_3PbCl produced in the liver is distributed within a minute throughout the body and can impact the chloride concentration. The metal and the chloride anion are effectively hidden within the surrounding carbon chains. Consequently, R_3Pb^+ can serve as a

carrier across the lipid membrane for chloride, facilitating it's transport. If the ATP pump is generating a high external H^+ concentration, which must require a high external Cl^- concentration, then R_3Pb^+ will serve as a fast moving piggy back carrier for Cl^- from the region of high external Cl^- to the internal low Cl^- concentrations.

Figure 8.6: Organo lead intoxication by leaded gasoline production workers caused hallucinations in which the workers thought they saw butterflies.

One of the most pernicious effects of organo-lead is, therefore, to decouple energy producing reactions from proton gradients used in the control mechanism. Consequently, one might expect that an immediate loss of metabolic activity in the affected organisms.

The transport of Cl^- can occur at other membrane interfaces and produce equally alarming consequences. Consider what happens to a dried up prune or raisin placed in water. It "plumps". Conversely, consider what happens when cooking eggplant. Most recipes exhort the cook to salt the eggplant and let it sit for 20 minutes before cooking. When the cook she/he observes that the eggplant has exuded or given up moisture and beads of "sweat" occupy the external surface of the cut eggplant. What has happened is a transfer of water across the lipid membranes in response to a difference in salt concentration across the membrane.

Now consider what happens when the ion concentrations of chloride and protons are out of whack in our membrane system. Water external or internal to the cell must move in response to the unanticipated ion concentration change. This causes swelling (plumping) of the tissue, or in medical jargon, edema. The swelling occurs with interstitial cell space and is normally drained by the lymphatic system. One of the clinical manifestations of organo-lead

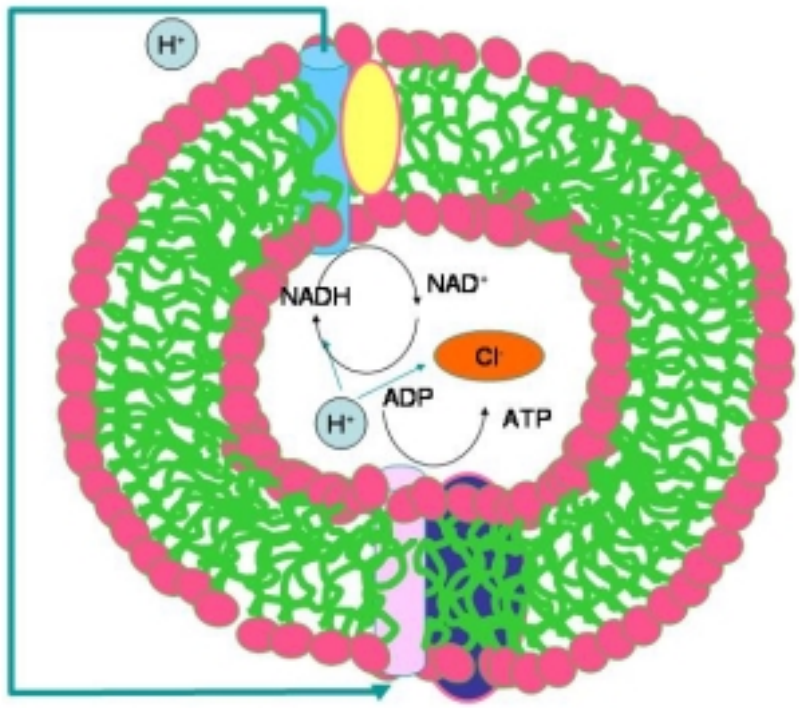

Figure 8.5: The proton pump drives energy metabolism. If the gradient for protons is disrupted by chloride ions then energy production is altered.

intoxication is edema of various tissues, including the brain.

In summary, we note that inhalation of organo-lead can be particularly toxic. In the first case, the transport of the compound into the blood stream is accelerated by facile transport of the intact compound across the blood vein membranes. In the second case the organo-lead substance is rapidly de-alkylated to form an organo soluble carrier of chlorides. Chloride concentrations are perturbed which impacts on respiration (energy metabolism), upon cell potentials, and induces edema of the tissue.

The chemical processes are relatively fast (minutes) and the biological consequences of these reactions can also be fast (death can be within 36 hours). Dermatologic exposure to organo-lead is also quite toxic because transit across the skin (cells and membranes!) will also be quite rapid.

Lead Bullets, Embedded

One rather uncommon way to be exposed to lead poisoning is through gunshot wounds as occurred with Andrew Jackson, early president of the United States. In general, old bullets pose no threat from lead poisoning to the patient, unless the lead is embedded in a joint and is exposed to the synovial (joint) fluid, or if the joint is arthritic. Both the effect of the synovial fluid and arthritis create a situation in which the lead is more rapidly converted from the large, insoluble form, to a more soluble form (Cagin and others 1978), (Dillman and others 1979). The synovial fluid acts as a better solvent than tissue or bone. Synovial fluid contains a large amount of mucopolysaccararides secreted by surrounding connective tissue. Leukocytic polymorphonuclear cells range from 2000 to 50,000 cells per mm^3 when the joints are arthritic. Rheumatoid synovial fluid has a low viscosity and high protein count with elevated immunoglobins. This highly proteineous fluid apparently promotes dissolution of the lead. Lead shot and .22 caliber bullets, smaller particles, are more likely to result in lead poisoning from retained lead projectiles. An example case presentation is given below (Cagin and others 1978):

A 19-year-old student was referred for the treatment of anemia on 29 July 1976. The anemia was discovered incidentally during evaluation for removal of a bullet from his left knee. The patient had been shot accidentally three years before referral and was well except for occasional aching pains in the knee, which had developed spontaneously about 6 months before referral. The patient remained in good health until 2 months before admission, when he began to lose weight (16 kg) despite an increasingly insatiable appetite. He also noticed progressive muscle weakness and fine tremors of his arms.

A second case presentation is given (Dillman and others 1979):

In August 1976, a 42 year old man was admitted to Ben Taub General Hospital because of severe anemia. His past medical history was remarkable for chronic alcoholism without moonshine consumption. In 1950, at the age of 16 years, he sustained a gunshot wound to the left hip with subsequent development of degenerative arthritis in the joint. There was no history of occupational exposure to lead. Because of incapacitating arthritis, he was admitted to the Ben Taub orthopedic service for a hip prosthesis in June 1975. At surgery, there was a metal foreign body and several small metallic fragments embedded in the joint. These were bathed in a gray, cloudy synovial fluid. Only local irrigation was performed, and all cultures were subsequently negative.

At the time of the August 1976 admission, the patient was a poor historian with mental confusion and slurred speech. He complained of chronic pain in the left hip and several months of intermittent nausea, vomiting, abdominal pain and headaches. He denied recent alcohol consumption.

On physical examination, he appeared chronically ill, although afebrile and normotensive. A dark line was present on the lower gingival margin. Voluntary guarding was observed on palpation of the abdomen. There was generalized muscle wasting and weakness, pedal edema and severe limitation of motion of the left hip in all directions. Stool guaiac was negative. The patient was oriented, but was confused about other facts.

Poisoning from embedded bullets can be transmitted to the fetus as was reported fro a maternal fetal case involving a 15 year old bullet (Raymond and others 2002).

Bullets can be harmful if swallowed. A 6 year old asymptomatic child was found to have an elevated blood lead level on normal screening (31 μg/dL). After a search for leaded dust, paint, ceramics, it was discovered that the child had been chewing on lead

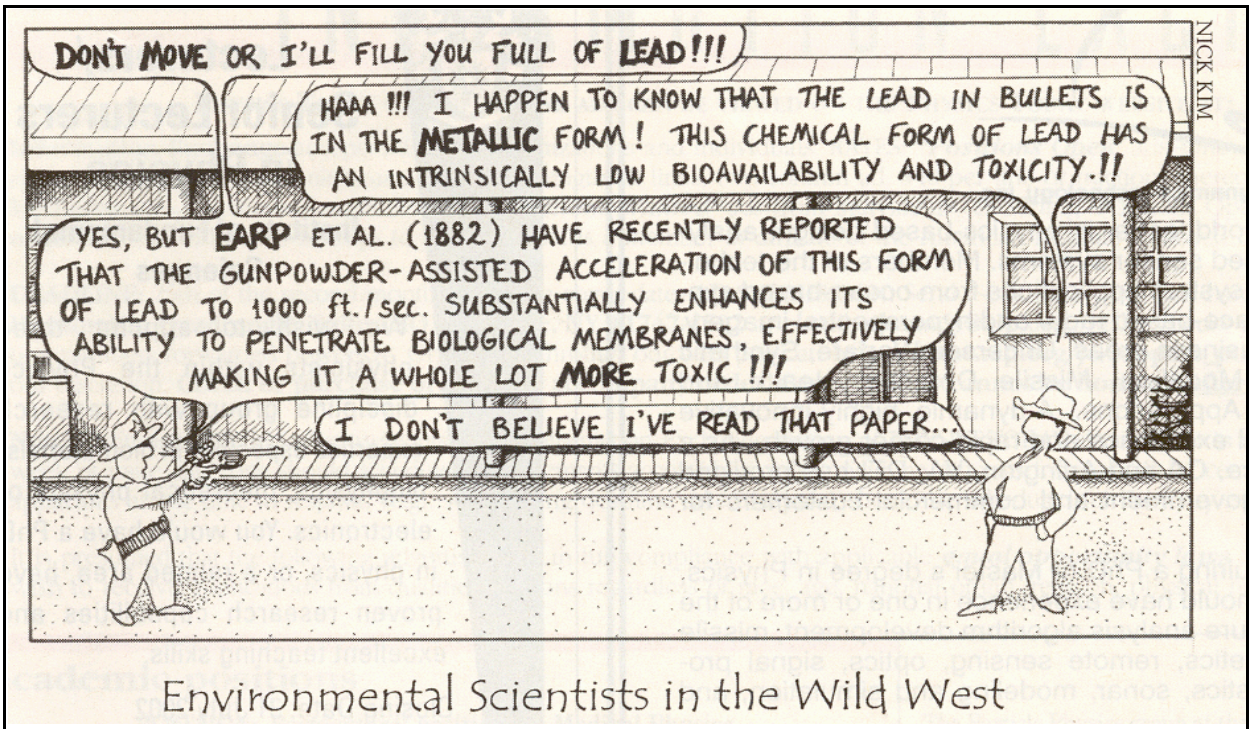

Figure 8.7. Wyatt Earp, a gunslinger in Tombstone, Arizona, was involved in a shoot out at the O.K. Corral in 1882 in which 5 were killed.

pellets from a sibling's pellet gun (Roberts and others 1998). Other similar cases involve lead poisoning following ingestion of 206 lead bullets and 20-25 lead fishing sinkers (McNutt and others 2001; Mowad and others 1998; Moward and others 1998). In the latter case an 8 year old boys blood lead level was 53 µg/dL.

Inorganic percutaneous Entry

For the most part lead is not transported in large quantities as an inorganic ion across the skin. This mode of transport, while documented (Stauber and others 1994), remains a minor pathway for the entry of lead into the body.

Inhalation of Particulate Lead

The most common groups of workers likely to experience intake of lead through inorganic lead airborne materials are demolition or construction workers, firing range (public/military) workers, and lead solder workers (radiator repair).

Demolition workers using an acetylene torch at 300ºC (Pb m.p. 328 ºC, Pb b.p. 1740ºC) were exposed to 21.33 mg Pb/m^3 and had a resulting blood lead level of 59 mg/100 ml. The allowable blood lead limit is 10 mg/100 mL suggesting that lead intoxication had occurred. Workers removing paint from a bridge in N.Y. caused airborne lead to rise from 600 to 4000 g/dL. The men worked an 8 hour/day, 5 day/week and had a blood lead level of 40-120 µg Pb/dL after four weeks. Clinical symptoms (anorexia, weakness, muscle soreness, vomiting) began two weeks after the work was initiated (Marino and others 1989).

Military personnel test firing howitzer picked up 600 µg Pb/m^3 when facing into the wind. Blood lead before firing was 5-6 µg/100 mL as a baseline and rose to 8 immediately after the one time only test firing. Blood lead levels continued to rise throughout the next 12 days to a level of 10-11 µg Pb/100 mL. This level persisted for at least seven weeks after exposure. Preliminary results suggest border line neurological response and impairments (Bhattacharyya and others 1993). Teenage marksmen also have been noted to exhibit blood lead levels of 18-28 μg/dL (Shannon 1999).

Unusual cases of lead poisoning related to dust derive from sanding paint from scrap fencing for the construction of a home fence (resulted in 52.4 μg/dL with symptoms of spasmodic abdominal pain, anorexia, bloating and constipation) (Laszloffy and others 1999) and from workers recycling telephone wire for the copper (Lax and others 1996). The copper

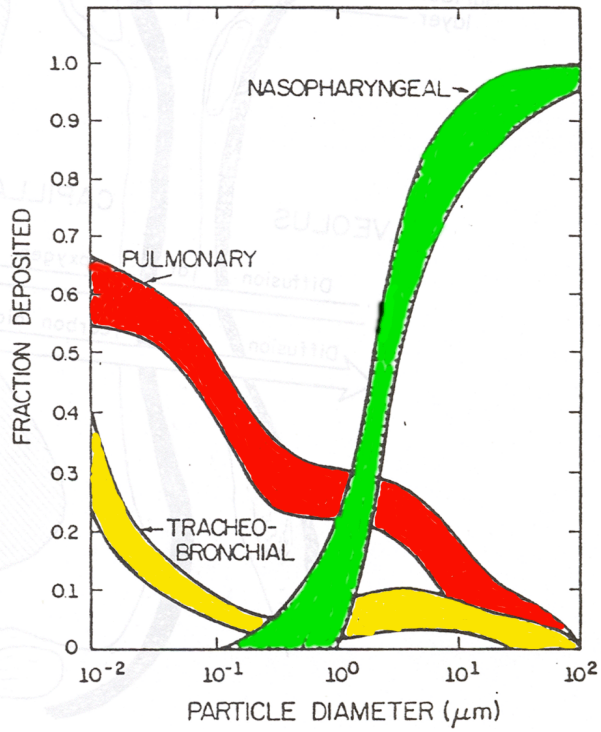

Figure 8.8. Particles above 10 microns (10^1 um) are trapped by the nasopharyngeal system and expelled. Particles less than 5 um are carried to the lung tissue. Adapted from N. Castellino et al, 1995 in *Inorganic Lead*, 1995.

wire is covered with a lead cover to shield the signal from external electric fields. Lead is either stripped off mechanically leading to mean air lead levels 2.7 times higher than OSHA standard (50 μg/m^3 8 hr) or by melting with air standards exceeded by 2.6 to 4.8 times.

It is clear that an increase in the ambient air of lead will eventually lead to an increase in the blood lead value. It has been observed that a 1-8 µg Pb/dL increase in blood lead level is the result of a 1 µg Pb/m^3 increase in the air.

These accounts suggest that one of the populations at risk for lead exposure are construction workers and military workers. For widespread exposure, in the past, particulate lead derived from auto emissions (see Chapters 7 and 10). Current wide spread exposure derives from various stack emissions (industrial and waste incinerators (see Chap. 10)) and from home renovations (wood stripping and sanding).

Inorganic particulate material moves into the respiratory track in response to a tidal flow of air in and out. The velocity and total quantity of lead inhaled depends on the respiratory activity of the individual. The upper portion (nasopharynx (West 1987)) of the respiratory system generally traps large particles (>5 µ) by a system of mucus coated cilia and simply by physics. By analogy, a large truck speeding at 75 mph will have a more difficult time maneuvering a sudden turn as compared to a smaller high performance car. This concept is related to inertia. Smaller particles will penetrate deeper into the respiratory system while larger particles will be trapped by their inability to maneuver.

In the lower trachea smaller particles can be deposited by eddy diffusion to the channel edges. Imagine a river with pools along side. The flow of water in the center of the river is linear, or uniform, but at the riverbanks the flow is turbulent with eddies. These eddies bring smaller particles to the trachea's viscous (gummy) sublayer where the force of the eddy can be sufficiently large to impel the particle into the surface (Owen 1969, p. 247). The flow rate, as mentioned above, will determine which particles have sufficient energy to stick to the trachea walls.

The bottom line is that there is a range of particle sizes (Figure 8.8 (Castellino and others 1995)) which are the most likely to penetrate to the depths of the lung and lodge in the alveoli. Once these small particles are embedded in the lungs the clearance time is much slower than the clearance time higher up in the respiratory system. In the upper region are the cilia (finger brushes (West 1987) about 5-7 µ in length, large enough to engulf a dust particle). These cilia beat at a rate of 1000-1500 times/min. During the beat, or contraction, particle matter is moved up to where it can be swallowed (into the digestive system) or coughed up. Clearance in this system is on the order of 6-8 hours.

For the small particulate matter macrophages (a large proteinaceous blob) can engulf the particle and move it along the surface to cilia escalator. Alternatively the small particle is so deeply embedded in the alveoli that it is pulled into the lymphatic system which is designed to suck large size particles from the alveoli via a "one-way" valve. Once in the lymphatic system the lead containing particle can lodge in nodules to form obstructive points within the lymphatic nodules. (This is quite common in coal miners, leading to pathologic changes in tissue).

Direct entry of the particulate, lead containing, matter into the blood stream can occur if the particle size is small enough to penetrate the channels between the lung cell tissue and the pulmonary capillaries (7 µ). Once in the blood, the amount of ionic lead (the toxic form) will depend upon acid/base and solubility

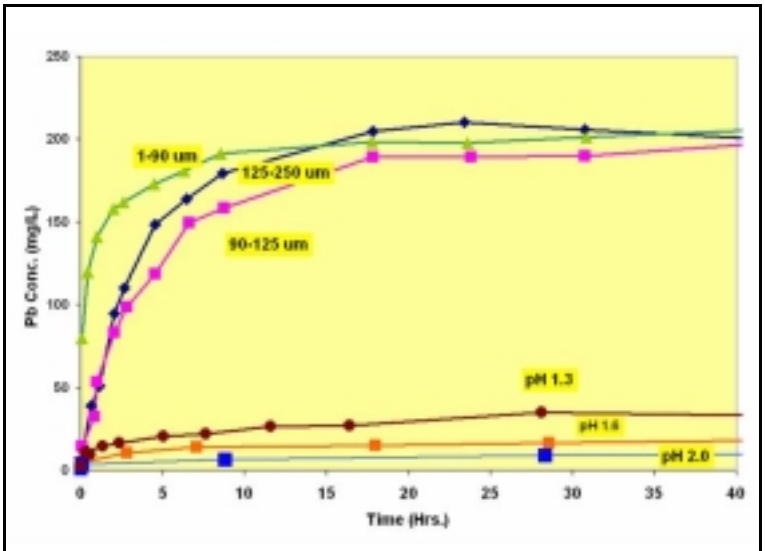

Figure 8.9. Formation of soluble lead from $PbSO_4$ in the stomach depends upon the pH and upon the particle size. The smaller the particle size the faster the solubilization. The lower the pH the faster the solubilization. Data adapted from Ruby, M. V.; A Darr, J. H. Kempton, J. W. Dreyle, P. D. Gergston, *Env. Sci. Tech*., 1992, 26, 1242-1248.

equilibria. The pH of the blood system is regulated by the diffusion of CO_2 (400 to 450 mL/minute) and O_2 (250 mL/min) across the lung tissue (Guyton 1971). Healthy lung tissue generally has a pH consistent with the blood supply, that is, it is buffered around pH 7. The amount of ionic lead likely to be present at this pH value, assuming that potential precipitating agents are carbonates and/or hydroxides, is low.

We can hypothesize that this amount of ionic lead is unlikely to create an initial severe reaction. This hypothesis is borne out by the time dependence of the demolition workers and military personnel exposed at the firing range as discussed above. Blood lead rises slowly as do the corresponding symptoms.

Lead Entry Through the Stomach

Refer to Figure 8.3. Note that the pH of the upper digestive track is approximately 2, controlled by HCl secretions and that the residence time within this portion of the stomach is two hours. Let us imagine that the particle that we inhaled has made it to the upper stomach by the clearance mechanism of the cilia. Again, let us assume that the particle is 5 µm in size and is composed of $PbSO_4$. Figure 8.9 illustrates that the particle is expected to be completely soluble in the acid media (Ruby and others 1992). The time for dissolving the particle, however, varies based on the area presented for attack by the acid (Barltrop and Meek 1979; Ruby and others 1992). Thus, if you intend to eat lead particles you are much better off eating large chunks vs grinding and eating the material. This brings us back to the point that the **physical** form of the lead will greatly impact on it's toxicity. It also allows us to note that the sanding of old painted surfaces is a particularly foolish way to remove lead. On the other hand, the **chemical** form is also important in that soils with similar lead do not present equal solubilities in gastric fluids (Gasser and others 1996; Hamel and others 1998).

After the first part of the digestive track is passed the mass of mashed material is moved into the intestine where the transfer of material into the blood stream begins in earnest. This transfer can occur via two mechanisms, a passive diffusion, or an active transport. The intestine has various active transport mechanism for other divalent cations (Ca^{2+} or Fe^{2+}). The similarity of charge and size must play an important role in the cation recognition process. Pb^{2+} masquerades as Ca^{2+} and is actively "pumped" into the blood stream. In addition, some lead diffuses (slowly!) across the lipid layer. Consequently, we can see why a person who is lead exposed is asked to add calcium supplements to their diets. The idea is that elevated calcium will compete well with the smaller amount of lead for the active transport sites (Mahaffey and Michaelson 1980; Mahaffy and others 1998; Markowitz and others 1990; Rabinowitz and others 1980; Ziegler and others 1978).

The equation which describes the two mechanisms uptake is:

[8.1]

$$\frac{d(x)}{d(t)_{total}} = \frac{V_{max} * C_M}{K_M + C_M} + KC_M$$

where the first term on the right hand side accounts for the saturation dependent active transport and the second term accounts for the passive, concentration driven, transport. V_{max} is the maximum rate for active transport and has a value of 1.44×10^{-5} µmol/min, K_M

has a value of 0.59 μM, C_M is the mucosal lead concentration, K is the diffusion constant (Aungst and Fung 1981).

Addition of calcium to the diet both swamps the passive and active transport systems and controls the entire Ca hormonal system, as will be described below under "molecular" toxicology. A low blood plasma level stimulates a high blood parathyroid hormone (PTH) which signals the body to begin increased bone remodeling (enhancing Ca supplies) and to increase Ca uptake through the gastrointestinal system. This latter effect is accomplished by having the kidney increase production of 1,25-$(OH)_2$ vitamin D which regulates Ca absorption. The role of Vitamin D in lead uptake can be shown by enhanced lead uptake with the addition of vitamin D. Consequently people who are hypocalcemic will experience greater effects from lead ingestion than those who are not. One of the prescribed dietary supplements is that of Ca (Edelstein and others 1984; Kallfelz and others 1967; Mykkanen and Wasserman 1982; Ooizumi and others 1970; Rosen and others 1980; Smith and others 1978; Wasserman and Taylor 1966).

Another dietary aid is the consumption of phosphate. The idea here is to create a more insoluble lead phosphate compound so that the dissolution of the lead is slower and less material is adsorbed during transport of the ingested material through the body.

Once lead has passed the upper gastrointestinal track it can be excreted in the feces. The amount of lead within the feces derives from the fraction material passed through the digestive track and bile excreted into the gastrointestinal track by the liver to aid in the digestion of fats. The fraction passed tends to be 50-95% of the sum of both sources. The timescale for passage is about 24 hours for the feces after injection.

The amount in the bile follows the rate at which lead is cleared through the kidneys, which tends to be within two hours (Castellino and Alog 1984; Castellino and others 1966; Castellino and others 1995).

Fate After Ingestion

Lead within the the blood stream is transmitted to soft tissues and bone materials. The half live of lead in the various organs and bones is shown in Table 8.1 (Nilsson and others 1991), see also Figure 8.3.

Blood

Once lead has entered the blood stream it can circulate within minutes throughout the body. Pb^{2+} is carried both as an ion in the plasma of the blood and as a hitchhiker on the blood cell external membrane surface where it apparently attaches to various S linkages. Lead is mainly bound to the erythrocytes (94-99%) with a 1-6% in the plasma, with the distribution depending upon the individual and the time of exposure (Ong and Lee 1980; White and Selhi 1975). The type of binding within erythrocyte fraction of blood depends upon binding to the external surface of the blood cell and uptake to the interior of the blood cell. Ong and Lee indicate that several chemical groups are involved in binding, the most important of which is a large molecule (130,000 m.w.), and to several smaller size peptides. One of the peptides contains a phosphorylated intermediate of the Na/KATPase system indicating that lead may inhibit enzyme phosphorylation.

The lead in the plasma (1-6% of the blood lead) consists of mostly protein bound lead (99%) and 1% free lead. It is the free lead which is likely to be the most formidable toxicologically. Lead induces blood thinning (reduces red blood cell count) a fact first pointed out in Laennec in 1831 (Laennec 1931). The low blood count is the result of both low heme synthesis caused by disruption of an enzyme cycle by lead (see below) and by disruption of blood cell lifespan. The clinically observed result is pallor and weakness.

The number and size of hemoglobin content in red blood cells is reduced by lead which also reduces the osmotic regulation of the erythrocyte, inducing mechanical fragility of the erythrocyte, resulting in reduced life span. Some indications of these effects are basophilic stippling of the cells (Figure 8.10). Red blood cells are produced in the bone marrow by alteration of normoblasts which lose their nucleus.

Table 8.1 : Half Lives of Lead in Biological Tissues

data: Nilsson et al., Pharmacol. Toxicol. 1991, 69, 477-484.

Compartment	Material	$t_{1/2}$
0	Blood	12-30 days
1	Kidney	7-63 days
1	Liver	7-63 days
2	Trabecular Bone	1.2 years
3	Cortical Bone	16 years (9.3-59 years)

They retain some mitochondria and ribosomes and a surface receptor for iron-transferrin complex. They stay in the bone marrow for 2.5 to 3 days and then are transferred to the blood stream. After a day in the blood stream they move to the spleen and get rid of the mitochondria and ribosomes. If ribonucleoproteins remain in the blood cell they can take up staining dyes (cresyl blue) and the result is a granulated blood cell, known as basophilic stippling. The content of the material appears to be soluble RNA, particularly messenger RNA (Jenson and others 1965; Pernis and others 1964).

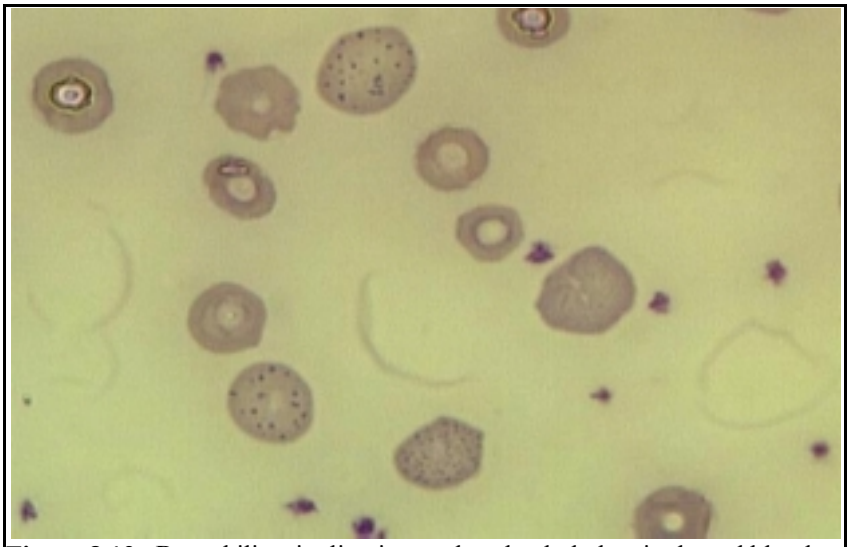

Figure 8.10. Basophilic stippling is noted as the dark dots in the red blood cell It is related to the nucleation of ribonucleoproteins in the presence of lead. This example is from dog blood. Http://www.vetmed.auburn.edu/distance/clinpath/morphol1/baso.htm Accessed: Nov. 12, 2002.

A second mode of lead action on hemeglobin is through disruption of the heme group to be inserted into the blood protein (Figure 8.11) (Fergusson 1990, p. 538). Lead interferes at several sites in this process by binding to sulphydryl groups (Moore and Goldberg 1985). The body will sense a decrease in the final heme and cause over production of zinc protoporphyrin. It is the porphyrin ring that is the active site oxygen transport throughout the body. In order to carry oxygen the center of the porphyrin ring must be occupied by iron. Iron prefers to have a coordination number of six. Four of those sites are taken up by the porphyrin ring, one more is a site on the rest of the enzyme to anchor the porphyrin within the enzyme and one site is left free to coordinate with oxygen. In order to produce active blood active heme must be present and the active form of heme must be built from the building block of a porphyrin group. Since lead interferes with the final insertion of iron into the porphyrin the body senses a decreased heme concentration and attempts to restore balance by an over production of zinc protoporphyrin. This over production serves as a convenient marker for lead poisoning (see Figure 8.12 (Hammond and others 1985)) (Blumberg and others 1977; Clark and others 1985).

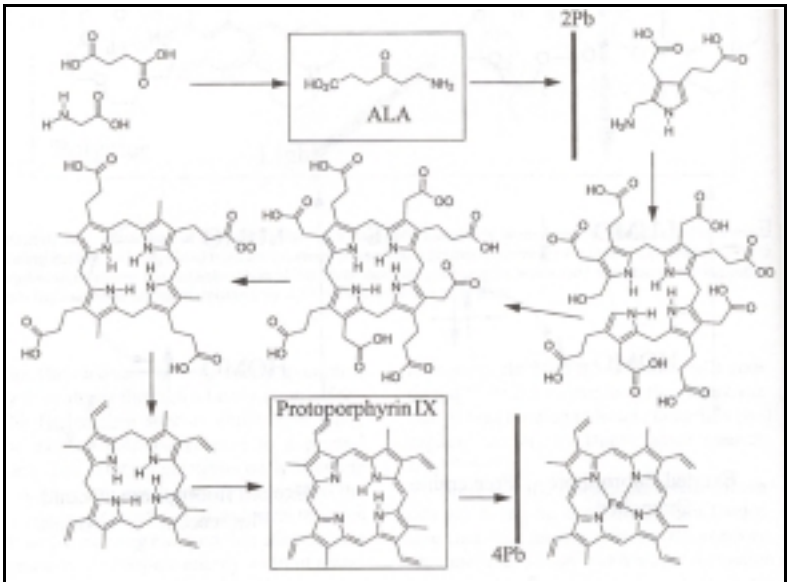

Figure 8.11. Lead disrupts the formation of the active oxygen carrying components of blood. The chemical precursors just before the reactions shut down points are ALA and Protophorphyrin IX. Data source: Warren et al, TIBS, 1998, 23, 217.

Lead inhibits the function of the enzyme catalyst ALA dehydrase (ALAD) which is also important in heme synthesis (Figure 8.11). The body continues to produce the precursor to this step sensing

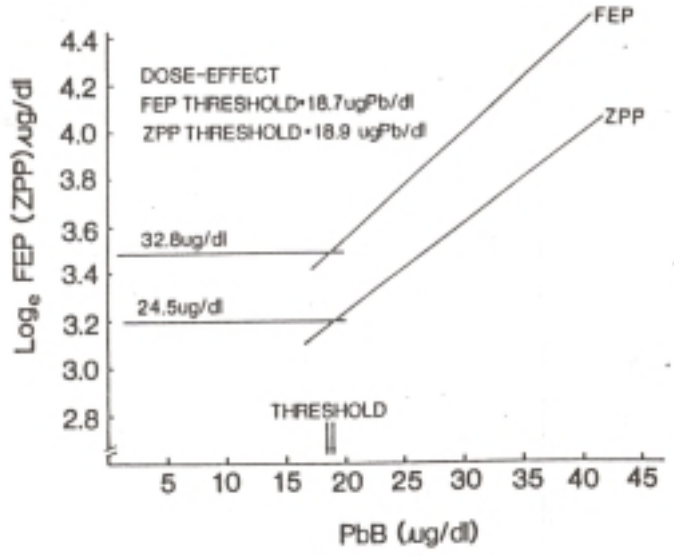

Figure 8.12. A rise in protoporphyrin IX is linked to a threshold value of lead in the blood. Figure from P. B. Hammond, R. L. Bornschein, P. Succop, Env. Res. 1985, 38, 187-196.

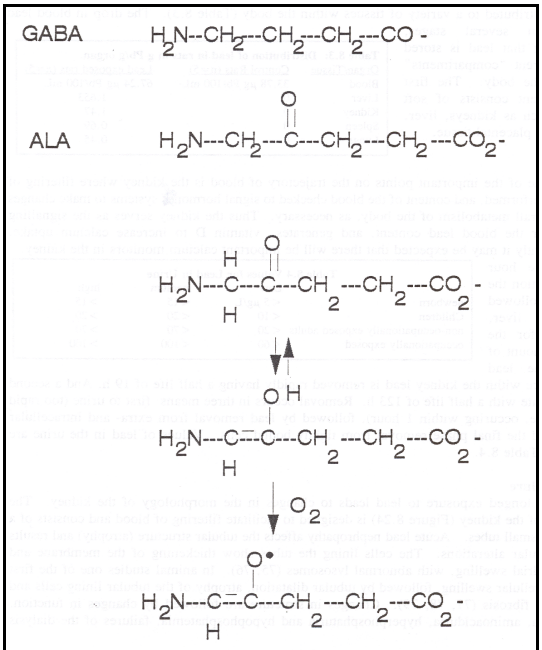

Figure 8.13: ALA can tautamerize to a form that looks very similar to GABA, a neurotransmitter.

an imbalance. This precursor, ∂aminolevulinic acid (ALA) correspondingly rises in concentration (Monteiro and others 1986). An overload of ALA is a problem for two reasons. ALA is similar in chemical structure to γ-amino butyric acid GABA (Figure 8.13). GABA is a compound which flows from neurologic to neurologic synapsis. It is found in the cerebral cortex and is associated with stress, anxiety, and hyperactivity. ALA, because of structural similarity, is apparently able to bind to GABA synaptic sites (Altmann and others 1988; Hermes-Lima and others 1991). This has been suggested to be the route by which lead causes attention deficit and learning disorders (Blais 1996; Dietrich and others 2000),, (Fergusson and others 1988), (Winneke and others 1990).

Zinc binding domains. **ALAD**. The enzyme has two separate zinc-binding sites: one made up of cysteine residues (the B site) and the other of more polar ligands (the A site) with the A site apparently essential for catalytic activity, with the B site helping to direct the correct folding of the protein. Lead binds to the cysteine, B, sites and could inhibit the enzyme either by steric obstruction or by its inability to function as a Lewis acid (Figures 8.14 and 8.15) (Warren and others 1998). The reason that lead does not function as a Lewis acid is due to its low charge density ratio (large atomic volume). Lead binds preferentially to the cysteine sites because the active group on the cysteine is sulfur, for whom lead has a particularly high affinity.

Disruption of ALA dehydratase function occurs in a hereditary blood disease or neuroporphyria. This disease causes symptoms similar to elevated blood lead poisoning because of an ALD deficiency. King George III (Figure 8.16) and other members of the English royal family have hereditary neuroporphyria. In King George III's case the disease was marked by learning disability (he did not read until the age of 12), and fits of rage. He was ultimately declared legally insane (Mamet and others 2001), (Warren and others 1998), (Warren and others 1996).

The ALAD system has been extensively studied because it is one of the earliest markers of the effect of lead on physiology. It has further been noted that the genetic code for ALAD has two different genotypes which are variability susceptible to lead poisoning (Gerhadrsson and others 1999; Jaffe and others 2000; Nomiyama and others 1999). A population of Taiwanese showed that these genotypes were distributed as ALAD 1-1 (95.4%) and ALAD 1-2 or 2-2 (4.6%) (Hsieh and others 2000). Individuals with ALAD2 alleles had 20% higher blood lead level, but the correlation was not maintained after correction for risk factors. An earlier study also suggested that

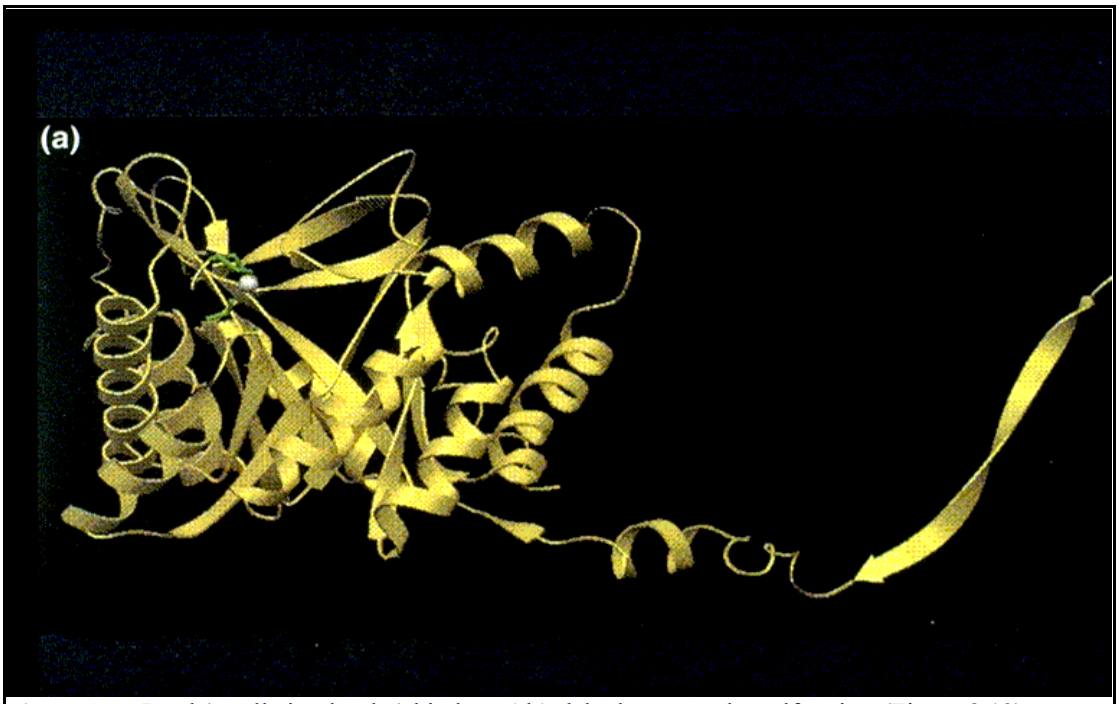

Figure 8.14 Lead (small circular dot) binds to AlA dehydratase at the sulfur sites (Figure 8.12) ultimately causing a disruption in the function of ALA dehydratase. Warrens et al TIBS, 1998, June, 23, 217.

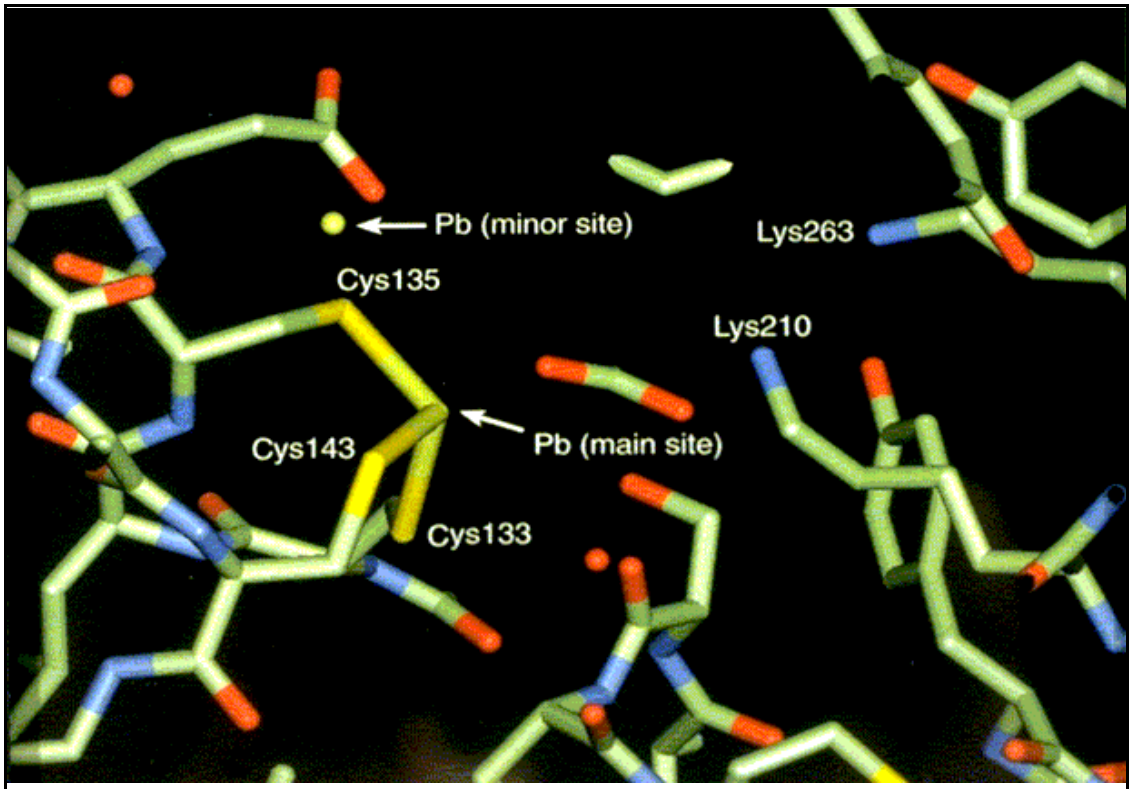

Figure 8.15: Lead binds to sulfur inthe cystein (Cys) sites in ALA dehydratase. Warren et al., 1998, TIBS, 23, 217.

the ALAD2 allele resulted in a higher risk for lead poisoning (Astrin and others 1987). The mechanism by which the second allele increases susceptibility to systemic lead poisoning has been postulated to occur via an increase in blood lead by attachment to the ALAD2 allele, which then is cycled to other organs in the body (Claudio and others 1997). It has been estimated that nearly 40% of lead in blood is bound to ALAD (Wetmur 1994).

A second gene, vitamin D receptor (VDR) is involved in calcium absorption through the gut, also exhibits VDR polymorphism which may influence the accumulation of lead in the bone (Onalaja and Claudio 2000; Schwartz and others 2000).

Another problem with an enhanced concentration of ALA is tautomerization of ALA to a form which makes it easy to form a radical. What this means is that a proton on ALA moves, allowing an electron rearrangement which makes final oxygen removal of an electron more facile. The resulting single electron is unsatisfied. These free radicals are capable of acting as loose cannons, indiscriminately scavenging electrons throughout the tissue system, potentially activating cancer sites.

One more specific site for free radical attack may very well be the oxygen containing form of the intact heme group. Since the heme group is specifically designed to facilitate electron transfer, enhanced and uncontrolled electron transfer events within cell walls may lead to cell wall destruction (Ribarov and Bochev 1982). The lifetime of the heme oxygen carrier is significantly reduced (20%) by the effect of lead within the body (Hammond and Dietrich 1990).

Figure 8.16: King George III of England suffered from a hereditary blood disorder which affects ALA dehydratase production, in essence, mimicking the effects of lead poisoning. This disorder left him unable to read until he was 12, subject to fits of raving, or foaming madness in 1788, 1891, 1804. He was declared permanently insane in 1810.

It is possible that changes in the structure of the blood cell and the decrease in the blood cell content in the plasma are related to changes in the blood pressure that result in hypertensive crises, particularly in the case of acute lead poisoning. It has been postulated that renal upregulation of blood pressure is involved.

It has been suggested that the preindustrial human PbB level would have been as low as 0.12ug/dL or 0.016 ug/dL (Flegal and Smith 1992; Mushak). These estimates of pre-industrial blood lead levels have been corroborated by an investigation of marine Northern elephant seals. These animals were chosen for study because it was felt that their unique physiological and behavioral adaptions shield them from exposure to terrestrial lead contamination (Owen and Flegal 1998). Seals contained 0.13 ug/dL blood lead.

Figure 8..17. Beethoven (Pen and ink by Al B. Benson, III)

Deposition to solid material

Blood is circulated throughout the body within about four minutes. From the blood lead is distributed to a variety of tissues within the body (Figure 8.3). The drop in blood lead occurs in several stages, suggesting that lead is stored into different "compartments" within the body. Lead is deposited rapidly to soft tissue and over a longer period to storage sites such as hair and nails, bone and teeth. Hair will not contribute to further episodes of lead poisoning as it is not readsorbed. It serves, barring contamination, as a permanent record of lead exposure.

Deposition to Hair: Beethoven

Lead is deposited through the blood stream to the hair follicle. The average growth of hair is 1 cm/month so sectioning of hair can give a record of the uptake. Deposition appears to derive from the soft tissue compartment since the kinetics following lead exposure do not match that of blood. The hair begins to show an increase after 30 days of exposure.

Children living near smelters have a high content of lead in the hair (Wibowo and others 1986). The relative amount of lead in the hair varies by age and gender and can be contaminated, particularly by smoking.

An example of diagnosis of lead poisoning by hair sampling is that of Beethoven (Figure 8.17). In 1795 Beethoven began to experience frequent and often intense abdominal pains (Bankl and Jesserer 1986; Martin 2000). By 1798 he was complaining of an inability to hear what people said and experiencing buzzing and ringing in his ears. In 1801 he had diarrhea, fever, abdominal cramping which stayed with him for the next several years. In 1802 Beethoven wrote a letter to his brothers describing his growing

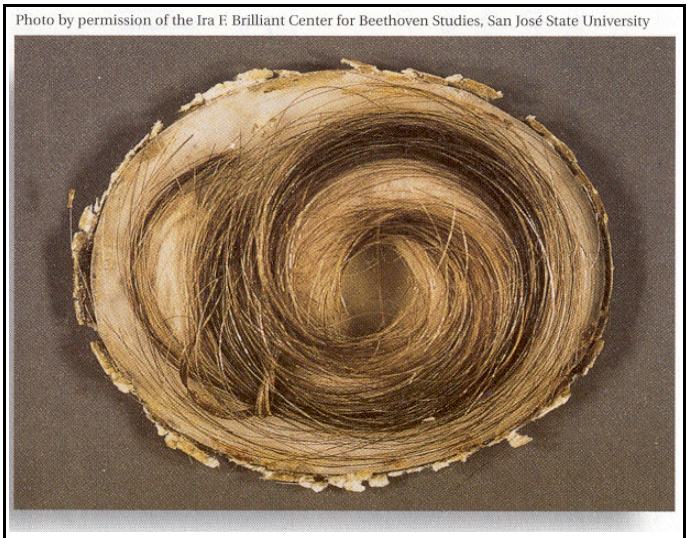

Figure 8.18 Beethoven's hair.

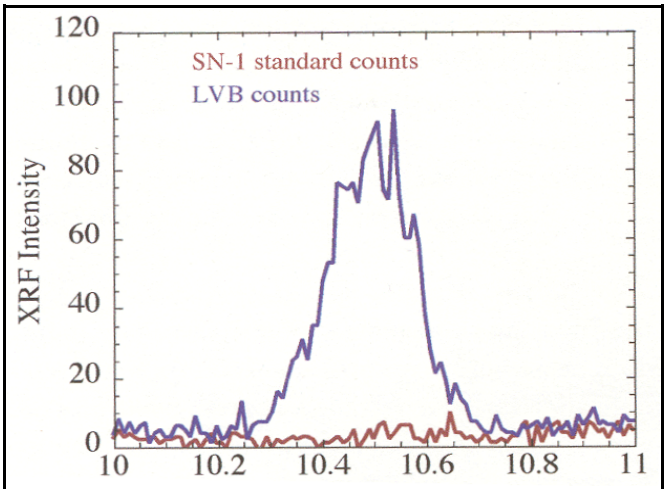

Figure 8.19 X-ray fluorescence of Beethoven's hair shows a characteristic peak for lead where the standard does not.

deafness, abdominal pains, irritability and depression severe enough to contemplate suicide. His personality changed during his illness from friendly and pleasant to irritable, hot tempered, and socially isolated with bouts of intense depression. In 1807 he had several teeth puled hoping to avoid his "gouty headaches". His hearing continued to decreased and he began to be plagued by rustling sounds. In 1820 all of the abdominal ailments returned in force along with rheumatism. The symptoms of diarrhea and constipation carried through to 1822. In 1823 he complained of a gout in his chest. In 1825 his abdomen began to swell and he had severe back pain. His final death was due to failure of his liver. In 2000 a lock of his hair (Figure 8.18) was analyzed at Argonne National laboratory with X-ray fluorescence (Figure 8.22). The amount of lead found within his hair was consistent with moderate to high lead poisoning (ANL 2002; Gorner 2000). The lead content was 60 ppm. For a non-exposed adult in 2002 a typical value would be 0.6 ppm. The fact that lead was found in his hair suggests that his lead exposure was either chronic (right up to his death) or that an early intense insult resulted in bone lead storage which was remodeled in his later years.

Lead and Storage in the Bone (Compartments II and III)

Early studies on lead deposition to bone suggested that most of the lead could be stored harmlessly within the bone (Aub and others 1924a; Hunter and Aub 1927; Minot and Aub 1924b), (Minot and Aub 1924a). Later studies showed that lead stored in the bone during high exposure can lead to episodic lead poisoning long after exposure has ceased.

Lead is deposited with the bone mass due to the very high insolubility of lead as a replacement for calcium in hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_6$). Lead is found in teeth and bone material. This process could be considered a simple solubility problem. However, it would be difficult to keep the bone either from dissolving or from precipitating throughout the body as the plasma concentrations of Ca^{2+} and PO_4^{3-} were either high or low.

As might be expected nature has devised a means of regulating the calcium supply so that bone material can be dissolved if necessary, as for starvation, pregnancy and lactation where Ca^{2+} is needed elsewhere (for example, in muscle tissue and in cell metabolism). Alternatively, bone material can be deposited if necessary. The total plasma concentration of calcium and phosphorus is 8.8 to 10.4 mg Ca^{2+}/100 mL (2.2 to 2.6 mM) and 2.8 to 4.0 mg P/100 mL (P as HPO_4^{2-} and $NaHPO_4^-$). The major control on bone turnover is the hormone parathyroid and vitamin-D which controls the cell level of Ca^{2+} in the collagen which forms the matrix in which bone is deposited.

Bone is categorized into two types according to density. Trabecular, for instance, is relatively porous and appears to the eye as "spongy" in texture (Figure 8.20). This type of bone can be found at the ends of major long bones (such as the femur or tibia) and

Table 8.2: Pb, ppm, in contemporary bones

a) Barry, P. S. I., Br. J. Ind. Med., 1975, 32, 119-139.
b) Gross, S. B., Pfitzer, E. A., Yeager, D. W., Kehoe, R.A., Toxicol. Appl. Pharmacol. 1975, 32, 638, 651
c) Barry, P.S.I., and Mossman, D.B., J. Ind. Med., 1970, 27, 339-351

	Non-exposed Population				Exposed
bone	Adult Male	Adult Female	Child	Average	Adult Male
petrous temporal	33.71[a]	26.6[a]	5.8[a]	22[a]	85.5[a]
tibia	23.4[a], 32.6[b]	15.9[a]	2.7[a]	14[a], 14.09[c]	74.01[a], 59.2[b]
calvarium	20.17[a]	16.46[a]	4.8[a]	13.8[a], 13.8[c]	59.75[a]
rib	8.85[a], 13.6[b]	6.77[a]	2.16[a]	5.9[a], 7.14[c]	29.92[a], 35.6[b]

makes up a large portion of the vertebrae, pelvis and ribs. Trabecular bone is characterized by its rapid turnover rate. That is, bone tissue is more rapidly forming and being resorbed in these areas of the body than in the more densely packed bone areas. The second type of bone, compact bone, is solid and dense. This type of bone can be found in the shafts of the long bones and in the skull. Turnover rates in these areas of the body are slower. Lead, therefore, while theoretically being deposited equally throughout the skeletal system, will be re-mobilized continuously from trabecular sources, while remaining as long-term deposits in compact bone. Lead levels in trabecular bone may therefore be indicative of short-term exposure (Barry 1975). The average half life for lead to be transferred between bone and slow bone is 1.2 vs 16 years. Deposition, on the other hand, can be very rapid (several days) for suckling rats.

Values of lead in a variety of long bones from 1975 can be seen in Table 8.9. The data in Table 8.2 indicate that lead is not homogeneously stored throughout the skeletal system. Bones with higher amounts of trabecular bone (and thus greater turnover rates) display lower lead values. Although the average adult bone calcium turnover is about 1 g/day (Hyvonen-Dabek and others 1981), lactating women and growing children will have higher turnover rates, and thus will exhibit lower levels of stored lead than adult males.

Because the bone material is constantly adsorbed and released, particularly during pregnancy transfer of lead from a mother to an infant can occur and should be considered in lead treatment. Bone lead in mothers has been identified as an independent risk factor for fetal neurotoxicity (Gomaa and others 2002). This study showed that the mental development index (MDI) scaled with maternal Xray fluorescence of bones. The data also indicate that lead exposed individuals have a significantly higher amount of lead in all bone types than non-exposed individuals. Lead is mobilized from the bones of mothers to children during nursing ((Gulson and others 1998).

Childhood lead exposure may also be linked to adult onset of osteoporesis. The authors of this study suggests that lead exposure during peak bone formation may prevent optimal density of bone formation (Wentzel 2002).

Bone lead can be an endogenous source of blood lead. Bone lead is capable of sustaining 35 g/dL of blood lead, leading to classic symptoms of lead poisoning even in the absence of ongoing exposure (Erkkila and others 1992; Schutz and others 1987):

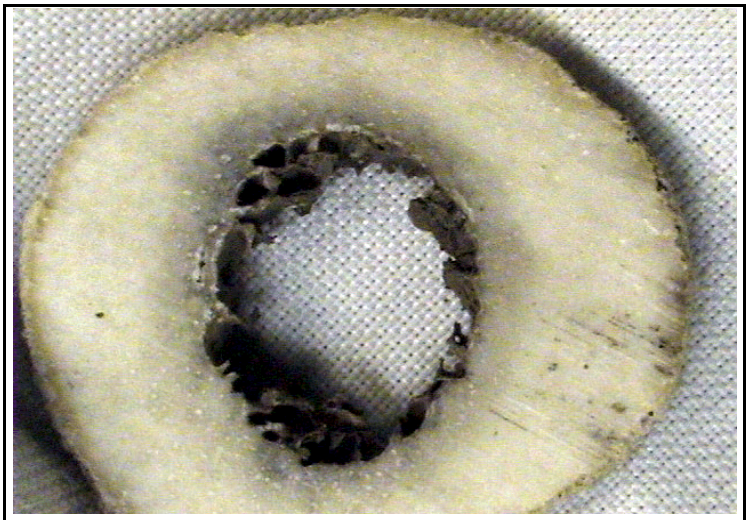

Figure 8.20. Bone section shows the interior of a bone mass with the porous internal matrix.

[8.1] $Pb_{sk} = 2.2xPb_{tibia} + 0.5xPb_{calcaneus}$

[8.2] $Pb_{blood} = 0.00218xPb_{sk} + 0.352$

where Pb_{sk} is the estimated amount of lead in the skeleton based on lead in the tibia and calcaneus bone (skull). Once an estimate of the total skeletal lead is made the blood lead can be calculated from equation 8.2.

One example of this is the case of a 72 year old man who 30 years previously had worked in a metal factory. He was admitted to the hospital with for headache, drowsiness, eand two generalized convulsions. Five years early he had developed hypertension, diabetes mellitus and chronic renal impairment (Teo and others 1997).

Women entering menopause have a higher level of bone turnover. Lead mobilized during this time can lead to greater hypertension (Nash and others 2003b).

Because of the impact neurologically on attention and executive effects, exposure presents a critical risk to children in the rapid learning ages. Also, risk to children is increased because of rapid bone turn over and storage (Hammond and Dietrich 1990).

Chronic levels of lead are thought to be tracked by bone lead. It was found that while low blood levels were observed that significant patella bone lead levels (measured non-invasively by X-ray fluorescence) were associated with hematopoieus (Hu and others 1994). In carpenters bone lead levels in the tiba (cortical bone) and patella (trabecular bone) means were 9.8 μg Pb/g bone and 14.0μg Pg/g bone. Both levels were correlated with age, welding, paint stripping, carpet laying, and lack of exercise which contributed to bone lead levels long after current activity. Carpet laying exposure correlation with lead is thought to be related to the carpet as it is a long term sink for leaded dust (Watanabe and others 1994). Bone lead exposure (long-term accumulation) appears to be an independent risk factor for development of hypertension in men (Hu and others 1994).

8.2.B. Compartment 1

We mentioned earlier that blood lead values drop rapidly and then slowly, indicating deposition first to soft tissue and then to the bone. Soft tissues include kidneys, liver, brain, and placental tissue (Figure 8.3 and 8.21).

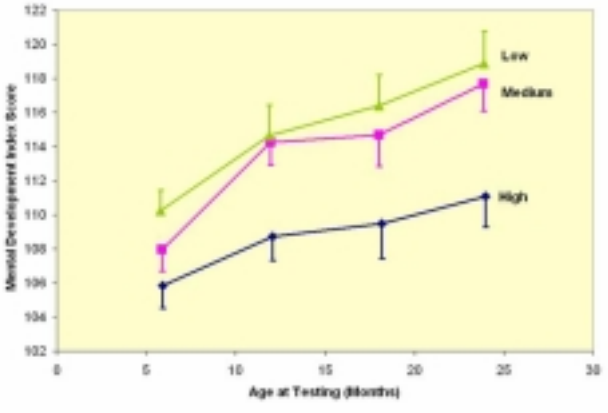

Figure 8.22: Mean Developmental Index Score increases with age. It also varies with the amount of blood lead in the umbilical cord at time of birth. Data source: D. Bellinger, A. Leviton, C. Watermaux, H. Needleman, M Rabinowitz. Ew England J. of Medicine, 1987, 316, 17, 1037.

Deposition to Placental Tissue

Maternal blood distribution to fetal blood results in transfer of lead to the fetal system, including the placenta tissue (Figure 8.22). The ratio of Pb in fetal blood compared to maternal blood is 0.73 to 0.92 indicating passive transfer of lead. The early literature was very clear on the possibility of spontaneous abortion, but the levels of lead exposure were also a lot higher. Later literature is not conclusive upon the effects of lower levels of lead and stillbirth (Sabatelli and others 1995). There does, however, appear to be a correlation. Placental lead correlates with negative outcome of pregnancy (Baghurst and others 1991; McMichael and others 1986). A correlation between placental tissue and stillbirth or neonatal death can be shown (Wibberly and others 1977).

Kidney

One of the important points on the trajectory of blood is the kidney where filtering of blood is performed, and content of the blood checked to signal hormonal systems to make changes in the overall metabolism of the body, as necessary. Thus the kidney serves as the signaling source for the blood calcium content, and generates vitamin D to increase calcium uptake. Consequently it may be expected that there will be important calcium monitors in the kidney.

One hour after injection, the kidney, followed by the liver, accounts for the largest amount of soft

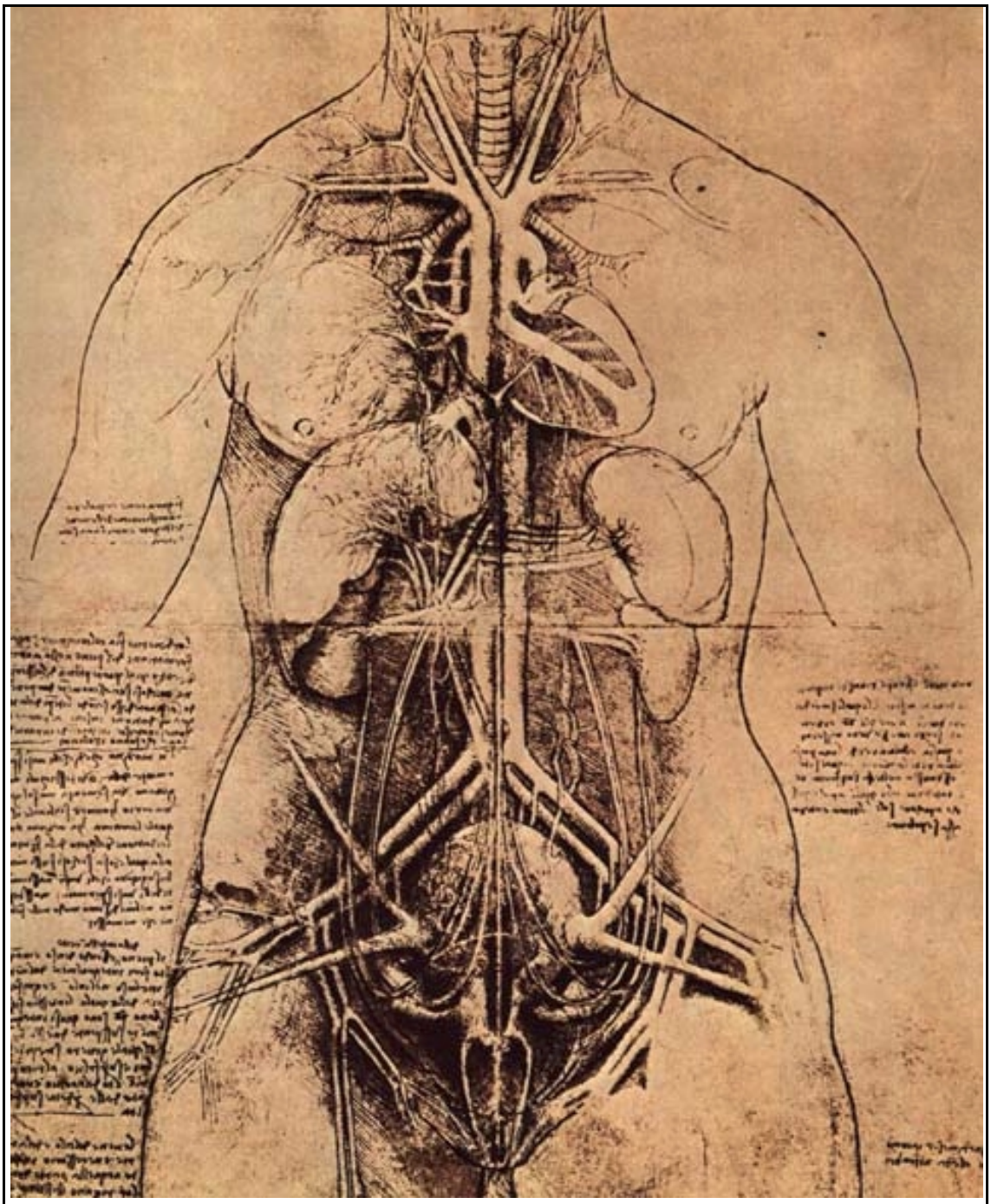

Figure 8.21: Compartment 1 for deposition of lead is to the "soft" organs in the main torso of the body, The four main organs shown in this diagram of Leonardo da Vinci are (clockwise from upper right): the heart, the spleen, the kidney (just under and behind the spleen), and to the left, the liver. (Leonardo da Vinci).

tissue lead (Castellino and Alog 1984). Once within the kidney lead is removed rapidly having a half life of 19 h. There is a second removal rate with a half life of 123 h. Removal occurs in three means: first to urine (too rapid to measure, occuring within 1 hour), followed by lead removal from extra- and intracellular

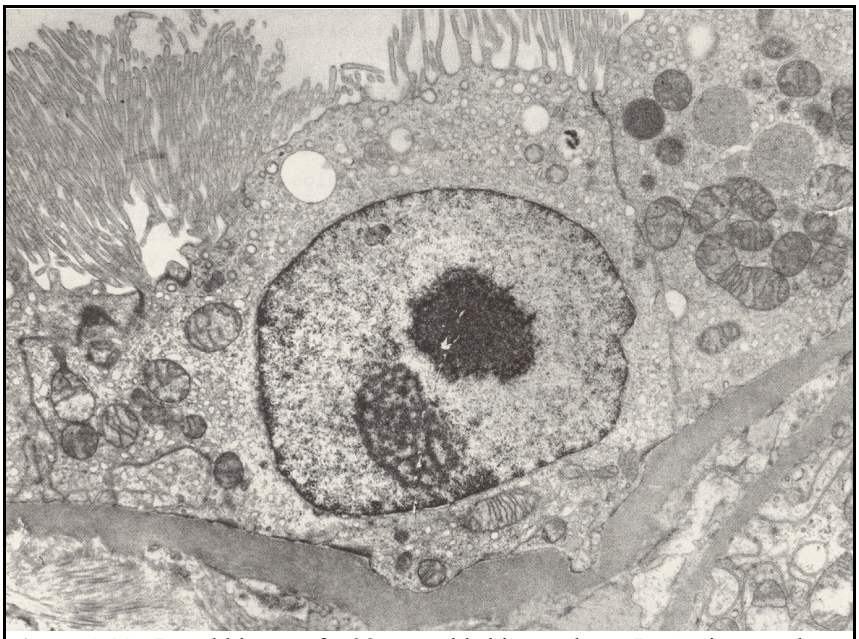

Figure 8.23. Renal biopsy of a 28 year old shipwrecker. Dense intranuclear inclusion body is characterized by a fibrillary outer margin. Cramer, Goyer et al, Brit. J. Indust. Med., 31:113-127, 1974.

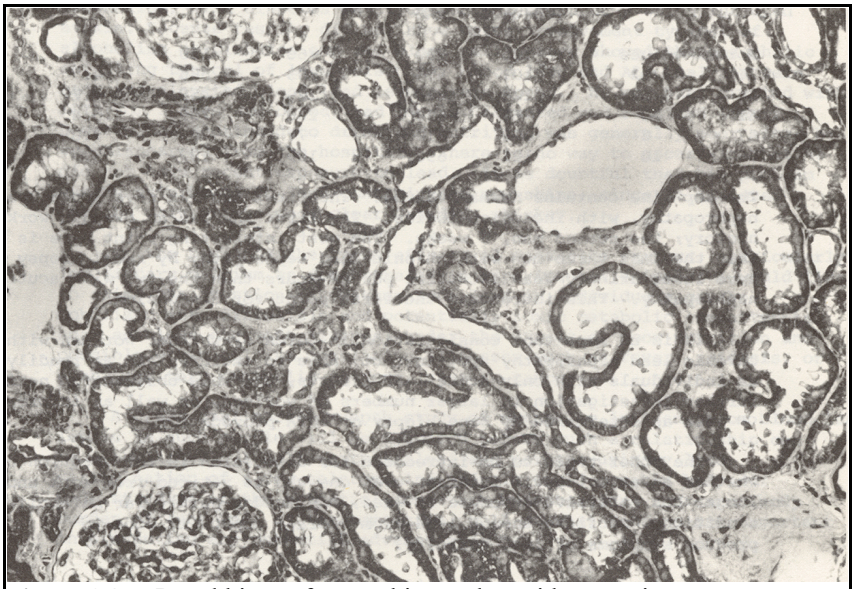

Figure 8.24. Renal biopsy from a shipwrecker with excessive exposure to lead showing interstitial fibrosis with atrophy of some tubular lining cells. Cramer, Goyer et al, Brit. J. Indust. Med, 1974, 31: 113-127.

fluids, and the final phase removal from tightly bound cells.

Renal Failure

Prolonged exposure to lead leads to changes in the morphology of the kidney. The structure of the kidney is designed to facilitate filtering of blood and consists of a variety of small tubes.

Acute lead nephropathy affects the tubular structure (atrophy) and results in glomerular alterations (Figure 8.24). The cells lining the tubes show thickening of the membrane and mitochondrial swelling, with abnormal lysosomes (Aub and others 1924b; Crosby 1957). In animal studies one of the first effects is cellular swelling, followed by tubular dilatation, atrophy of the tubular lining cells and interstitial fibrosis (Figure 8.14) (Goyer 1968; Goyer and others 1970; Vyscocil and others 1989). Changes in structure are followed by changes in function. Glycosuria, aminoaciduria, hyperphosphaturia and hypophosphatemia, failures of the dialysis system, are part of the symptoms of acute lead intoxication (Chisholm Jr. 1971).

The link between the kidney and acute lead poisoning was first described in 1862 in *Gazette Medicale de Paris* by Lancereaux. The case involved a painter who began painting at the age of 12 and was hospitalized 22 years later. On hospitalization she had pallor, loss of weight, paralysis of the upper and lower limbs, convulsions, muscular atrophy, violent muscular pains. After death her autopsy showed (Castellino and others 1995):

The kidney volume is reduced, the fibrous capsule is easily detached from the cortex, the surface is disseminated with small, white, miliary granulations. Tubular atrophy. Renal atrophy is more pronounced in the right than in the left kidney. Tubular epithelium is partially destroyed; interstitial matrix is increased

[hyperplasia].

Low dosages of lead have not yet been proven to cause renal effects in the general public.

The Kidney and Blood Volume

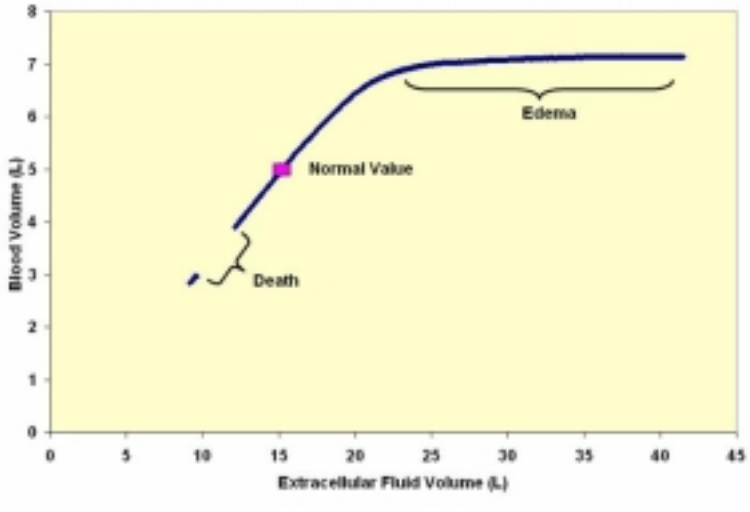

Figure 8.25. Relationship of blood volume to extracellular fluid volume.

The failure of the kidney has two important consequences. The first is an inability of the body to regulate the blood volume and the second is an inability to regulate uric acid cycles.

The kidney not only filters but controls the total volume of liquid retained or excreted from the body. The total volume of body fluids (~40L) is partitioned into 5 L of blood, 25L of cellular volume and 15 L of extracellular volume. The extra cellular volume is controlled by the intact function of the kidney in excretion of urine. Decrease in kidney function causes extracellular fluid volume to increase. When the extracellular fluid volume exceeds ~20L, the blood volume goes up (hypertension) and edema can result (Figure 8.25).

In late 2002 a study from John Hopkins University indicated that 16 to 19% of deaths due to cardiovascular

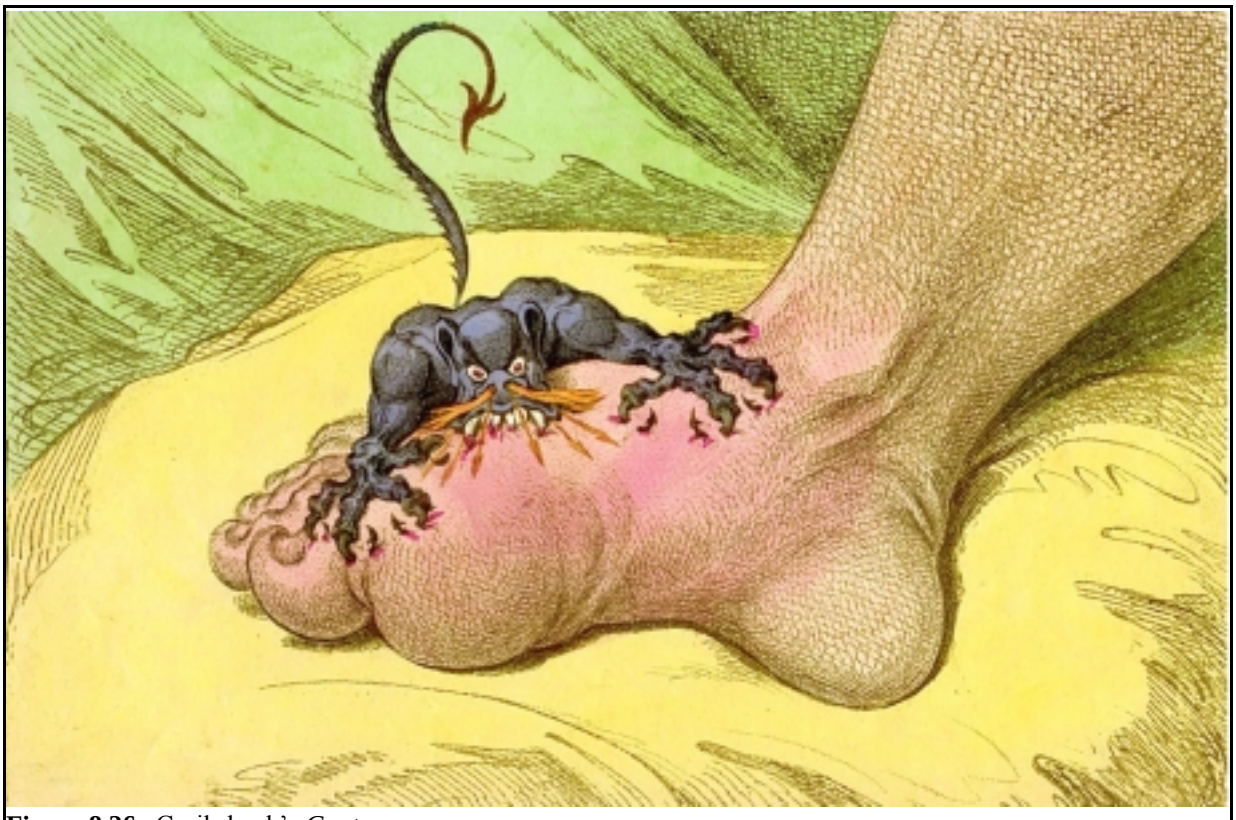

Figure 8.26. Cruikshank's *Gout*.

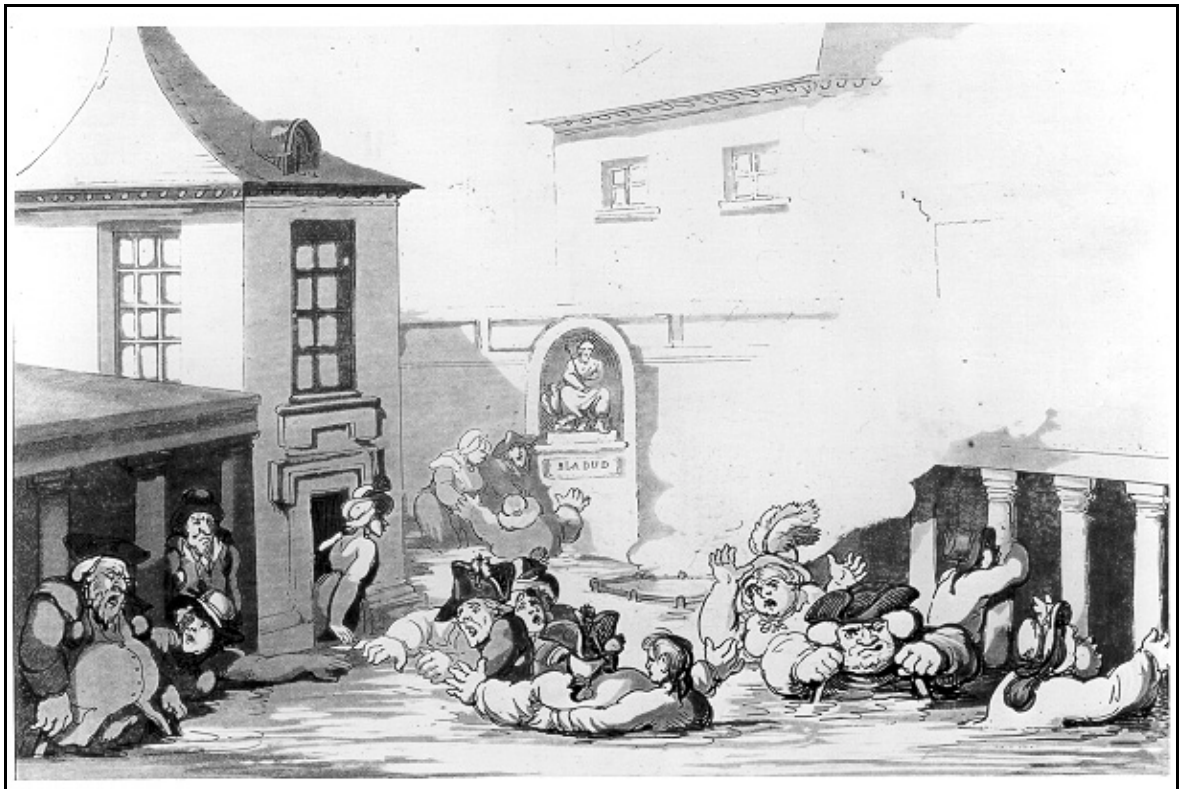

Figure 8.27. Thomas Rowlandson's *The King's Bath*, 1794. Gouty gentlemen and a few women take the prescribed bath treatment. From *The Comforts of Bath*.

Figure 8.28. Bathing in Bath in the late 1800s. Http://www.bathspa.co.uk/projects/health.html accessed Nov. 14, 2002.

disease can be attributed to lead exposure. These deaths represent people who had prior lead exposure. The study accounted for other risk factors such as age, sex, smoking, wight, education, neighborhood, exercise, and income. The fact that so many deaths can be attributed to lead may explain the overall higher rate of cardiovascular disease in the American black population (Nash and others 2003a), (Lustberg and Silbergeld 2002).

The Kidney and Gout

Gout is a disease involving a disturbance of the uric-acid metabolism and is marked by arthritic attacks. Excessive production of purines and decreased excretion are implicated in gout. The free purine bases (xanthine) are used to form new nucleotides and some are excreted (urine). Excess uric acid can be crystallized as sodium urate in the joints at pH levels higher than 7.4. Precipitation as amorphous sodium urate occurs in any tissue except the central nervous system with minimal inflammatory response. Precipitation as microcrystals in the synovial tissues and spaces (joints) leads to an attack of the crystals by

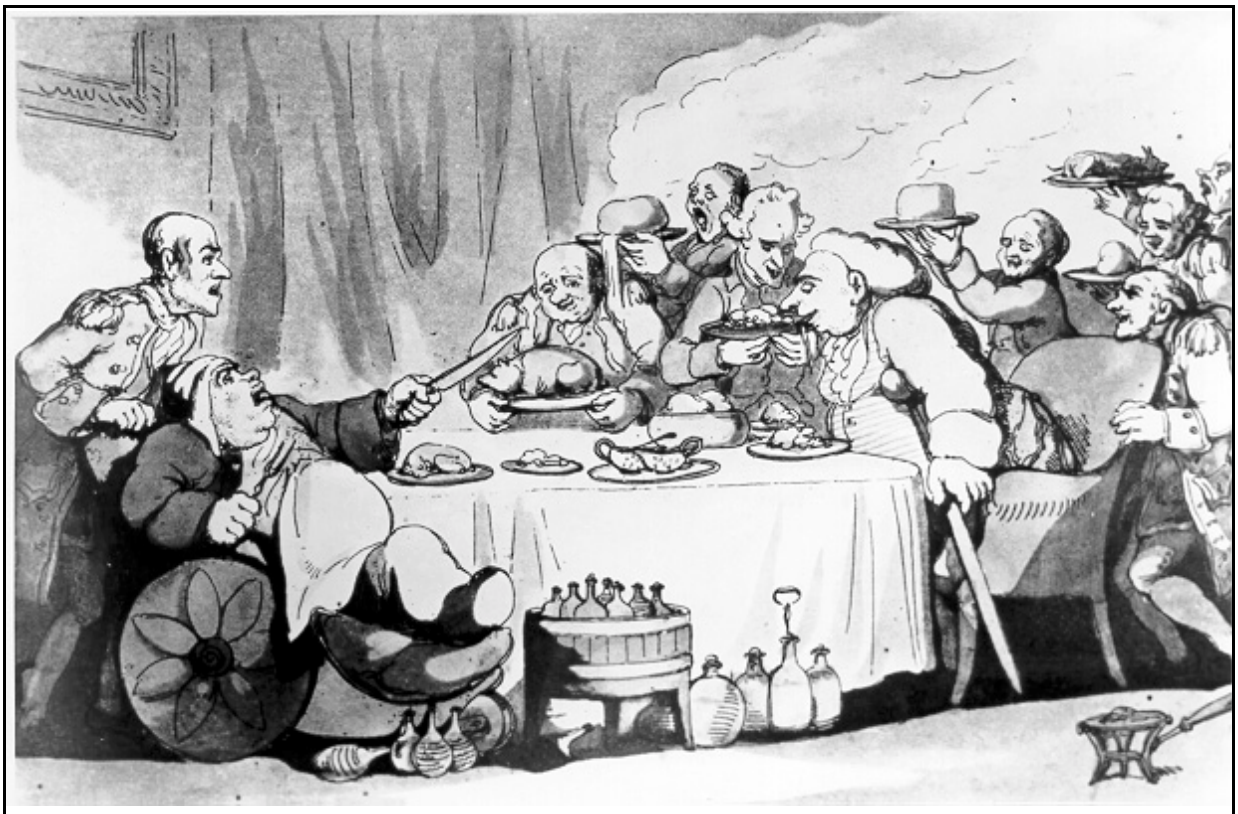

Figure 8.29. Thomas Rowlandson's: *The Dinner*, 1794. Gouty gentlemen drink and eat lavishly. From *The Comforts of Bath.*

leukocytes. This involves release of lysosomal enzymes upon destruction of the leukocyte cell membrane with release of the cell content into the surrounding tissue. The result is suicide of the cell and the initiation of an inflammatory response (swelling and pain of the joints (Figure 8.26)). Acute gouty arthritis has been described by Sydenham:

it [the affected part] is not able to bear the weight of the cloths upon it, nor hard walking in the chamber....[the pain is] like the gnawing of a dog.

Gout has been correlated with lead exposure, with Garrod in 1859 first suggesting the correlation, on noting that 37% of his gouty patients were painters (Garrod 1859). Arthritic lesons associated with gout are normally found in the metatarsophalangeal joint, but can be observed in gout associated with lead in the wrists, knees and hands, as was observed in 1881 by Lanceraux (Lancereaux 1881). Gout is the result of uric acid hyperproduction (15-20% of the cases), reduced renal excretion leading to hyperuricemia (15% of the cases), and increased production, decreased excretion occurring in 70% of the cases. Lead initiates gout by affecting the renal tubes and reducing excretion, a theory proposed by Garrod in 1859. The excess amount of uric acid crystallizes within the joints.

Gout and Bathing

Immersion of the body up to the neck in water of any temperature causes a pressure gradient from the head to the body. Blood is squeezed toward the brain increasing the blood volume of the head. The body compensates by increased urination to reduce the blood volume. Increased urination increases the excretion of various electrolytes including calcium and lead.

Gout was very prevalent in the upper classes of England between 1700-1850, most likely related to lead treated wines. The standard treatment for gout was a several week therapy of bathing in Bath. (Figures 8.27 and 8.28). Historical records found by Audrey Heywood indicate that 7% of paralytic Bath patients were diagnosed with *colica pictonum* (a lead disease related to consumption of lead laced cider). Other patients suffered from "Dropsy" which was edema or swelling of the limbs. These patients benefited from the

bath therapies.

Advertisements for the Bath regimen indicated that

The Most Sovereign Restorative
Wonderful and most EXCELLENT agaynst all diseases of the body proceeding of a MOIST CAUSE as Rhumes, Agues, Lethargies, Apoplexies, The Scratch, Inflammation of the Fits, hectic flushes, Pockes, deafness, forgetfulness, shakings, and WEAKNESS of any Member - Approved by authoritie, confirmed by Reason, and daily tried by experience.

The list of diseases cured by bathing could double as a list of symptoms associated with lead poisoning (Epstein 1992; Heywood and others 1986; O'Hare and others 1985).

Liver

One of the functions of the liver is to produce bile which is put back into the gastrointestinal track to assist in digestion of fats. Lead appears to be excreted from the liver into the bile readily and forms one of the sources of lead in the feces. The uptake of lead into the liver, like that into the kidney, is rapid (1-2 hours) and the removal, like that of the kidney, is biphasic. There is rapid excretion into the bile, followed by slower removal from intercellular material and from strongly bound cells.

Acute cases of lead poisoning can lead to minor levels of increase in serum hepatocellular enzyme levels (Anzelmo 1995).

The liver tissue goes in for its share of lumps, too. The liver is crucial in the metabolism of carbohydrates, fats, and proteins. Because of its high metabolic function the disruption of oxidative phosphorylation (ATP-ADP) that we examined earlier is particularly bad. A loss of energy control can result in major structural changes in the liver (Franchini and others 1992). The liver gets a double whammy because it is involved in production of blood. Lead ion, Pb^{2+}, attaches itself to the erythrocyte (red blood cell) membrane, which is then transferred to the liver. Lead, as a result, is delivered at higher rates to the liver. The liver is also involved in storing small colloidal particles, so that lead in the liver again is elevated (Cornell and Filkins 1974).

Lead and the Brain

The brain tissue also shows accumulation of lead as part of the soft organs of the body. Autopsies

Figure 8.30: Goya's *Reason Takes Flight*

on humans show concentration in tissues including the brain (Schroeder and Tipton 1968). Analysis of animal parts found the pigs contained measurable lead levels in the brain (Cattaneo and Balzaretti 1984). Similar distributions have been found with experimental suckling rat studies (Kostial and Kello 1979). Deposition was in the order liver>kidney> brain (7.1%, 1.8%, 0.23%). Deposition to the brain is slower than to the other tissues (Keller and Doherty 1980). Within the brain lead is concentrated in the white vs cortical grey matter. It is suggested that lead is transported to the white matter by edema fluid formed by damage of vessel walls (Lindh and others 1989).

The toxicology of lead within the brain is complex. At very high levels of lead (>120 ug/dL, adults) encephalopathy (swelling of the brain) leads to decreased alertness and loss of memory, orientation and perception. At a later stage patients may have convulsions and severe deterioration in the state of consciousness. The symptoms do not respond to barbiturate treatment but do respond to chelation therapy. These symptoms are associated with blood lead levels greater than 120 ug/dL.

Peripheral motor neuropathy is associated with muscle fatigue, aching and tenderness of the muscles and shaking, and wrist dangles at blood lead values

Figure 8.31: Clinical Presentation of Child Lead Poisoning (TSDR)

A 5-year-old boy is brought to your office by his mother, who is concerned that her child is hyperactive. At a parent-teacher conference last week, the kindergarten teacher said that he seems impulsive and has trouble concentrating, and recommended evaluation by a physician as well as by the school psychologist. The mother states that he has always seemed restless and easily distracted, but that these first 6 months in kindergarten have been especially trying.

Family history reveals that the boy lives with his sister, mother, and maternal grandparents in an older suburb of your community. The child's monthly weekend visits to his father's house are working out fine. However, he seems to be fighting more with his sister, who has an attention-deficit disorder and is repeating first grade. Since the mother moved in with her parents after her divorce 4 years ago, she has worked with the grandfather in an automobile radiator repair shop, where her children often come to play after school. She was just laid off, however, and expressed worry about increasing financial dependence on her parents. She also worries that the grandfather, who has gout and complains increasingly of abdominal pain, may become even more irritable when he learns that she is pregnant. Her third child is due in 4 months.

On chart review, you see that the boy was last seen in your clinic for his preschool physical 1 year ago, results of which were normal. A note describes a very active 4-year-old who could dress himself without help but could not correctly name the primary colors. His vision was normal, but hearing acuity was below normal, and speech and language were slightly delayed. Immunizations are up to date.

Further history on that visit indicted adequate diet, with no previous pica. Spun hematocrit was diminished at 30%. Peripheral blood smear showed hypochromia and microcytosis. There was no evidence of blood loss, and stool examination was negative for occult blood. The diagnosis was "mild iron deficiency anemia" and iron therapy was prescribed. The family failed to keep several follow-up appointments, but the child did apparently complete the prescribed 3-month course of iron supplements. He receives no medications at this time and has no known allergies.

On physical examination today, you note that the boy is in the tenth percentile for height and weight. His attention span is very short, making him appear restless, and he has difficulty following simple instructions. Except for language and social skills, he has reached most important developmental milestones.

between 80 and 100 ug/dL. Nerve conduction velocity (NCV) measurements allow the beginning of the effects to be noted. The test is essentially a knee jerk test accompanied by voltage measurements. An index measures the response time, which is 121-145 for lead exposed adults and 92-112 for non-exposed adults (Bergamini and F. 1960). Maximal conduction velocity of motor fibers (MMCV) have been measured and show electrophysiologic disturbances related to lead exposure even for lead exposure levels as low as 50 ug/dL (Seppalainen and Hernberg 1972; Triebig and Velentin 1984).

Motor neuron disease (MND) is a degenerative damage to the spinal motor neuron, with motor deficit, muscular atrophies. The atrophy to these is related to the central motor neurons as is determined by involuntary laughter and weeping and other symptoms of insanity (Figure 8.30). One case study involved an occupationally exposed subject (Simpson and others 1964). The patient worked in a lead exposed workplace. His first symptoms were abdominal pain, constipation, followed (5-6 years later) by giddy turns and blackouts, weakness and wasting of his right hand. On hospitalization years later he had an expressionless face, lethargy, twitching of the muscles in all limbs, upper limbs with gross weakness and wasting of muscles.

The mechanism of lead uptake to the motor neurons has been postulated to occur from skeletal muscles, where it is bound, and taken up by motor end-plates and transported the neuron cell bodies by retrograde flow (Conradi and others 1980).

At low exposure rates of blood lead (40-80 ug/dL) it is harder to make definitive measurements of

Figure 8.32: Cruikshank: The Colic,

the effect of lead, however one measurable index of lead exposure is the rate at which voltages are transmitted through the central nervous system. This is measured by auditory evoked potentials (AEP) and visually evoked potentials (VEP). In these tests measurable effects on the response of children can be found at lead levels less than 30 ug/dL blood (Araki and others 1992; Otto and others 1982; Otto and others 1985) (Figure 8.31).

Calcium Implicated

Lead Poisoning Symptoms Reviewed

As described above lead poisoning leads decreased blood supply (pallor and fatigue), elevated ALA values (which can affect the central nervous system), and caused swelling of tissue in the kidney and elsewhere. Swelling within the kidney can lead to renal failure and gout (severe pain in the joints). Swelling within the brain leads to convulsions.

Other effects that have been described are not attributable to these functional changes. Some of the other symptoms described include some difficulty balancing, vision, wrist drop, followed by stumbling, acute colic, gastrointestinal spasms (Figure 8.32), deposition of lead along the gum lines, and hallucinatory behavior (ASTDR 1990). (Despite the acute toxicity of inorganic lead few cases of adult death in the last 100 years have been reported (CDC 1991). There are several documented deaths of infants from consuming paints. There is one known and unsuccessful attempt to commit murder with lead by doctoring of food stuffs (Horing and others 1991).)

Lower lead levels in the body will have a variety of clinical presentations. All told, the effects

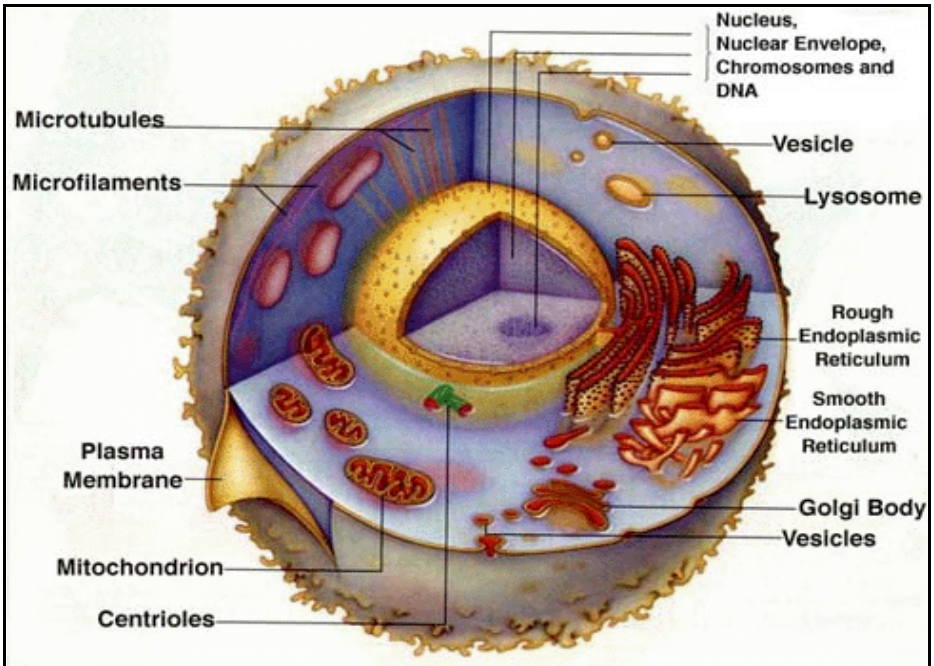

Figure 8.33. A cartoon of the eukaryotic cell. Calcium is transported from the external (extracellular) fluid to the internal fluid (intracellular) where its concentration is regulated by binding to the smooth endoplasmic reticulum (SER) and themitochondria. Image source: Dr. Veomett's Cell Structure and Function (BIOS201) class at the University of Nebraska, Lincoln; http://www-class.unl.edu/bios201a/spring97/group6/ access date: 8/4/2003

of lead exposure run from minor anemia, to lowered mental capacity and attention deficit Horing, 1991 #1877; Bellinger, 1987 #194; Bellinger, 1989 #1658; Bellinger, 1994 #1635; Bellinger, 1986 #1657; Bellinger, 1987 #1359; Bellinger, 1985 #1360], to infertility, to failure of motor coordination, to mental disorders, convulsions, and death. These symptoms are not associated with those gross organ changes described above. The likely source of those symptoms is a generic disruption of the calcium regulatory system (Masii and Bongaryone 1995).

The Calcium Regulatory System

Calcium is important as a regulatory agent and is absolutely essential for cell life.. As such it is closely regulated for uptake and excretion. The average adult ingests about 750 mg Ca per day of which nearly all is adsorbed with 635 secreted to intestinal juices. Ca in the plasma runs at 2.5 meq/L as a protein, 2.3 meq/L as the divalent ion, and about 5% or 0.2 meq/L as diffusible through the capillary membrane.

The amount of Ca^{2+} within a cell is far smaller. Figure 8.33 shows the structure of a typical eukaryotic cell. The total cell calcium is about 2 mM. The smooth endoplasmic reticulum binds about 30% of the total calcium, the nucleus binds about 20%, the vesicles about 20%, the mitochondria about 20%, and the external cell membrane about 10%. Calcium is typically 0.2 mM externally to the cell and 0.1 to 10 μM inside the cell (a three to four order of magnitude difference in concentration). This means that the internal cell concentration of calcium is very sensitive to changes in the extracellular environment and serves a means to signal information throughout the cell. A change in cell potential causes a calcium cell channel to open allowing calcium to flow into the cell. The higher concentration of calcium in the cell affects a variety of binding reactions which exercise control activities.

The internal cell calcium concentration is controlled by binding at the smooth endoplasmic reticulum (SER) and at the mitochondria (Mit) (see also Figure 8.33) (Campbell 1987). Once within the cell calcium is transported into the smooth endoplasmic reticulum (SER) by calcium pumps (SERCA) whose opening is triggered by the protein $InsP_3$. Once within the SER calcium is bound by calcium binding proteins calsequestrin and calretinin (Figure 8.34).

The remainder of the calcium in the intracellular compartment binds to calmodulin. Calmodulin is a protein that is essential for all cell life (Chin 2000). The calmodulin class of calcium trigger includes troponin C, parvalbumin, intestinal calcium binding protein (IcaBP), osteocalcin (also known as bone Gla protein BGP), and calmodulin (Figure 8.35 and 8.36). Troponin C regulates muscle contraction (Herzberg 1987). Isolated frog muscle fibrer contracts when placed in solutions containing

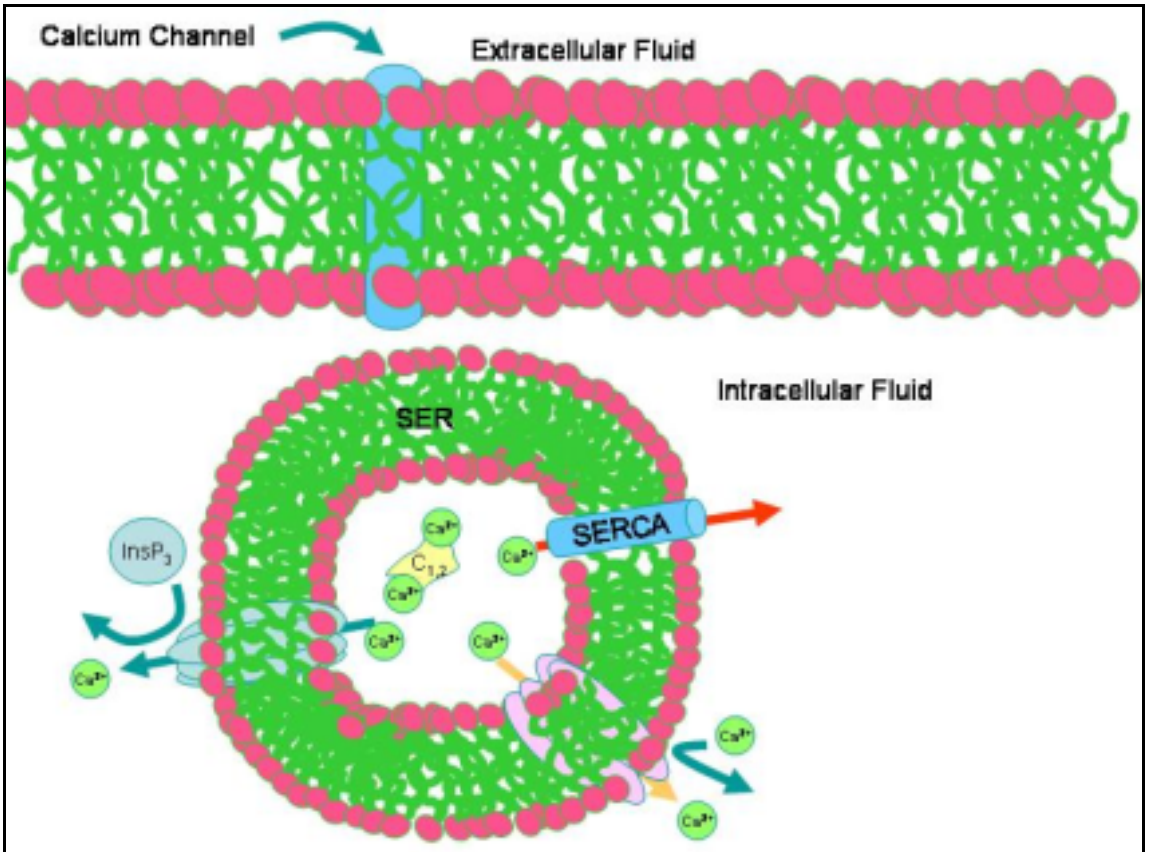

Figure 8.34 The internal calcium concentration is regulated by binding at the smooth endoplasmic reticulum (SER). Transport in and out of SER is controlled by a calcium pump (SERCA) and by Ca^{2+} release channels, one controlled by $InsP_3$ and the other by Ca^{2+}. Within the SER calcium is bound by Ca^{2+} binding proteins, $C_{1,2}$ (calsequestrin, and calretinin).

Ca^{2+}. The effect is due to binding of Ca^{2+} to one of three subunits of the troponin protein which acts in coordination with actin and tropomysin to contract the muscle (Ebashi 1988). The effect of lead on muscle spasming occurs within the muscle itself and is independent of other effects occuring in nerve conduction (Reznikoff and Aub 1927).

These calcium binding proteins contain a loosely prescribed structure where a series of carboxylate and carbonyl groups on a well formed continuous loop is locked between two helices and supported by a small preformed β sheet. The degree of rearrangement of the backbone of the site on binding Ca^{2+} is slight but it has a large effect on the helices and is further amplified at the loops distant from the calcium "hands" (Williams 1987). The protein contains two binding domains, each binding two calcium (Babu 1987). The two domains are connected by a long central helix that serves as a flexible connector, such that the domains can move largely independently of each other. Upon binding calcium ions the helices change orientation, opening up to reveal a surface with hydrophobic amino acids. These hydrophobic residues form the binding site for target enzymes (Figure 6). Two calciums are bound at domains 1 & 4, which are between the two helices bound by the beta loop. This type of site is found in parvalbumin and bovine intestinal calcium binding protein. The binding sites are conserved genetically from enzyme to enzyme and involve amino acid residues 20-31, 56-67, 93-104, 129-140. The coordination of calcium within the site is sevenfold, although two of the oxygens both occupy a z' position, making the site a distorted octahedral site (Forser 1987), or a pentagonal bipyramidal structure. The oxygens are donated by carboxylates from amino acids aspartate and glutamate, while threonine offers a carbonyl for binding. The affinity constant (binding) of

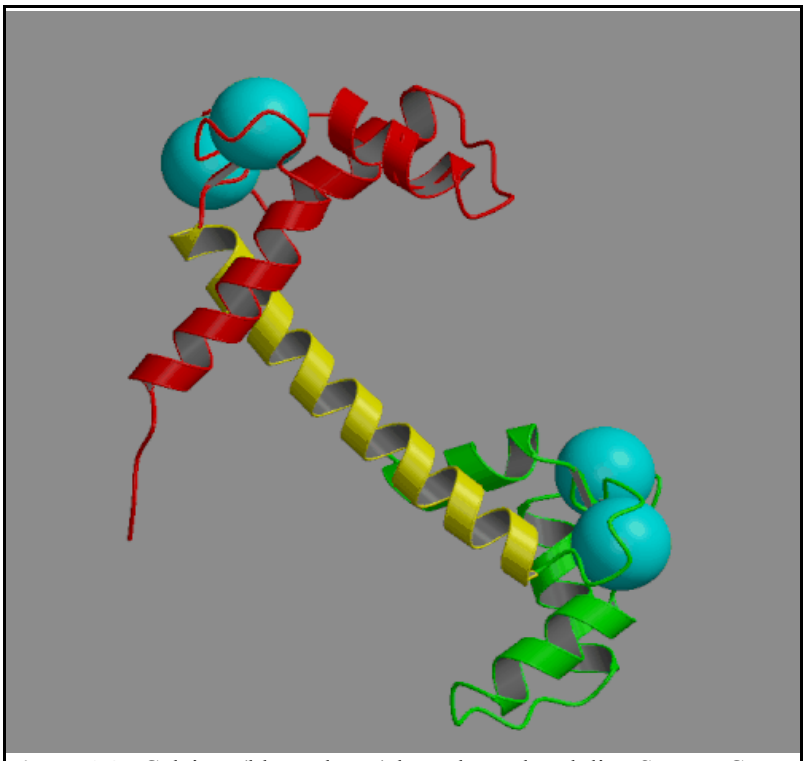

Figure 8.35 Calcium (blue spheres) bound to calmodulin. Source: C. Yang, G. S. Jas, and K. Kuczera, J. Biomolecular Structural Dynamics, 2001, 19, 257-271.

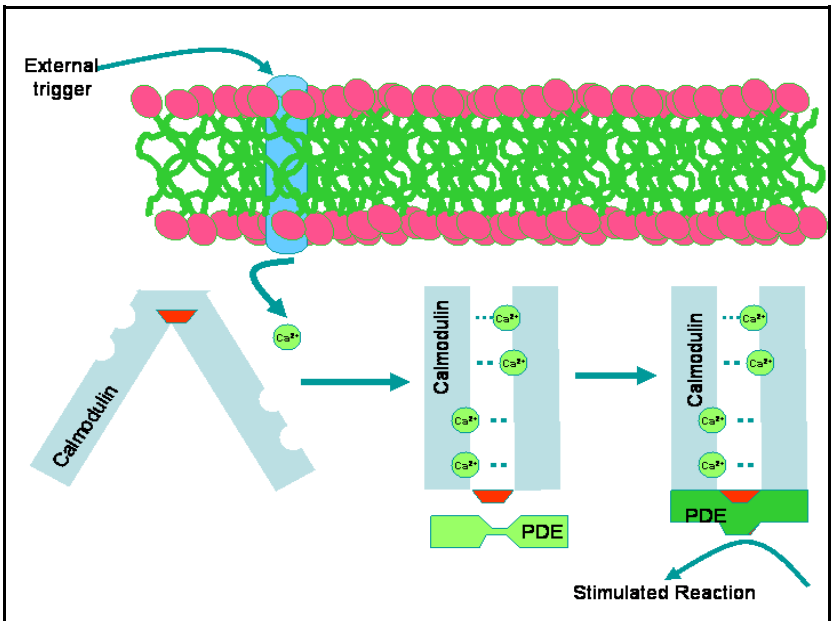

Figure 8.36. Calmodulin acts as a trigger to acrivate enzymes. When a change in calcium concentration occurs in the cell calcium binds to calmodulin exposing a hydrophobic siteswhich activates other enzymes.

calcium is 10^6 (Williams 1987) or $6x10^8$ (Forser 1987).

The binding of calcium is cooperative, meaning that the first calcium enhances the binding of subsequent calcium. Mutation of the gene produces mutants which change the carboxylate binding sites. Substitution of pro 20 to become glycine, or gly with asp 21 deleted, or deletion of the glycine lead to calcium binding with no cooperativity. This suggests that the coordination between all seven oxygen sites is necessary, in a proper structural alignment (bond distances to calcium) to "trigger" the large structural changes in the protein backbone that lead to full calcium sensitivity (Figure 8.36).

A second class of calcium regulating enzymes are the phospholipase A.2 triggers (Williams 1987). These enzymes have a very tightly controlled binding pocket, so that large conformational changes in the enzyme on calcium binding are not observed. The binding sites are oxygen. Here the calcium serves to cross-link the distance between parts of the enzyme. This type of binding is weak (K affinity 10^3), and is found in extracellular triggers for phospholysis. It is typically found in nucleases and in alpha lactalbumin. The rate of binding is slower in this enzyme than in the calmodulins due to a structural barrier (calcium must find it's way directly into the pocket).

Flow of calcium into and out of the cell is controlled by calcium channels (Figure 8.37) which are triggered to allow calcium into and out of the cell by a variety of internal and external receptors for calcium and for ATP and InsP3 (Kostyuk and Verkhratsky 1995). Calcium control in the larger mammalian body is exercised by the kidney where the glomerular filtration rate is controlled by various proteins, by deposition to the bone which is controlled by various hormones (cortisol, for

Figure 8.37: The opening and closing calcium channels are triggered by a series

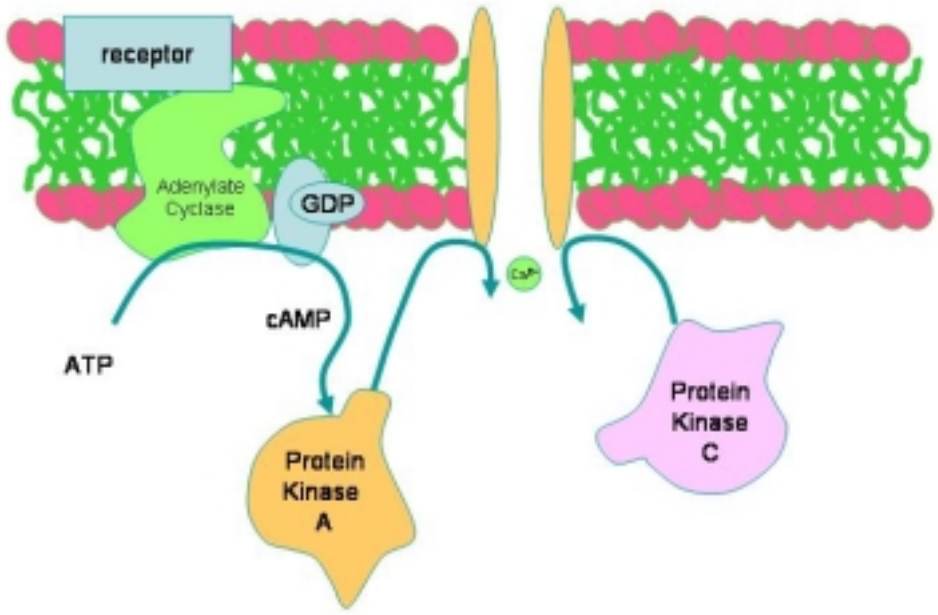

Figure 8.37. Flow of calcium into the cellis triggered by a receptor which begins a series of reactions involving numerous proteins. Protein kinases A and C signal to calcium channel to open.

example), and growth regulators such as the parathyroid hormone (PTH). Uptake of calcium from the gut is controlled by Vitamin D and the proteins calcitriol and calcitonin (Peacock 1988).

The PTH hormone works to control the concentration of calcium in the extracellular fluid. This is a feedback loop in which extracellular calcium controls intracelluar calcium (described above) which in turn triggers secretion of the parathyroid hormone (Aurbach 1988). The parathyroid hormone works with the kidney to affect the rate of reabsorption of calcium during glomerular filtration (Schaafsma 1988)). The nephrons in the kidney, through which fluid flows for exchange of material to the urine, are sensitive to parathyroid hormone and calcitonin. The hormone calcitonin, which affects the kidney function and bone resorption is also affected by intracellular messengers clacium and cyclic AMP (cAMP).

Uptake of calcium through the gut (calcium absorption) is both passive and active (subject to regulation). The active calcium transport system takes place in the upper intestine and is subject to control by vitamin D (Bronner 1988).

If lead ions masquerade as calcium ions we expect the following symptoms upon exposure to lead: muscle contraction (colic, and trembling of extremities). The ability of lead to cause contractions was noted by medical doctors as early as the 1700s (see Chapter 6). We also expect that lead would cause alterations in information flow in the synaptic pathways due to changes in the cell potential (controlled by extracellular and intracellular concentration gradient) and due to triggering of various protein function by lead binding calmodulin. Finally, we expect that lead would have a differential effect upon children as compared to adults due to the different modes of action of calcium in the developing brain and in the mature brain.

The activity of lead on regulatory enzymes suggests that small amounts of lead lock the system into an "open" or high calcium message. Hypercalcemia (15-20 mg% Ca) is noted by central and peripheral nervous system depression, muscular weakness, constipation, abdominal pain, lack of appetite. At higher levels of lead some of the regulatory enzyme functions become depressed suggesting that the system is locked into a "closed" or low calcium message. Hypocalcemia (7 mg% Ca) is manifested by increased excitability in the central nerons system and peripheral nerves with most symptoms manifesting peripherally. Nerve fibers become so excitable they discharge spontaneously, causing tetanic contraction or spasming.

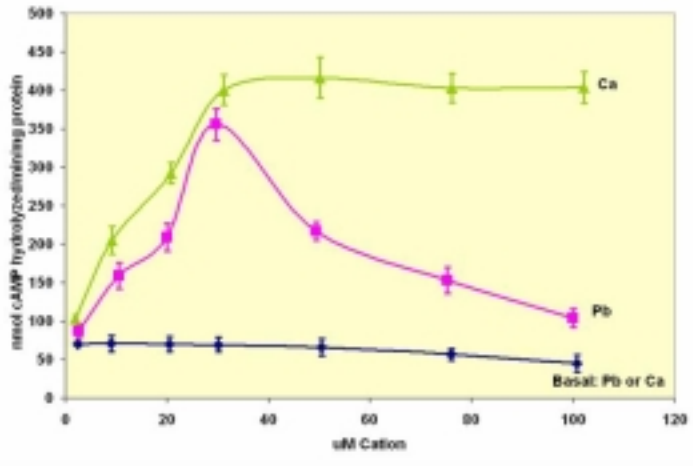

Figure 8.38. CAMP phosphodiesterase activity is a measure of the activity of calmodulin. In the absence of Ca or Pb no activity is observed (blue line). In the presence of Ca activity increases to a plateau. Small amounts of lead cause calmodulin to function as if it had sensed Ca, but larger amounts shut calmodulin down. Data source: Sandhir and Gill, Exp. Molecular Path. 1994, 61, 69-75.

Lead as calcium

Lead looks, from a distance, "like" calcium, with a similar ionic radius and divalent charge and could therefore be mistaken by the enzyme for calcium. Lead affects the functioning of calmodulin. One study suggests that lead stimulation of calmodulin begins inappropriate initiation of protein phosphorylation by CaM kinase or cyclic AMP-dependent protein kinase, which at the physiological level inhibits neurite initiation in cultured rat neurons (Kern and Audesirk 1995).

cAMP dependent synaptic vesicle protein phosphorylation was inhibited by enhancing calmodulin activity indirectly by lead treatment (Chao and others 1990; Tosig and Suszkiw 1993). Biological activity of lead vs calcium on calmodulin activity of cAMP Phosphodiesterase is shown in Figure 8.38. A small amount of lead stimulates activity (hypercalcium is perceived) with yet higher amounts of lead having an inhibitory effect (Sandhir and Gill 1994a; Sandhir and Gill 1994b; Sandhir and Gill 1994c; Sandhir and Gill 1994d). Similar results have been observed by others (Goldstein and Ar 1983). One group indicates that lead stimulates activity at free lead ion concentrations in the picomolar range (Haberman and others 1983; Kern and Audesirk 1995). Similarly Pb^{2+} can activate the troponin C activity of myofibrils in muscles. Again, an inhibitory effect is noted at high lead levels, presumably through direct lead binding to sulfur linkages on the enzyme (Chao and others 1990). Vitamin-D induced intestinal calcium-binding proteins (CaBP) bind lead in identical stoichiometry as calcium, but with a higher affinity. It was suggested that on the basis of size alone lead would fit in the calcium binding site, but may form covalent bonds with oxygen, accounting for the higher affinity (Fullmer and others 1985).

Calcium Triggers in the Nervous System

The brain is the processing unit for the nervous system. The nervous system is divided into the central nervous system (CNS) composed of the brain and spinal cord and the peripheral nervous system (PNS) which connects the body to the CNS. Information in the central nervous system is carried by voltages which stimulate the dendrites of the neuron. The axon of the neuron relays the input signal to the tips where synaptic terminals reside. The synaptic terminals release neurotransmitters in response to voltage changes. Changes in the presynaptic membrane potential causes calcium ions to travel into the neuron ultimately triggering release of neurotransmitters.

Lead alters this process indirectly and directly. Indirectly, lead alters the release of the neurotransmitter gama-aminobutyric acid (GABA), which is involved in the secretion of growth hormones and control of skeletal muscles, by inhibiting the functioning of ALA-dehydrase (ALAD). Inhibition of ALAD results in an overproduction of ALA. ALA blocks the release of GABA. Low amounts of GABA may increase the body's sensitivity to seizures and stress. Anxiety and hyperactivity may occur as well as the onset of attention deficit and learning disorders (Figures 8.11-8.13).

GABA plays a role in directing the development of the brain (Andersen and others 1998; Chen 1995; Diabira 1999; Gao and van den Pol 2001; Hagberg and others 1997; Herschkowitz and others 1997; Tyzio 1999) Figure 8.39 shows the amount of various amino acid information transmitters and their receptors in the brain as a function of age pre- and post-natal (Herlenius and Lagercrantz 2001). The number of GABA receptors is significantly larger in the immature brain than in the brain of a 2 year old child. This explains why early exposure to lead and the

rise in GABA-like compounds due to the alteration of the blood synthetic process differentially affect children as compared to adults, such that levels of lead tolerated occupationally (by adult males) are not tolerated by children. Figure 8.40 (Ben-Ari 2001) shows the effect of GABA on the proliferation and growth of the narrowness in the neonatal rat hippocampus. The grow of the neural network is greater in the presence of GABA or GABA plus another compound, glutamine. The activity of the brain (shown in the lower trace) is also greater in the presence of GABA. Interference with GABA during early brain development "may affect the development of neuronal wiring, plasticity of neuronal network, and also have aprofound influence on neural organization" (Herlenius and Lagercrantz 2001). To underscore the difference between the developing brain and a more mature brain it is noted that GABA switches from an excitatory to an inhibtory neurotransmitter around birth in the rat (Miles 1999).

In plants, w GABA has been shown to direct pollen sperm to the eggs of a flower, similar to the method in which GABA is proposed

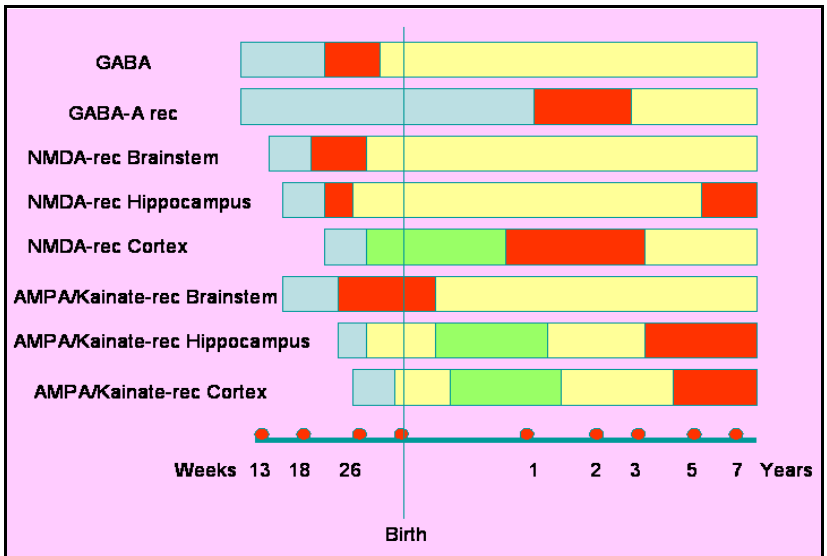

Figure 8.39: Expression and arbitrary levels of receptors of amino acid transmitters versus age. Data from Herlenius and Lagercrantz, 2001.

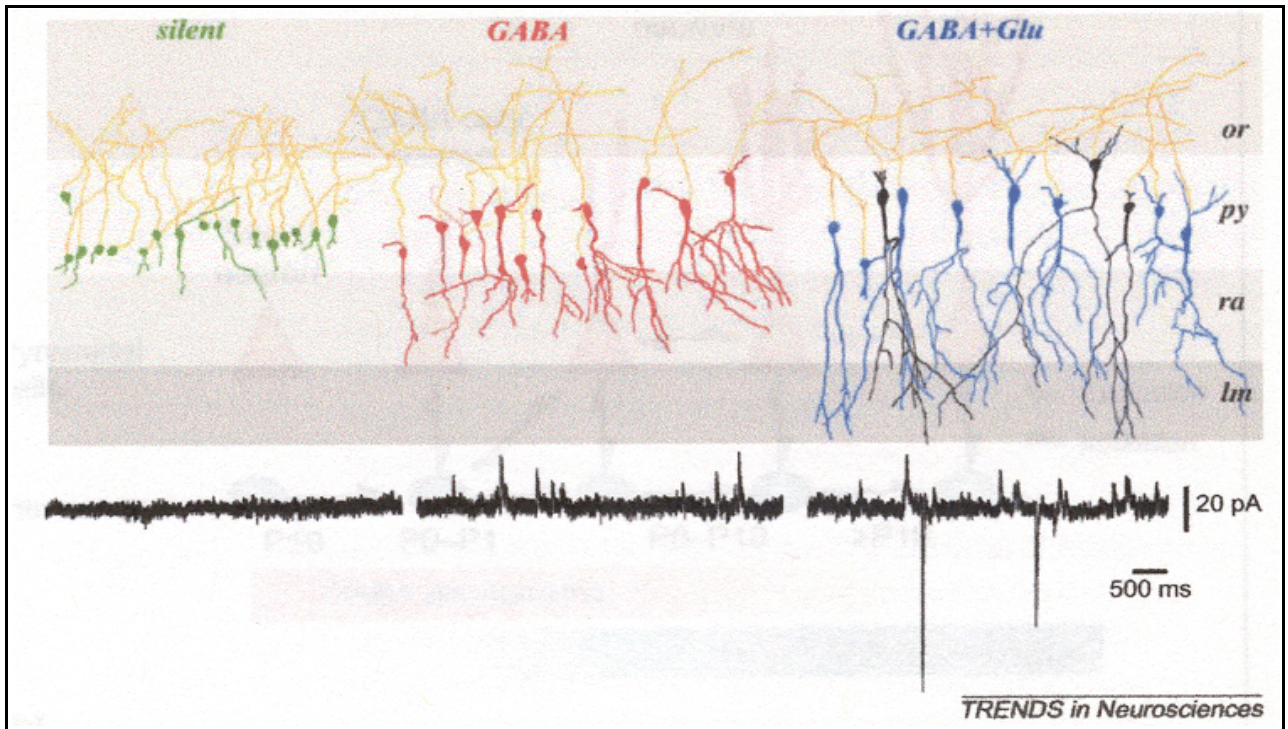

Figure 8.40: As the neonatal rat hippocampus matures and GABA sites are activated synaptic transmission accelerates. Image from: Ben-Ari, 2001

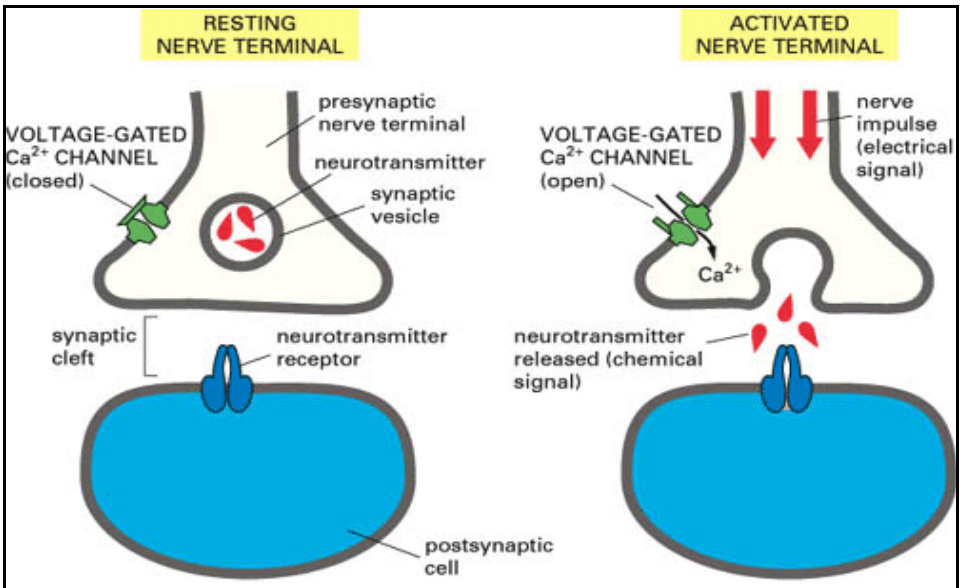

Figure 8.41: Neurotransmitters are released from vesicles upon activation of a voltage gated calcium channel. Image source: 1998copyright: Alberts, Bray, Johnson, Lewis, Raff, Roberts, Walter, obtained 8/4/2003/ http://www.accessexcellence.org/AB/GG/convert_Sig.html

to guide newly formed neurons to their proper places in the brain (Preuss, Daphne and Laura Brass, U of C, Cell). Pollen apparent sense the presence of the GABA compound and build a tube toward the region of high GABA concentration.

GABA works in coordination with calcium ions on the immature mammalian brain ((Schwartz and others 1998; Yuste and others 1992) in producing activity in the early nervous system before full synaptic networks are developed. During neuron development calcium channel development precedes sodium channel construction. The presence of more calcium channels in the developing brain is likely due to the fact that the growth of neurites is "critically" dependent on calcium concentrations (Anglister and others 1982; Meiri and others 1981).

Once developed the brain continues to be affected by calcium ion concentration. Since lead masquerades as calcium ions it may also affect any of the control operations performed by calcium. Figure 8.41 shows a cartoon of a presynaptic nerve terminal cell (Blaustein, M. P.). A change in the potential of the cell causes calcium to flow inward across the cell membrane in the region of the synaptic contact. In the nerve cell, depending upon the internal calcium concentration after its regulation at the SER and mitochondiral surfaces, Ca^{2+} triggers fusion of synaptic vesicles (Figure 3) with the plasma membrane, which then allows the neurotransmitters to be released (Blaustein 1987). Lead can alter the triggers for vesicle release (Bouton and others 2001; Westerink and Vijverberg 2002).

The excitability of the neurons is related to minute changes in calcium concentrations within the cell. When the neuron cells experience a massive overload of calcium cell death may result. The mitochondrial calcium binding system overloads (Trump and Berezesky 1985).

Lead acts directly at the calcium trigger for the central nervous system neurotransmitter dopamine. Dopamine controls movement and emotional response (Trope and others 2001).

Lead also acts directly at the calcium trigger for the peripheral nervous system neurotransmitter acetylcholine. Acetylcholine (Ach) is responsible for control of muscular contractions. A decrease in Ach at the preganglionic nerve endings at neuromuscular junctions are believed to cause certain gastrointestinal symptoms of lead poisoning. When blood lead levels reach 80-100 µg/dL peripheral motor neuropathy is manifested by muscle fatigue, tender and aching muscles, uncontrollable shaking, and wrist dangles. These effects are seen more commonly in adults.

In children the central nervous system is more highly affected by lead. Certain areas of the brain appear to be more highly affected such as the prefrontal cortex (Lasley 1992) which is responsible for problem solving, critical thinking, expressing emotions and organization; the hippocampus that controls memory, and the cerebellum which is involved in motor coordination, body movement, posture and balance (Struzynska and others 2001). Lead affects protein kinase C (pk-C) which regulates long-term memory storage and helps regulate membrane channels (Bressler and others 1999; Goldstein 1993; Johnston and Goldstein 1998). Binding of lead may alter

membrane channels (Bernal and Ruvalcaba 1996) and increase permeability of the blood brain barrier (Bradbury and Deane 1993). Increased permeability allows fluid to move into the brain causing cerebral edema (swelling) and seizures. Symptoms occur at blood lead levels of 120 µg/dL and greater. For children binding of lead to pk-C causes altered synaptogenesis that can lead to learning deficits.

Other Molecular Biological Studies of Lead:

Leadzyme. The lone pair electrons were very important in the role of lead to serve as an oxygen carrier (lead acetate) catalyzing various oxygen additions. Lead is able to easily give up the oxygen due to the distortion on binding that the lone pair exerts, for a C.N. of 6 (octahedral bonding) or in forming tetragonal vs tetrahedral bonds. In some cases lead can serve biologically as an oxygen catalyzing site resulting in tRNA cleavage as shown in Figure 8.42 and 8.43. RNA is inheritably unstable due to a 2'-OH group on the ribose ring as compared to DNA where the site is occupied by a proton. This renders RNA susceptible to metal ion catalyzed cleavage. Lead binds to an oxygen group on a "leadzyme" and can mimic the behavior of lead acetate by acting as a source of metal bound OH groups (Brown and others 1985).

Synthetic "Lead Fingers" In order to reduce the complexity of the system work at the end of the last century moved in the direction of creating partial proteins rich in cysteine sites that would allow a fuller
comparison to be made of the binding of lead as compared to zinc. These partial proteins have been dubbed "lead fingers" (Payne and others 1999). It was found that binding of lead vs zinc was under equilibrium as opposed to kinetic control and that lead did not stabilize the correct fold of the peptides.

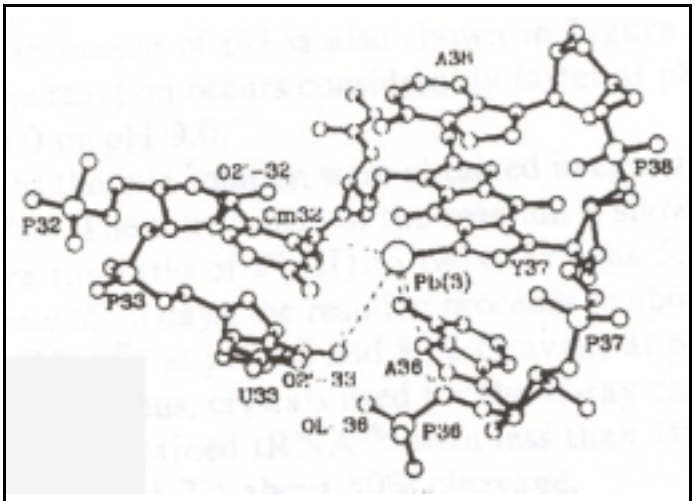

Figure 8.42. Leadzyme is a naturally occurring enzyme that binds lead. With lead bound cleavage involving oxygen transfer is facilitated. Linda Behlen, 1990.

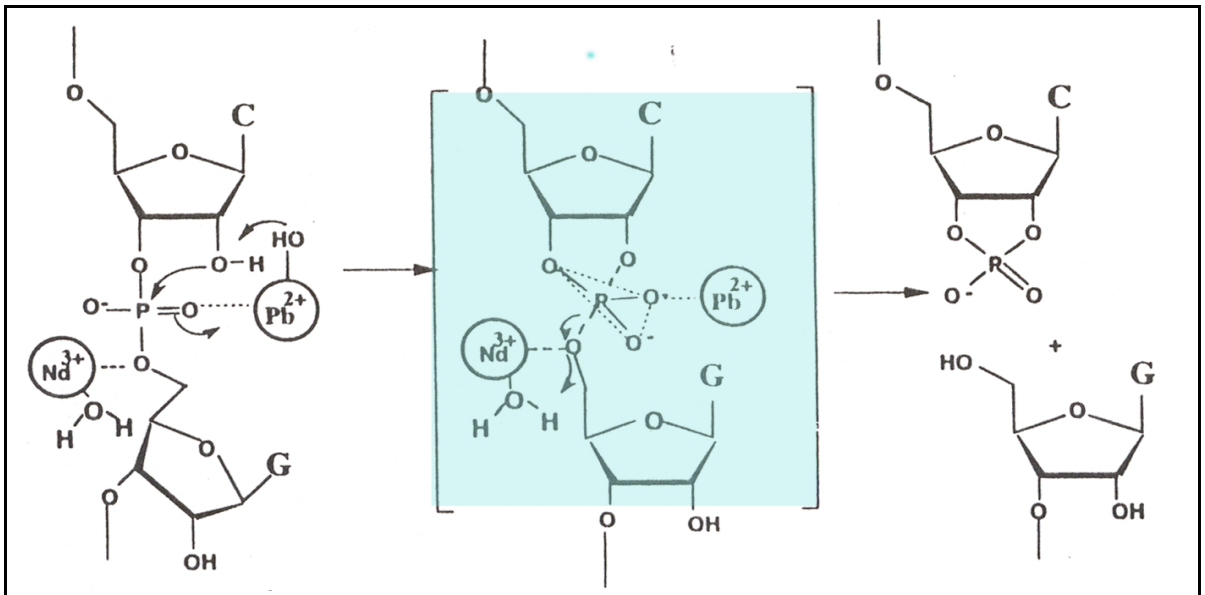

Figure 8.43. Leadzyme helps catalyze RNA cleavage by lead. Lead acts as an oxygen transfer reagent.

Therapy: Chelation Chemistry

Thus far we have traced lead as it is ingested into the human organism and followed it's trajectory through the body with particular emphasis on how the **chemistry** of lead controls it's interaction with the body. For a complete "cradle to grave" picture of lead in the body we need to understand how lead could be removed from a biological organism using chemical principals.

The standard method for treatment of acute lead poisoning is chelation therapy (Aposhian and Aposhian 1990; Chisholm Jr. 1971; Chisholm Jr. 1990; Chisholm Jr. 2000; Graziano and others 1988; Kapoor and others 1989; Markowitz and Rosen 1984). Chelation therapy was one of the lifetime achievements associated with Dr. JulianChisholm of the Kennedy Kreiger Institute. His story will be picked up again in Chapter 10, when we exam how society came to a social definition of lead poisoning.

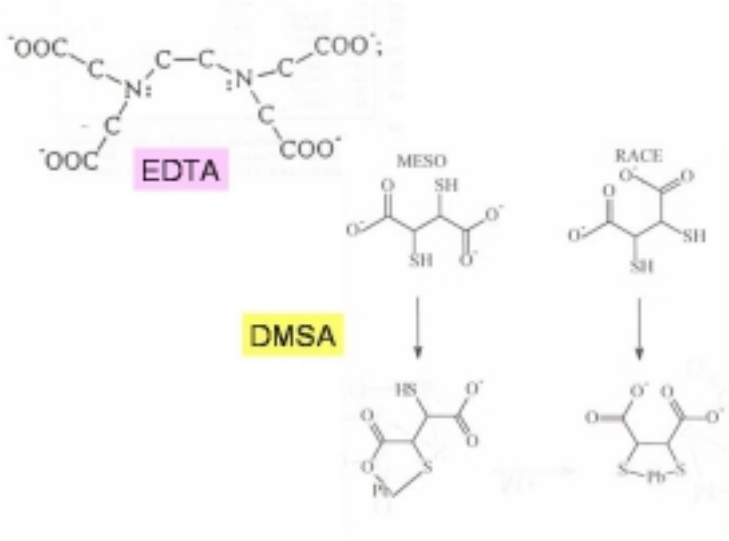

Figure 8.44. Structures of the two main oral chelates for lead poisoning therapy. DMSA is also known as succimer.

The goal of chelation therapy is to provide more effective bonding for lead than occurs in the human body (Basinger and others 1981). Figure 8.44 shows two chelating (chelate derives from the word claw) used to capture lead. The first is **e**thylene**d**iamine**t**etra**a**cetic acid, EDTA. The capture is driven by enfolding lead within the pinchers of the chelate. Six coordination sites are provided, two from the lone pairs on nitrogen and 4 from the oxygens associated with the acetate (COOH) functionalities. Because of the involvement of the acetate groups we note that the effectiveness of this chelate will be highly pH dependent. EDTA is a highly effective reagent at localizing metals, and we will encounter it's chemistry again when we look into methods of cleaning soils.

The second, more recent candidate for capturing lead is meso 2,3 **dim**ercapto**s**uccinic **a**cid (DMSA) also known as succimer. The logic behind the development of this oral chelating agent is to provide an alternative S source for binding with lead. At first glance this chelating agent does not look able to provide much efficacy. There is no possibility of engulfing the lead as with EDTA. Binding of lead will occur either between the terminal oxygen and its adjacent sulfur or between the two sulfur groups. Which bond forms will depend upon the **enantiomer** of the chelating agent present. The more effective form is the racemate.

Which of these two chelating agents might be better to give to scavenge lead from the body? At a first guess we might expect the one with a larger affinity for lead, EDTA. The equilibrium constant, K, is three times larger for the reaction of lead with EDTA than it is for the reaction of lead with DMSA. Indeed, we find from pharmacologic studies that the administration of EDTA pulls lead out of stored tissue and bones, but does so **too** effectively. A transient increase in lead in the blood stream results, which can be a cure more sinister than the original lead poisoning as the elevated blood EDTA lead can cross the blood brain barrier and exacerbate problems in this area (Figure 8.45) (Graziano and others 1988; Jorgensen 1993). This effect is particularly worrisome for nursing mothers who are known to have higher rates of calcium turnover from bone mass due to milk production. Succimer has lower equilibrium constants and so could be expected to be less effective at mobilizing lead from the bones.

It should also be noted that the complexation constant of EDTA for other essential (biologically required) metals, Zn^{2+}, Ni^{2+}, and Cu^{2+}, is equally high, thus the EDTA that we send on a hunt and capture mission will be indiscriminate, capturing many other metals that are essential metabolically. Consequently, one of the side effects of EDTA therapy is nausea and general weakness. DMSA, on the other hand, while

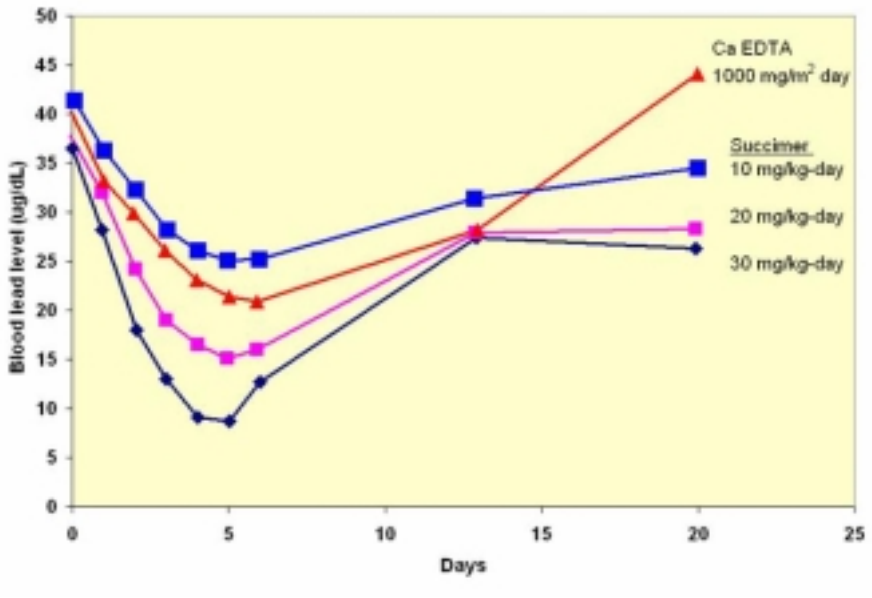

Figure 8.45.Chelation therapy reduces the lead in blood. Increasing the amount of succimer enhances the therapy. EDTA, however, ultimately increases the blood lead value by removing lead from compartments 1 and 2 in the body (bones). Data Source: F. M. Jorgenson, Family Phys. 48, 8, 1496.

less effective at its strength of capture acts more like a smart bomb targeting lead preferentially.

There is an additional reason for the use of DMSA. EDTA captures calcium fairly effectively, but does not require all of its coordination sites to do so. Recall that it has six lone pair electron sets which need to find positive charge. A few of these may be satisfied by calcium in a 4 coordinate form, but the remaining are free to seek relief elsewhere. Thus is has been suggested that a cross linking of EDTA to other metals within the body can occur in localized spots, particularly facilitating the necrosis of the kidneys.

These side effects related to EDTA (redistribution of lead to the brain) can be amelioreated by combined treatment with DMSA. On the downside, there is an elevation of serum transaminase activity, creatinine levels and depletion of blood zinc level using the combined treatment (Flora and others 1995).

Despite the success of DMSA in ameliorating the excesses caused by EDTA, neither chelate shows long term impact on blood lead levels (Jorgensen 1993). Use of chelating agents is confined to cases of acute toxicity where the blood level must be dropped rapidly.

DMSA reduced Pb induced mobility problems in mice, but the effect was dependent upon gender. Blood lead level did not drop as low in female mice as in male. The authors speculate that this is due to the lead and not DMSA, in that female mice show different blood lead levels on lead exposure as compared to males. It is speculated that females have a more rapid replacement of blood lead from the bone as compared to the males (Steward and others 1996).

One way to follow the metabolism of DMSA is through urinary excretion of products. One of the metabolites is the formation of a mixed disulfide consisting of one DMAS and 2 L-cysteine residues. Peak excretion of the disulfide coincides with peak excretion of lead (Maiorino and others 1987; Maiorino and others 1989) providing a convenient means of tracking therapy.

Another potential lead antagonist is diethyldithiocarbamate (DDC) and 2,3-dimercaptopropane-1-sulfonic acid (DMPS) (Llobet and others 1990). DDC resulted in 100% mortality of the mice while the second had a therapeutic effectiveness of 1.31 compared to DMSA (1.22).

To date no truly lead specific chelate has been devised.

LEAD and Companion and Avian Species

Humans did not evolve with a mechanism for using or protecting against lead. Neither did other species, for the same reason: evolution occurred in a low lead environment. It is not surprising that other species should experience difficulties with lead. Which ones might we expect to be at highest risk? We would expect animals living in the human environment (companion pets, livestock) to be at high risk. Among wildlife we expect animals to come into contact with lead as a result of feeding behavior in contaminated locales.

Companion Animals

There are a variety of companion animals, the most prevalent are dogs, cats, and small caged animals, such as birds, ferrets, iguanas, rabbits and the like. Dogs are highly at risk for lead poisoning due to their chewing habits (Srebocan and others 2001). Their risk correlates with the general poverty of the originating neighborhoods (deteriorated paint), as shown in studies in suburban Illinois (Thomas and others 1975) in which 100% of the suburban dogs had "ordinary" blood lead concentrations, while 22% pound dogs and 15.3% of low income family dogs had elevated blood lead levels. Case presentation was also found to be higher in urban than in rural areas, consistent with the higher incidence of lead contaminated homes in urban areas (Zook 1973). In the Boston region, the number of cases correlated with the cases of childhood lead poisoning throughout the city region. The blood lead level of affected dogs (acutely poisoned) ranged from 40-460 μg Pb/dL with a mean of 106 (Morgan 1994). The total number of cases had declined with increased public awareness of lead poisoning, as compared to an earlier study (Morgan and others 1999).

There is a seasonal pattern to presentation of dog poisoning with the greatest number of cases occuring in the summer (Jul-Oct). Puppies are more prone to lead poisoning (Zook and others 1972). Similar results were found in a parallel study in N. J. (Zook and others 1969). It is speculated that summer produces more Vitamin D with prolonged exposure to sunlight and that vitamin D aids in the intestinal absorption of ingested lead (Hamir 1981). An alternative explanation is greater access to outdoors. An opposite seasonal pattern was observed in 34 cases of lead poisoned dogs in Australia (Berny and others 1992). Other workers indicate that the high January peak for Australia correlates better (southern hemisphere) with July of the northern hemisphere, explaining the difference in seasonal variation in the studies.

One dog presented with mild abdominal discomfort (frequently getting up and down), and basophilic stippling. Based on the stippling the dog was tentatively diagnosed with lead poisoning and blood lead determined to be 140 μg Pb/dL. The dog was treated with EDTA. During hospitalization interviews with the owners indicated the dog attending one hour weekly obedience training classes at an indoor shooting facility of a gun club. No other dogs became ill, but dust wipe of the floor indicated that the dust was 89.5% lead. The obedience trainer's dogs were tested for blood lead before and after training with a dramatic increase in blood lead upon exposure (Table 8.3).

The presenting symptoms are similar to those in humans: Dogs have a history of colic, and of vomiting of about 7 to 10 days duration. Nervous disorders have occurred within the last few hours or day. Dogs show neurological disorders, clonic-tonic convulsions, psychomotor seizures characterized by sudden apparent fright and blindly running about while continuously barking, tremors, ataxia, extreme nervousness, behavioral changes. Younger dogs more likely present with signs of hysteria and abdominal pain than older dogs who had larger amounts of seizures (Morgan and others 1999; Morgan and others 1991). The blood test shows evidence of damage of blood cells by a process called stippling (Zook 1973; Zook and others 1969; Zook and others 1972; Zook and others 1970).

Table 8.3: Dog Blood Lead
(After training in an indoor firing range)

Dog	Number of Previous Exposures	blood lead μmol/L after treatment 6 h prior	16 h after
1	3	0.29	3.33
2	9	0.67	1.11
3	>15	1.74	2.75

In Morgan's study it was found that dogs were most commonly poisoned by paint (29.1%) with other sources including linoleum, a leaded door, plumbing solder, window caulking, and a golf ball. (Golf balls in the past were surface enameled with lead based white paints.) Dogs can be treated by CaEDTA, which results in blood lead decrease, but not necessarily survival.

Several studies attempted to show that dogs can be used to "sample" the lead environment. The studies showed that there was a correlation between indoor dog (and cats) blood lead concentrations and the concentration of blood lead in young children (Berny and others 1994; Berny and others 1995).

Cats are less likely to be lead poisoned than dogs (less chewing activity). Presentation of cat saturnism has similar features to that of dogs and humans.

A cat who had been missing from home for 5 days presented with vomiting, anorexia, hypersalivation, ataxia, and hypermetria, as well as seizures. The cat was treated with CaEDTA and began to eat on the third day of therapy. Four days later the cat was again anorexic and owners refused treatment, so the cat was put to sleep (Hoffheimer 1988).

Companion bird lead poisoning can be recognized by an increased frequency of very liquid droppings (diarrhea or polyuria), regurgitation, anorexia, and lethargy. Parakeets were ataxic, paralytic, and unable to perch. Cocatiels had lethargy, seizures, and weight loss more often than other birds (Morgan and others 1999). For birds the source of lead was cage solder in two cases, and a lead headed roofing nail used to tack up a loose cage board in another. In the classical study of companion poisoning by Morgan and co-workers birds were exposed to lead from tile grout, stained glass, sheet rock, and a chess set.

Although one parrot was successfully treated with CaEDTA (Tully Jr. and Morris 1990), treatment of birds with CaEDTA was less successful than treatment of dogs or cats. Overall 86% of the animals treated by Morgan responded to the chelation therapy.

Table 8.4 shows the blood range measurements for a number of cases of lead poisoning for companion animals while Table 8.5 shows a recommended range for lead poisoning of livestock as well as companion animals.

Table 8.4: Blood Lead for Intoxication of Animals
Morgan, 1991

Species	Range (μg Pb/dL)
dogs	40-530
cats	70-131
rabbits	67-190
birds	44-7,090

Table 8.5 Blood lead levels μg Pb/dl of Farm Animals
D.J.Humphreys, Br. Vet J.,1991,147, 18.

Species	Normal	Toxic
Ruminants	2.5-10	>35
Horses	10.7	20-38
Pigs		14300
Chickens		1300
Dogs	5-10	22- to >60
Cats	<5.2	
Swans		3290
Ducks		1000

Livestock

Lead is one of the most common causes of cattle poisoning due to contamination of soils, or more commonly, lead shot in silage (Guan and others 2002; Takahashi 2002). The government of the Province of Alberta, Canada reports that 700 cases of cattle poisoning were reported over a 20 year period, and likely to have caused the death of thousands of cattle. Most cases involved the accidental consumption of used crankcase oil, discarded batteries, grease, leaded gasoline and used engine foil filters from junk piles in pastures. Calves are more greatly affected because they are "curious feeders" and because they have a greater absorption of calcium than adults. Because poisoning is related to pasturing cattle outbreaks occur in the spring, or in the fall when cattle are held in yards.

It has been suggested that 85% of cattle lead poisoning is from crankcase oil, batteries, grease, leaded gasoline and used engine oil filters, putty, paints discarded into junk piles in pastures (Province of Alberta). A case report of horse lead poisoning was attributed to foraging in the vicinity of a lead acid battery recycling plant (Palacios and others 2002).

The presentation of the disease (disorientation, loss of appetite, nervous behavior) is similar to that in humans. The distribution of lead in the organs is also similar (bone, kidneys, liver, muscles, and blood).

An acute contamination of cattle occurred in 1989 in Northern Netherlands where 15,500 head of cattle were fed a feed concentrate composed in part of rice bran which was contaminated with 1280 mg Pb/kg. The animals showed loss of appetite, slowness, nervous ear twitching, pushing, and gnashing of teeth. It was estimated that the cattle consumed 1000 kg of lead. Only 30 died due to EDTA chelation therapy (Baars and others 1992).

In another case, several calves died unexpectedly after walking into walls or standing about in a blind stupor. As one might suspect, for a case of lead poisoning, the autopsies revealed elevated liver (141.5 µg/g) and blood (244.5 µg/100 ml) lead. The source of the lead was thought by the farmer to arise from sludge amendments to the crop soils, but paint chips in the barn were found to contain 21.3 µg Pb/g (Dorn and others 1986).

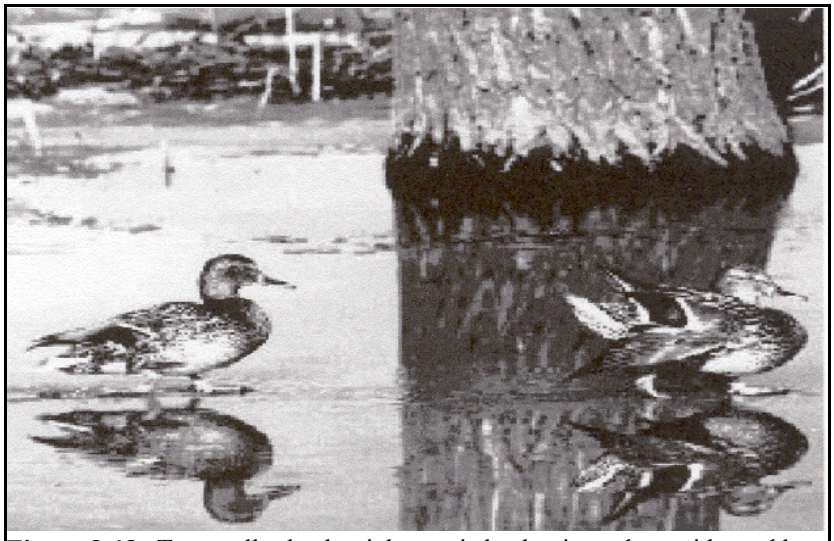

Figure 8.46. Two mallards, the right one is lead poisoned as evidenced by the upright position of the wings. Waterfowl Management Handbook, Milton Friend, 13.2.6. Lead Poisoning: The Invisible Disease.

In areas of lead mining in England, lamb loss increased due to heavily contaminated pastures (Clegg and Rylands, 1966; Nisbett, 1957).

Zoo Poisonings

Several sandhill cranes in Florida presented with anorexia, green diarrhea, pectoral muscle atrophy, and weakness. They were successfully treated with EDTA. They had been temporarily housed in an enclosure which had paint with a 27% lead content.

Unusual Bird Poisoning

More than half million seabirds of 15 species nest on the Midway Islands. It is home to the largest colony of Laysan albatross, who return to the islands in November to lay eggs. The Midway Islands had a human population high of 3,000 in 1957, has since dropped to 400, with abandonment of roads and runways, houses, etc.. In 1982 20,000 5 month old chicks were found dead at a mortality rate of greater than twice that expected. 1983 five normal fledgling and 12 "droop-wing" albatrosses were captured and blood lead samples obtained. Lead was found in the liver as inclusions, the blood value in normal birds was <0.1 ppm, and ranged from 0.03 to 4.8 ppm in droop-wing birds. The sacrificed droop wing birds were autopsied and paint chips were found in the proventriculus. The paint chips were found to contain between 322-144,000 ppm lead. Other pathological features were found. Paint chips from peeling buildings were found to contain from 1500 to 247,250 ppm dry weight lead.

Clinical trials on lead acetate treated pigeons were performed to determine the efficacy of EDTA, DTPA, DMSA, and PA (penicillamine) on treating avian lead poisoning (Mautino 1990). The latter two chelating agents were found to be most effective.

Wild Waterfowl

The earliest call to alarm for waterfowl population lead poisoning came in 1930 (Philips and Lincoln 1930). A major study by the Illinois Natural History Survey in 1959 (Bellrose 1959) concluded that there was a massive die off of ducks in Grafton in 1948, with large losses in the late 1800s and early 1900s in Texas, N. Carolina, Puget Sound, Wa., Back Bay, Va., Hovey Lake, Indiana. Die off appears to be most closely linked to the end of the hunting seasons. The Mallard duck is the most commonly affected of the wildlife die offs associated with lead gunshot ingestion (Figures 8. 46 and 8.47). Ducks experimentally fed shot began to exhibit diarrhea on the 2nd day, with greater diarrhea in the high fiber diet. Anorexia was manifested by the 3rd day and weakness by the 5th day,

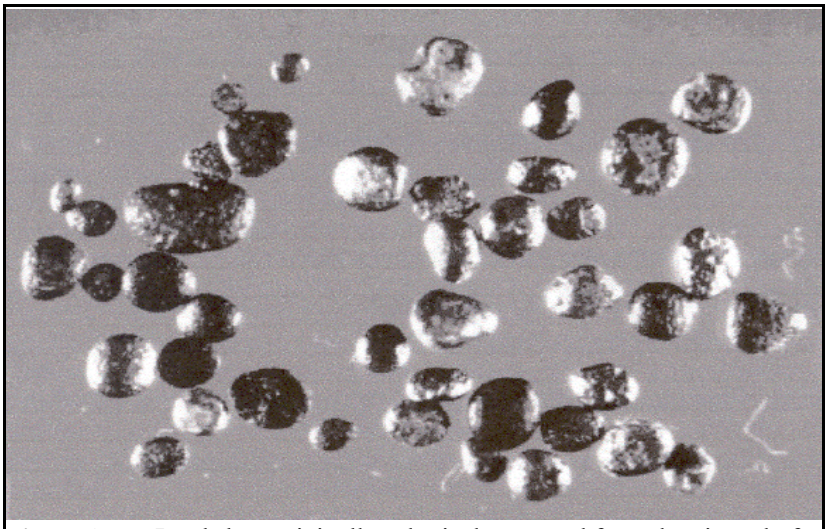

Figure 8.47. Lead shot, originally spherical, removed from the gizzard of a lead poisoned mallard. The shot has been ground and smoothed into odd shapes. Waterfowl Management Handbook, Milton Friend, 13.2.6. Lead Poisoning: The Invisible Disease.

Figure 8.48. Lead poisoned goose has lost ability to keep neck extended. Neck folds along the back of the animal. Simpson et al. Env. Poll. 1979, 18, 87.

again with symptoms aggravated by high fiber (Clemens and others 1975; Del Bono and Braca 1973). The loss of duck and geese combined is thought to be > 1,000,000/year (1975). Lead poisoning of ducks is not limited to the U.S. with reports originating from Portugal and Spain (Mateo and others 2001).

Geese are another species which has had a hard time with lead. Geese are bottom feeders, so they ingest a disproportionate amount of lead if the bottom of the river is contaminated. The principal problem with migrating geese is ingestion of spent lead shot by migrating birds feeding in heavily hunted areas. The pellets are retrieved from the marshy bottoms of shallow water by the waterfowl in search of feed and grit. The lead shot is then retained in the gizzard where it is solubilized by a combination of the powerful grinding action and the low (2-3.5) pH of the gizzard. Contamination can occur from mine wastes (Sileo and others 2001). This has occurred in Idaho, where the sediment contained 2,400 to 8,700 µg Pb/g. Geese in Delaware have been reported poisoned(Bagley and others 1967) with lead shot obtained from the gizzard. Experimentally poisoned geese were found to exhibit symptoms within 5-7 days of ingestion of lead pellets. Ingestion of >25 pellets lead to death within 10 days. Ingestion of <10 pellets lead to survival as long as 72 days. Pellets erode at a constant rate regardless of number in the gizzard. Normal lead levels for geese were 0.018-0.037 mg/100 g blood, while that of poisoned geese had values peaking at 0.320 to 1.680 mg/100g (Cook and Trainer 1966).

Of 43 swans found dead in a mining area, autopsies revealed 38 from mine contaminated waters had 6-40 µg Pb/g liver while the remains from 5 swans from uncontaminated water ways had no lead (Blus and others 1991). Contamination is more usually caused by lead shot from hunting or fishing lures. It is estimated that lead shot is responsible for the death of 3,370 to 4,190 mute swans/year in England alone (O'Halloran and others 1988a; O'Halloran and others 1988b).

Poisoning continues to occur throughout the United States (Franson and Smith 1999). In 1997 25% of swans from a herd examined were diagnosed with lead poisoning and were given EDTA (Routh and Painter 1997). Long term survival of swans poisoned with lead shot and treated with EDTA is better than non-treatment, but not great. Only 22% of the swan

remained alive after 2 years (Sears and others 1989).

Swans can also be poisoned from lead fishing weights as observed from a sick herd on the River Trent in Nottingham, England. These swans would "graze" along a stretch of the river heavily utilized by fishermen with fishermen debris. Lead was obtained on post mortem of 17 mute swans (from a herd of 30) found dead. Birds up river, feeding in areas lower in fishermen activity did not exhibit the same mortality rate, or blood lead sample (Simpson and others 1979). Similar results from lead fishing sinkers have been reported for swans in Scotland (Pennycott 1998). Other swans were recognized as chronically lead poisoned by abnormal carriage of the neck where the lower third of the neck was supported against the back (Figure 8.48). On land birds would stand only for short periods and tended to lie with the full length of the neck resting along the back or along side the body on the ground. Extremely poisoned swans became paralytic just before death.

Swan populations in Idaho, Montana, Wyoming, and western Washington have been declining from 1976-1987. 20% of the recovered carcasses have symptoms of lead poisoning (Blus and others 1989). While Trumpeter Swans in British Colombia have experienced unnaturally high mortality due to lead poisoning (46% of collected carcasses), the populations in the region were increasing in 1998 (Wilson and others 1998).

Similar data has been observed in the duck, geese, and swan populations in Japan with each of these species containing substantial % of the population with ingested lead shot (Ochial and others 1999).

Canada began debate in 2002 over outlawing the use of lead sinkers in fishing. Mr. Carry Breitkreuz (Yorkton-Melville, Canadian Alliance) spoke against the motion:

As with many environmental issues that come before us, this issue has a lot of emotion, but science is really lacking.

Mr. Breitkreuz's objection is to regulation. He suggests that a) more science is needed; b) an awareness campaign be launched to the public and to c) various agencies and organizations, followed by d) a stakeholders decision making process (Parliament 2002).

Other Hunted Species

Other species can pick up lead shot from a highly hunted surrounding. Examples consist of perching birds in a trap and skeet range (Vyas and others 2000). Lead exposure at the skeet range was determined by counting shot, and measuring the amount of lead in the soil and in earthworms. Lead pellets shot into trees have been picked out by woodpeckers leading to lead poisoning of wood peckers (Morner and Petersson 1999). Lead shot in hunting ranges can varying from 3,228 shot/ha (pre-hunt) to 860,185 shot/ha post-hunting (Best and others 1992; Castrale and Oster 1994). This shot can be consumed by doves, bobwhite, frogs, and small mammals (Lewis and Schweitzer 2000).

Raptors

Loons are also affected by fishing weights. These are piscivorous birds which can be exposed to lead intoxication by ingesting escaped fish carrying hooks, fragments of fishing lines, and sinkers or by picking up sinkers with stones from the bottoms of lakes and ponds. Liver lead in the loon were 20.6, 46.1 and 38.52 (wet weight) as compared to other non-lead poisoned loons with liver lead levels of less than 1 ppm wet weight (Locke and others 1981). The death of loons is particularly worrisome because they are designated as an endangered or threatened species. A second study found several lead poisoned loons presenting with depression (coming onto land to rest), trying to retch or vomit, weakness, inability to fly or escape, head tilt, abnormal neck carriage, convulsions, green-stained vent area, and emaciation (Pokras and Chafel 1992). These loons were found to have been feeding heavily on crayfish which are slow moving instead of their normal fast swimming prey (perch).

Raptors are also subject to poisoning from eating of the lead poisoned ducks, swans and fish and mammals. Several large scale die-offs have been reported for raptor birds (Friend 1989). Eagles have been recently identified as suffering from lead poisoning from their intake of lead containing prey. Examples include the Steller's and White-tailed Sea Eagles of Hokkaido, Japan (Kim and others 1999). The source of lead was from the lead shot embedded in their prey. Similarly for Canadian bald eagles, lead shot associated with waterfowl hunting was suggested to be the main route of poisoning (Wayland and bollinger 1999). This suggestion was based on a correlation of high lead in bald eagles in areas with high waterfowl hunting intensity. Golden eagles, however, apparently picked up lead through upland game birds and mammals. Golden eagles prey on live

Figure 8.50. The California condor came within 20 breeding pairs of extinction from DDT poisoning. Captive breeding brought the bird back to a sustainable level. Birds are now dying from eating prey debilitated from gunshot wounding. Chicago Tribune, June 21, 2001.

small animals and scavenge other animals such as carcasses of large game, deer and antelope. The dead carcasses may contain lead shot. The smaller mammals can also pick up scattered lead shot in areas of high hunting intensity (Stanseley and Rosecoe 1996). In some cases leaded pesticides may be at fault (Shimmel and Snell 1999). A review of 14 years of eagle mortality showed a verifiable relationship to lead poisoning ((Wayland and others 2003).

Condors in America dropped to near extinction in 1973 as a result of DDT effects on the strength of their nesting eggs (Figure 8.49). In 1982 the population reached a low of 22. A captive breeding program was deemed so successful that a sub-population of the species was returned to the wild in 1994. The population in 2001 was 56 wild animals and 128 in captivity. Since 1997 there have been 4 fatalities and 13 elaborate drug treatments of lead poisoned condors, particularly in the state of Arizona. The poisoning is related to the feeding habits of the birds. The condors actively scavenge the carcass they feed upon for calcium in the form of bone shards and are thought to pick up lead shot from wounded prey they feed upon (Schoch 2001).

Turkey vultures have also been found to occasionally be lead poisoned ((Carpenter and others 2003).

Other

Flying fox (fruit bats) have also been found to be lead poisoned (Sutton and Hariono 1987), (Skerratt and others 1998). The clinical symptoms of lead poisoning is an inability to fly, muscle fasciculation, uncoordinated movement, inappetance, excess salivation, and diarrhea. The level of lead in the flying fox is correlated with an urban vs rural environment. It has been found that 55 to 75% ingested lead is absorbed (Harrons 1991).

One unusual wildlife case involves a lead poisoned snapping turtle. A 9.8 adult male snapping turtle (Chelydra serpentine) was brought to Tufts Wildlife clinic and was depressed, weak, and unable to rise on its forelimbs. It did not exhibit snapping behavior (Borkowski 1997). X-ray analysis showed a lead sinker embedded with line in the intestine. Blood lead level tested to 3.6 ppm. The turtle was treated with EDTA therapy, as well as penicillin, and suture to internal perforation. Blood lead dropped with chelation therapy. The veterinarian expressed caution in the treatment since little is known about reptilian lead poisoning.

Kakadu crocodiles were reported lead poisoned in 2003 ((Jeffree 2003).

Failure of motor coordination of the extremities ("wrist dangles") may not be confined to human species. An unconfirmed report (Cole 1992) suggests that a herd of elephants in Zimbabwe whose water source is Lake Kariba, a shrinking lake body (concentrating lead), exhibit a flaccid trunk paralysis prohibiting normal trunk usage for foraging and drinking.

Lead and Other Species

For species that are directly out of the range of immediate human contact lead poisoning would have to enter the food chain through either water or the soil. In essence soil is the "blood" of the natural environment (compare Figures 8.3 and 8.50).

Lead in Soils

The amount of lead in soils depends upon the balance of inputs and outputs. Total inputs of lead into the soil include airborne sources, point sources, leaded paints, and "natural" values of soil lead. Total outputs include subsurface transport to lower soil depths, transport through the soil to groundwater, dust carried by winds elsewhere and dust carried into homes.

"Natural" sources of lead

The estimate of the natural soil lead can be calculated from the amount of lead present in surface rocks (see Chapter 1). Surface rock lead content is shown in Table B.15 (Davies 1983; Linzon and others 1976; Present and Tupper 1965; Wixson and Davies 1993). The average rock is thought to contain 16 ug Pb/g. Normal levels of lead in the soil are generally less than 20 ppm. Rural soils in the United States were reported to be 11 µg/g (Holmgren and others 1983).

Soils in Britain tend to be higher in lead due to Roman and British mining, as well as gasoline production. An estimate of 2.4 g/m^3 soil has been given with 3 g emitted from the 18th century and 0.4 g from gasoline (Chamberlain 1983). Uncontaminated soils in rural England were found to be 42 ppm (as compared to the 20 ppm of the U.S.). The highest average concentrations are observed for the most industrialized cities (Table C.8 and C.9). Within an industrialized area the suburbs tend to have less than the main part of the city (LaBelle and others 1987).

The soil lead content ranges from 5 ppm (remote Canada) to 30,000 ppm (lead belt of Missouri).

Dispersion from Gasoline

We saw in Chapter 7 that leaded gasoline generally resulted in widespread dispersion of lead into the environment, particularly in soils adjacent to highways. Soil lead derived from gasoline ranges from 250 to 500 ppm.

"Point" sources of lead (battery recycling)

In the earlier 1990s approximately 85% of batteries in the U.S. were recycled for their lead content (~12-17 lbs of lead). By 2000 this value has increased to 97%. Recycling involves cracking of the case, recovery of the lead and case plastic, and neutralization of the acid. The lead is re-smelted and the plastic recycled.

Many of the superfund sites in the U.S. are due to battery recycling operations. These sites can be extremely high in lead with major human health consequences. One case is that of a family occupying land built on a battery site in Jamaica. The soil contained lead ranging from a low of 1,800 ppm to a high of 27,300 ppm. The two year old in the family was admitted to the hospital with epileptic seizures and paralysis of the left side of his

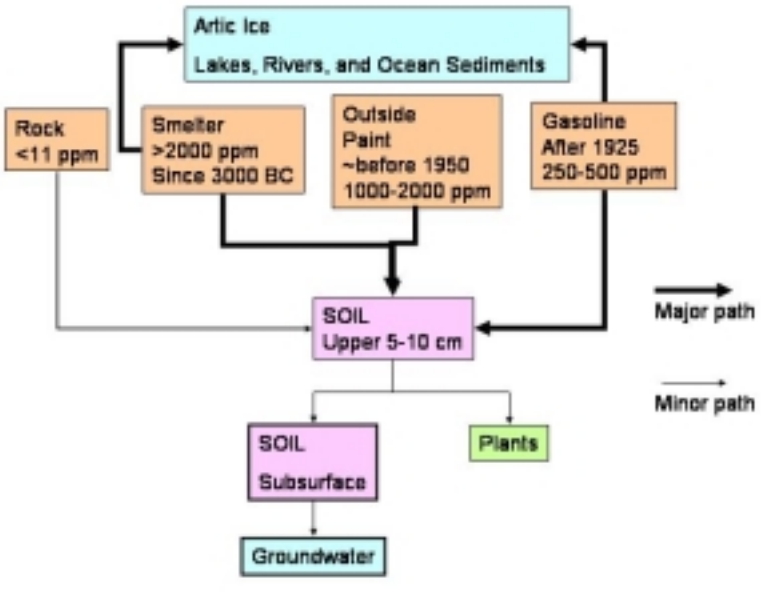

Figure 8.51 Soil as the central medium for exposure of various species to lead.

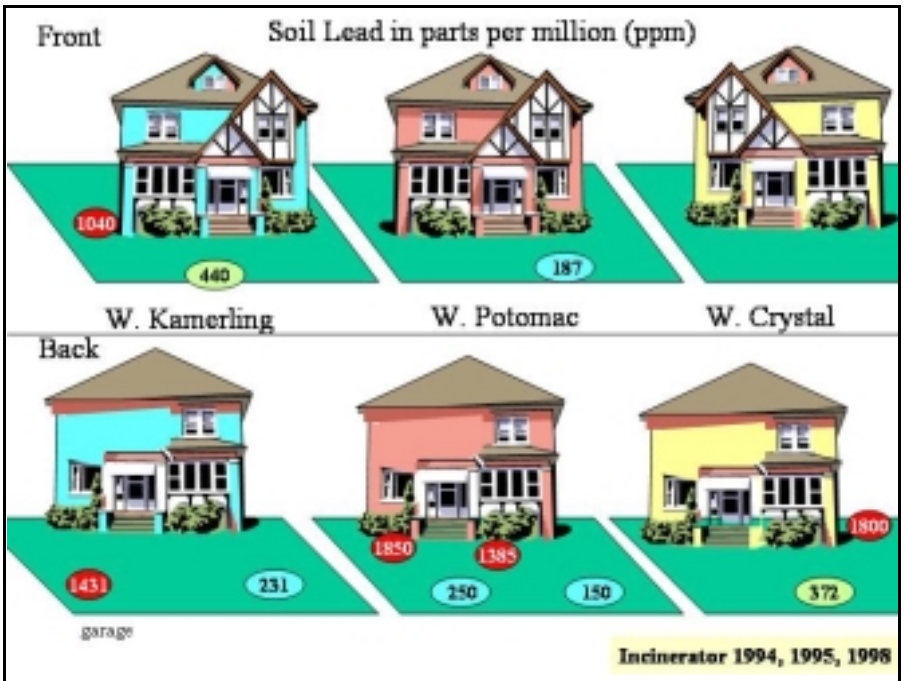

Figure 8.52 Soil lead is high near homes where lead paint has flaked as compared to a yard or two away from the wall line. Soils were sampled by Loyola University chemistry students. (Source: author.)

Figure 8.51 shows a Loyola University Chicago undergraduate survey of several homes from 1920 which indicate higher lead near the house edge line and lower values of lead further away.

Fate of Lead in Soil

The chemistry of lead within the soil itself is fairly innocuous. Lead tends to form insoluble, inert compounds and to remain "fixed' within the soil at the upper surface (Figure 8.52)

Some lead can be translocated by soluble soil organic acids or small colloids. In general, however, lead remains spatially fixed at the point of entrance into the soil system. The fact that lead does not move downward means that mining slags erode with their lead into river systems and that lead is in a location that is actively explored by children and household pets.

body. Two weeks later his six year old sister was admitted with paralysis of the ankles. The two year old's blood lead level was 218µg/dL and he died of cardiac arrest. The six year old sister with a blood lead level of 235 µg/dL survived, but has an assessed mental age of 3 and suffers paralysis of the limbs (Chang-Yen and others 1995).

"Point" Sources of Soil Lead: Pigments and Paints

Paints contribute to total uptake of lead both via direct ingestion (paint chips) and via dust. Lead containing paint chips are most often to be found in older housing stock where the mildewcide (heavy duty outdoor white paints) were brought indoors. The common chipping areas are along the window trims and radiators. The total layers of paint can be as large as 45 complicating the measurement of lead, where the lead may underlie the latest paint layer (see also Table G.5.

Paint contribution to soil lead follows a pattern of distance from the building, so that the heaviest contaminated sites lie closest to the building structure. This forms an important route of lead into the house dust as lead from the soil close to home is often tracked indoors to contaminate the dust indoors Table G.2) (Wixson and Davies 1993).

Uptake by Plants

Plants growing in a lead enriched medium can take up lead through active (acid dissolving) and passive exchange mechanism (Figure 8.53). The result is an uptake of lead in **some** crops (Spittler and Feder 1981). Uptake of lead by tobacco mirrors air lead concentrations, decreasing as airborne lead decreases. The decrease, however, has leveled off around 1985 which suggests that contemporary cigarette lead content is controlled by the soil fixed forms of lead and not by atmospheric lead. The content of cigarette lead is sufficiently high as to be a major source of lead exposure for the smoking population (Rickert and Kaiserman 1994).

Crops can be contaminated with lead by aerial deposition and by root uptake. Aerial deposition is not unambiguously related to internal plant lead concentration (Zimdahl and Skogerboe 1977). 96% of the lead on spruce needles in southwest Germany derived from airborne lead. Data obtained in Mexico on airborne contaminated crops (Albert and Badillo 1991)

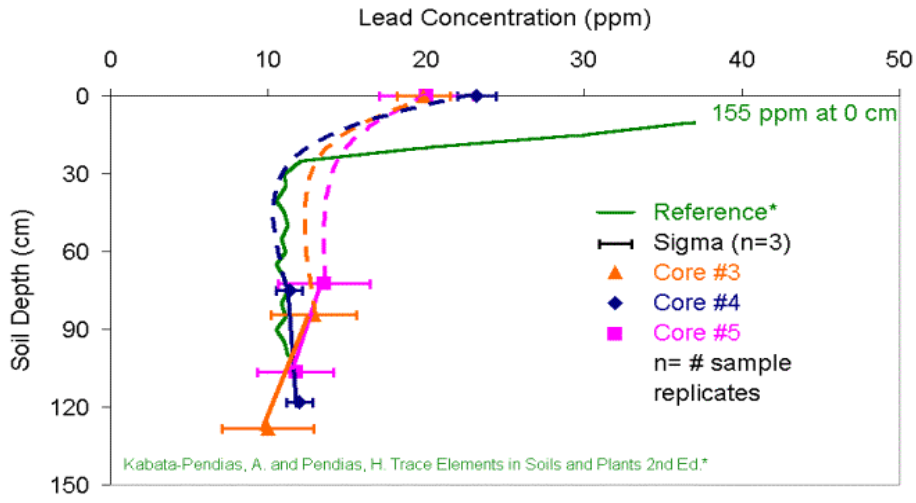

Figure 8.54 Lead remains localized at the surface of the soil because it is insoluble. Data from the dissertation of Luke Augustine, Loyola University Chicago, 2001.

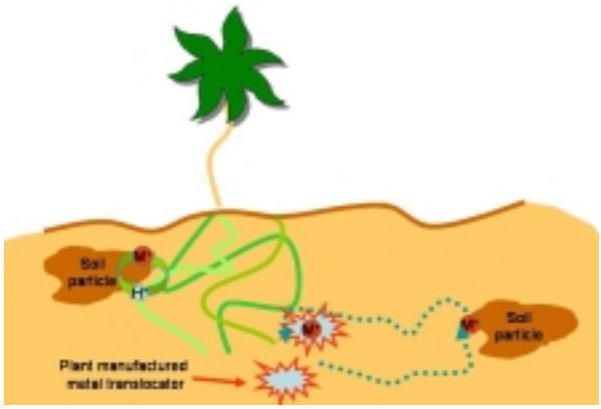

Figure 8.55. For insoluble species like lead, pPlant roots must be in contact with soil particle holding metal, M (lead) or must exude material which can fetch the metal.

shows that 97% of the lead could be accounted for by washing of the vegetation. Other studies reveal similar results with 50-90% of the lead in the plant removable by washing (Lagerwerff and others 1973) (Table C.14). Lettuce grown on contaminated urban soils resulted in high lead leaf concentrations, but the value was less than would be obtained by direct ingestion of the soil or dust ((Sterrett and others 1996).

In general the transfer coefficient (% material in plant compared to soil) from soil to crop is low (0.01 to 0.1 (Table C.12 and C.13) (Forstner 1995). Root plants tend to retain more lead than fruits and vegetables. If the soil is to be used for crop production (urban gardens?), the exact distribution of lead among the various forms (organic and inorganic) is important in determining plant availability and crop contamination (Albasel and Cottenie 1985; Giordano and others 1983; Harter 1983; Sposito and others 1982).

Crops exhibit toxicity to lead in hydroponic media and from lead in the upper 5-10 cm of soil (where lead is localized). Lead of values of 100-2000 ug/g will reduce growth of corn (Hassett 1974). The mechanism of toxicity in plants is similar to that in animals and humans: phosphate deprivation in cells due to solubility problems with lead, and problems with ALA conversions (Scarponi and Perucci 1984). Symptoms of poisoning can be stunted growth and reduction in leaf development, changes in production of root systems (Carelli and others 1995) (Walker and others 1977). Other mechanisms of plant toxicity implicate heavy metal interference of calcium binding to calmodulin, as was found for Cd^{2+} on radish seed germination which reduced the growth of the embryo axes ((Negrini and others 1995; Rivetta and others 1997).

Use of isotope ratios on deliberately contaminated soils lead to the conclusion that lead within grass came 90% from the soil (Bacon and others 1995).

Tree ring studies have also been attempted to monitor the deposition flux of lead, particularly by tracking the isotope ratios. One difficulty of these studies is that despite higher lead fluxes during the leaded gasoline period very little lead was increased in some tree species (for example red oak). A tree that does record lead is the sycamore (A. Pseudoplatanus L.) which deposits non-essential elements. Isotope ratios in sycamore were found to change after 1993, correlated to changes in lead derived from vehicle

emissions (Watmough and others 1999). At another site which had multiple sources of lead no such change in isotope ratio could be tracked. Cypress wood has also been capable of tracking isotope ratios for pollution source. The results indicate that Pb uptake was dominated by local scale root processes (water driven) as opposed to aerosol. The source of lead in the cypress was apparently sludge discharged in the Louisiana Bayou (Marcantonio and others 1998).

Phytoremediation

Because plants acquire much of their mineral matter by passive diffusion of soluble soil components attempts to remove from soils by harvesting plant material are less than totally successful. Plants which do accumulate lead are known as hyper-accumulators, such as Asiatic Reynoutric japonica Houte (Hulina and Dumija 1999). Other species which have been investigated for tissue accumulation, harvest, and removal are Helianthus annuus (Abruzzese and others 2001), river birch and smallwing sedge (Klassen and others 2000). The smallwing sedge was able to tolerate up to 1000 mg Pb per kg dry tissue weight. The birch tolerated up to 200 mg Pb/kg dry tissue weight. Other species investigated are maize and Indian mustard. Over a two year cropping period for maize grown on 65,200 ppm soil lead, maize had less lead per tissue weight but removed a greater total of lead from the soil (0.2 mg/pot) (Bricker and others 2001) Legumes Vicia faba, Pisum sativum, and Phaseolus vulgaris were compared for uptake from hydroponic solutions of lead (Piechalak and others 2002). P. vulgaris took up lead up to 75 mg/g dry weight. Other aqueous plants have been studied for remediation of wetlands. Some plants shown to be good candidates for phytoremediation are calmus (Wang and others 2002), duckweed, and hydrilla (Gallardo-Williams and others 2002).

For species of plants which do not accumulate lead some method of boosting transfer of lead to the plant root is required. Either synthetic chelates can be added which then must be replenished, or the soil can be inoculated with bacteria that produce chelates which serve to translocate lead to the plant root. The bacteria may be either wild type or genetically altered to produce lead chelators (Burd and others 2000; Diels and others 1999; Kraemer and others 1999; Pasca and others 1998; Shenker and others 2001).

Marine and Water life

The source of lead uptake in marine and waterlife has been linked to uptake of organolead compounds such as tetraethyl lead in mussels along the Adriatic coast (Mikac and others 1996) as well as in salt marsh periwinkes (Krishnan and others 1988). Plankton assemblages can be used to track lead in a marine environment (Flegal and others 1993).

SUMMARY

Lead has a wide range of symptoms clinically. Patients can expect to begin with fatigue, some difficulty balancing, vision, wrist drop, followed by stumbling, acute colic, gastrointestinal spasms, generalized wasting, deposition of lead along the gum lines and hallucinatory behavior, followed by acute spasms to death. At the lower exposure end, the effects of lead exposure run from minor anemia, to lowered mental capacity and attention deficit. Inorganic lead, the most common source of lead, will have a greater impact if it ingested via fine particles in the respiratory track. Lead is rapidly moved through the blood stream to various organs involved in forming blood (liver) and cleaning blood (kidney). Lead is deposited in the bone and can have a long half life there.

Lead masquerades as calcium from a distance but once within the calcium regulation sites has a different structural rearrangement of the bulk protein structure involved in triggering calcium events. This is most likely due to the lone s^2 electrons on lead, although this has not yet been proven or investigated. Chelation therapies have some success although they tend to mobilize the lead from bone material and into the blood stream where toxicity becomes more prevalent. The side effects of chelation therapy are related to the indiscriminate chelation of lead over zinc, and copper. No truly specific lead chelate has yet been devised.

Other species have had greater generalized mortality to lead than humans. These are species with feeding behavior for contaminated sludges, as well as domesticated animals with high oral activity (birds and dogs).

Lead is toxic to plants by similar biochemical mechanisms (ALA disruption). Plants growing hydroponically are severely impacted by the presence of lead. Plants growing in soils often grow reasonably well unless the soil is extremely contaminated. This is because lead in soil tends to be insoluble and not available to plants.

Chap. 8 Underlying Chemistry of Toxicology

A. Covalent bonding of Lead to Carbon

The unstable covalent bonding of lead can be rationalized by reference to the periodic chart. As might be expected, lead is less electronegative than carbon (lower position in the periodic table). The bond strength (as measured from thermochemistry) is lower than that of a true covalent bond between C and C. This lower bond strength means that the organo-lead can be rapidly de-alkylated (removed from a carbon chain) in the liver, the organ responsible for detoxification. This process is accompanied by a loss of an electron (carbon being more electronegative gets the electron that was shared by lead):

[8.4] $R_4Pb \rightarrow R^{\cdot} + R_3Pb^+$

where R is a carbon chain (for example CH_3-, CH_3CH_2-$CH_3CH_2CH_2$-).

In reaction [8.4] we are left with a radical to be scavenged by a charged species. Since a charged species requires some compensation this compound is found as R_3PbCl:

[8.5] $R_3Pb^+ + Cl^- \rightarrow R_3PbCl$

B. Chelation Therapy

The two enantiomers of DMSA are shown in Figure 8.54. Notice that both structural formulas show essentially the same compound. The difference between two lies in the transposition of the bottom O and OH around the carbon. Since these are the same formula compounds and differ only by a change in directionality they are termed enantiomers. The stronger bond actually turns out to be a single S bond, showing preference to the O-Pb-S link (Fabri and Castellino 1995; Rivera and others 1989a; Rivera and others 1989b). This form is also the more soluble for of the chelate (Fang and Fernando 1994). The more effective chelate is the racemate. This is because the meso form in solution can chelate to form a double chair configuration which has few ionic groups giving solubility. Table D.12 shows a series of chelates and their binding constants for lead as compared to Ca and Zn. The chelates are clustered in order by O, O+ N, N, N+S, S+O, and S binding functionalities (Cheng 1992). There is no apparent discernable trend in enhancing the selectivity of lead over these other metal ions based on the ligand alone.

D. The Possible Lone Pair Effect of Lead in Molecular Biology

The binding of lead in enzymes has not been well studied from a structural point of view (Abu-Dari and others 1993; Battistuzzi and others 1996). We can, however, reason what might be the difference in binding of lead as compared to calcium within enzyme structures. Since lead disrupts many of the calcium functions lead can not be engaging in a simple substitution for calcium. That is, once lead, perceived as calcium, is brought into the calcium binding site, it behaves differently. What accounts for this difference?

We begin by a review of what we have learned about the unique features of lead chemistry. Lead exists in three valence states: Pb^0 ($s^2d^{10}p^2$) which can be sp^3 hybridized for covalent bonding, tetrahedral in shape; Pb^{2+} ($s^2d^{10}p^0$) which contains an s^2 lone pair of electrons (unlike Ca^{2+}) , and Pb^{4+} ($s^0d^{10}p^0$).

The tetravalent lead, in an oxygen rich environment forms β PbO_2, a rutile structure, and α PbO_2, (hexagonal close pack), structure, both with a coordination number of 6. The densities of these oxides are high and there is no particular distortion of the basic structure anticipated by calculation the cation radius to anion radius ratio. Minium contains both divalent lead and tetravalent lead. The tetravalent lead is in an octahedral arrangement (6 C.N.).

Divalent lead, on the other hand, while at first "looking like calcium" has the additional feature of 2s electrons. The formation of α PbO (tetragonal) and β PbO (orthorhombic) both show "open" oxide structure due to the effect of the lead lone pair. In α PbO (litharge, reddish yellow) each PbO bond is equal in length, while in yellow massicot β PbO (orthorhombic) 2 PbO bonds are 2.21 Å and 2 are 2.498 Å.

Some examples of distorted octahedral bonding occur in binding of lead to small ligands. The lone pair has been postulated to change from stereochemically inactive to active with a shortening of Pb-N bond lengths (Hancock and others 1988). Where the Pb-N bond length is 2.37-2.56 Å the lone pair is active, while the bond length of 2.62-2.88 Å results in an inactive lone pair. This is consistent with the requirement that the ligand penetrate deep enough to the central metal atom such that that atom experiences

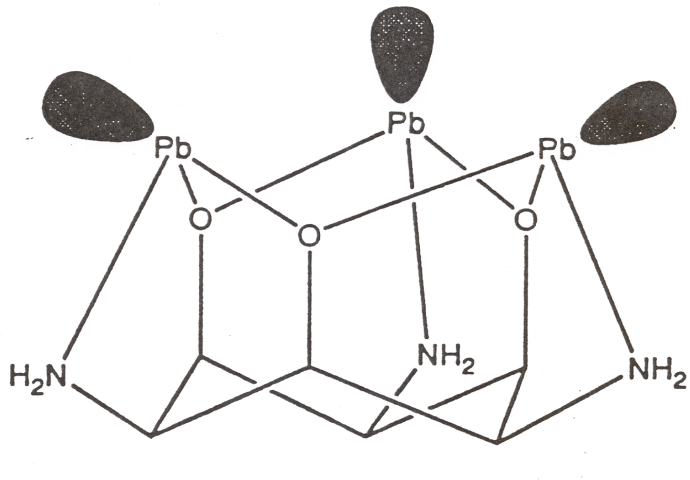

Figure 8.56 Lone pair electrons on lead are activated by the distortion in bond lengths between oxygen and nitrogen with lead. Source: Hegetschweiler, 1993.

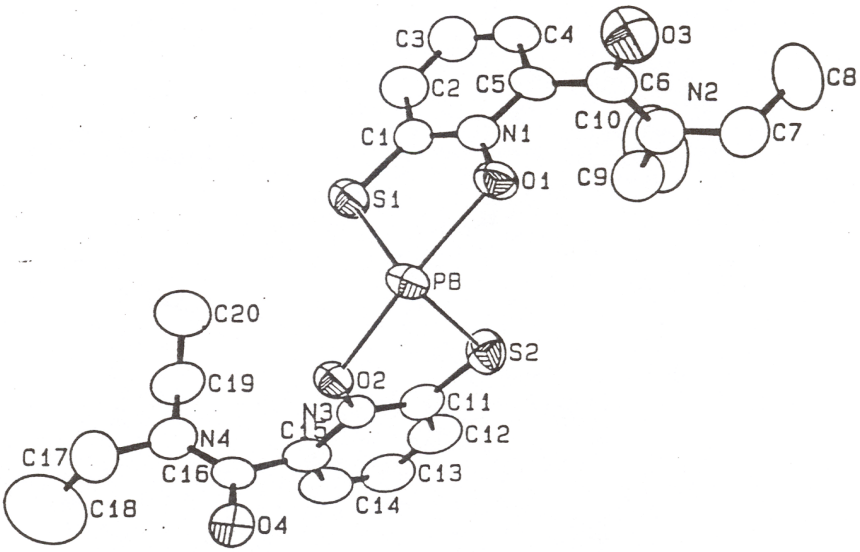

Figure 8.57 In this compound the lone electron pair on lead (invisible) is oriented through the center of the compound along the axis running through lead. The open space around lead is due to the effects of the lone electron pair. Source: Abu-Dari et al. 1993.

distortions in its electronic structure. The key is to create a bond length that is short enough to force the lone pair out and away.

Lead in 1,3,5-triamino-1,3,5-trideoxxy-cis-inositol) becomes stereochemically active as shown in Figure 8.56. In the configuration each lead has 2 O and 1 N in a distorted pyramidal shape. A nitrato ligand fills the 4th C. N. site (C. N. #4). Another example of the lone pair effect is given by bis(6-(diethylcarbamoyl)-1 hydroxy- 2(1H)-pyridine-2-thionato-O,S)-lead (II) (Figure 8.57). When the chelate dimerizes lead goes from a square planar coordination sites to a distorted octahedral coordination site. This compound introduces not only O and N, but S into the binding. The long S-Pb bond implies S contains most of the charge, less is shared with Pb, and implies that it is a thiol (Abu-Dari and others 1993).

Lead has different coordination preferences depending on the flexibility of the ligand site (which could be related to the rigidity of the chelate in forcing the lone pair out of the way). In lead EDTA solid crystals lead adopts a 4 coordination structure while in solution it is six coordinate (Langer 1964; McConnell and Nuttail 1977). Presumably in solution there is greater flexibility of the ligand, as well as on/off motion of the ligands. When bound to various crown ether compounds the coordination number has been reported as 9 and 10 ((Lamb and Nazarenko 1997; Nazarenko and B.` 1995; Nazarenko and others 1995; Nazarenko and Rusanov 1994). In calixarene type compounds lead assumes an 8 fold coordination complex ((Cadogan and others 1999).

A review of lead coordination in PbS_4 compounds as influenced by structural constraints imposed by the chelates has recently been given (Caruso and others 1997). The lone pair of electrons is expected when the Pb-S bond is longer and the S-Pb-S bond angle is larger than expected. The lone pair should occupy the apex of a pyramid opposite the S atoms and be stereochemically active. The pyramid has equal trans angles (113.3 °).

Based on the distortions felt within the

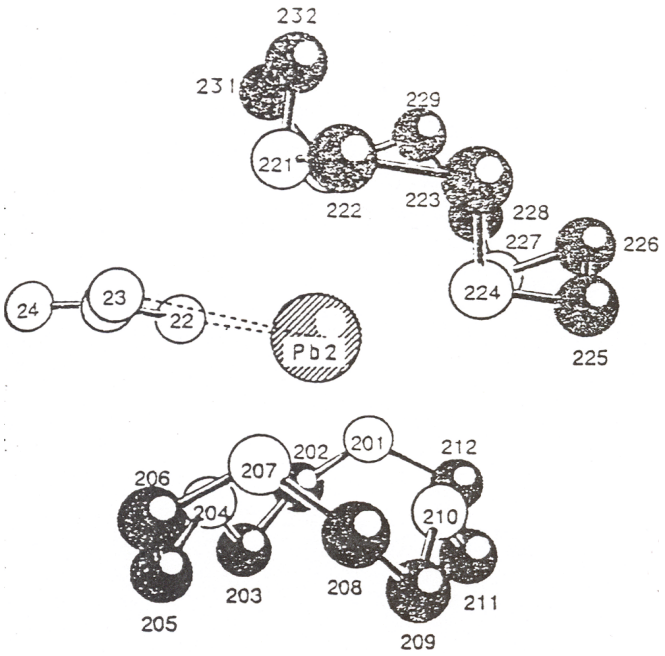

Figure 8.58 This drawing represents the binding of lead with two crown ligands, each containing four oxygens. Like the compound in Figure 8.50 there is an open space around lead imparted by the invisible lone pair of electrons. To the left is a third coordinating compound, nitrate. [Pb(12 -crown-4)$_2$(NO_3)]$^+$. Data source: D. G. Nicholson, I. Sylts, A. K. Vasudevan, L. J. Saethae, Acta. Chem. Scan. 1992, 46, 358-362.

flexible 6 C.N. as well as 4 C.N. it appears likely that lead binding into the 6 C.N. oxygen ligand pocket of the calmodulin type enzymes would tend to have a stereochemically active lone pair of electrons which would change the backbone structural rearrangements necessary for calcium triggering.

On the other hand, investigation of binding of calcium with various crown ethers does not appear to support the hypothesis of an active lone pair. Crown ethers have an open oxygen environment capable of multiple coordination with ions, similar to the enzyme studies. Of the two crown ethers shown the larger ring (18-crown with 6 binding oxygen) did not show involvement of the lone pair (Figure 8.58) (Drew and others 1992; Rogers and others 1996). The dimeric 12-crown ring with each 4 oxygen binding sites (total of 8) indicated involvement of the lone pair (Nicholson and others 1992) (Figure 8.51).

SOIL Transport

Survey of the Soil Matrix affecting its chemistry

Soil consists of a mixture of various sized solid materials, degraded organic material, connected by a large variety of pore spaces, and under variable amounts of water. The solid materials range from clay (< 2μm in size), to silt (2-50 μm), to sand (50 μm to 2 mm).

The reactive part of the soil is the clay fraction. Clay is formed in the soil in situ by percolation processes which dissolve easily solubilized minerals at the top, transport the dissolved species lower where there can be a pH change, and formation of new crystalline materials. A typical soil profile will contain a leached region near the surface, followed by a depositional layer some distance (depending upon age of the soil and climate (tropical etc), and groundwater) below (Figure 8.59).

The process by which material is translocated from the surface to a depositional layer under the influence of time and climate is called soil weathering. The region of altered material at the surface of the earth (the "soil") can be 4 feet deep and may have been formed over a 10,000 year period in temperate climates. The process of weathering involves dissolution of less soluble material and reprecipitation as the oxygen and carbonate (and hence pH) of the soil changes with depth.

The solubility of minerals depends upon the temperature at which it was formed from the magma. Minerals that crystallized first are the most unstable, with those crystallizing last the most stable (Table B.7). Olivines and plagioclases are weathered first. A typical example is the weathering of albite, a feldspar:

[8.7] $NaAlSi_3O_8 + H_2O + 4H^+ + time \rightarrow Na^+ + Al^{3+} + 3Si(OH)_4$ (soluble)

The reaction will tend to increase the pH since protons are removed. The Na^+ can be carried to the sea (Table C.4) while the aluminum will generally precipitate at a lower level due to its higher charged density. Such precipitation results in the production of clays:

[11.3] $Al^3 + Si(OH)_4 + 1/2H_2O \rightarrow 3H^+ + 1/2Al_2Si_2O_5(OH)_4$ (kaolinite)

In this reaction note that the pH can be decreased, made more acidic. The clay so formed can be weathered in

Figure 8.59. A relatively new soil profile on glacial till, Batavia, Illinois. Below grass is a dark organic layer, followed by a bleached (leached) layer, followed by red clay depositional layer. Below the clay deposition is unweathered glacial till. Photo by Luke Augustine, Loyola University Chicago.

situ to form other clays and minerals

[11.4] $Al^{3+} + 3H_2O \rightarrow 2H^+ + Al(OH)_3$ gibbsite

In this weathering scheme note that some of the ions will weather faster or be removed from the soil more quickly. This leads to the difference in plant mineral content and the production of pot ash (burned trees) high in potassium carbonate as opposed to sodium carbonate, which in turn affects processes such as glass production.

K, Mg, Si weather, or are translocated, more slowly than Na, Ca, or sulfate. Fe, Mn, Ti, and Al precipitate while Cu, Zn are somewhat more mobile. The first stage of weathering of a soil will result in loss of Ca, Mg, Na, and K and the production of clays. The total phosphorus content in soils changes little with time, due to the extreme insolubility of the phosphate. The source of phosphate in soils (apart from fertilizers) is that of the natural mineral apatite $Ca_5(OH,F)(PO_4)_3$.

The residence time of a mineral in the soil can be determined from the total soil content divided by the rate of loss due to weathering. For sodium the soil sodium is approximately 0.4% or 50,000 kg/ha-m. Loss is 300 moles/ha-m, or 7 g/ha-m, resident time is 10,000 years in 1 meter of soil.

The soil depositional layer "grows" clay minerals. The setting is not a perfect supersaturated solution for crystal growth (being open-ended) and the crystal that forms may be "deficient" in charge, creating a negatively charged, high surface area, particle. Thus soils have a solid surface that is generally negatively charged, with the charge dependent upon the pH of the soil solution (protonation/deprotonation reactions of the solid surface)

. The net negative charge of the clay fraction requires cation balance imparting a cation exchange capacity to the soil (Table C.1). The cation exchange capacity depends upon the amount of exchange of metal for Al or Si in the aluminosilicate lattice. It is this ion exchange capacity that makes soils easily supply nutrients to plants, and can contribute to the ability of the soil to retain various cations, including toxic metals.

When the clay is high in iron, it can have redox properties. A clay near the surface of the soil profile will appear reddish (Fe^{3+}) while clay lying below near the water saturation line will appear bluish (Fe^{2+}). The redox state of the soil is "buffered" by these clays. The redox state will determine whether sulfur is present as sulfide or sulfate which has implications for the precipitation reactions of lead.

The clays themselves can be coated by organic material. The common model for the organic material, black, is shown in Figure 8.60. The black color derives from the large number of organic functional units on the material. These functional units derive from the death and decay of microorganisms and plant material and condensation of organic fragments from these materials to the longer, polyelectrolyte, polymeric form of the humic and fulvic acids. Humic

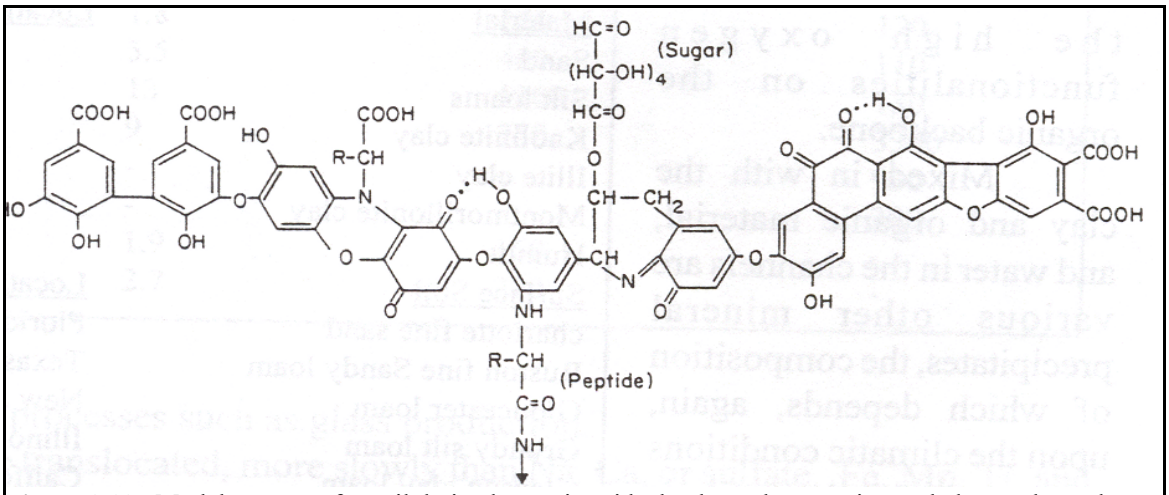

Figure 8.60. Model structure for soil derived organic acids that have the capacity to chelate and translocate metals. Stevenson 1982.

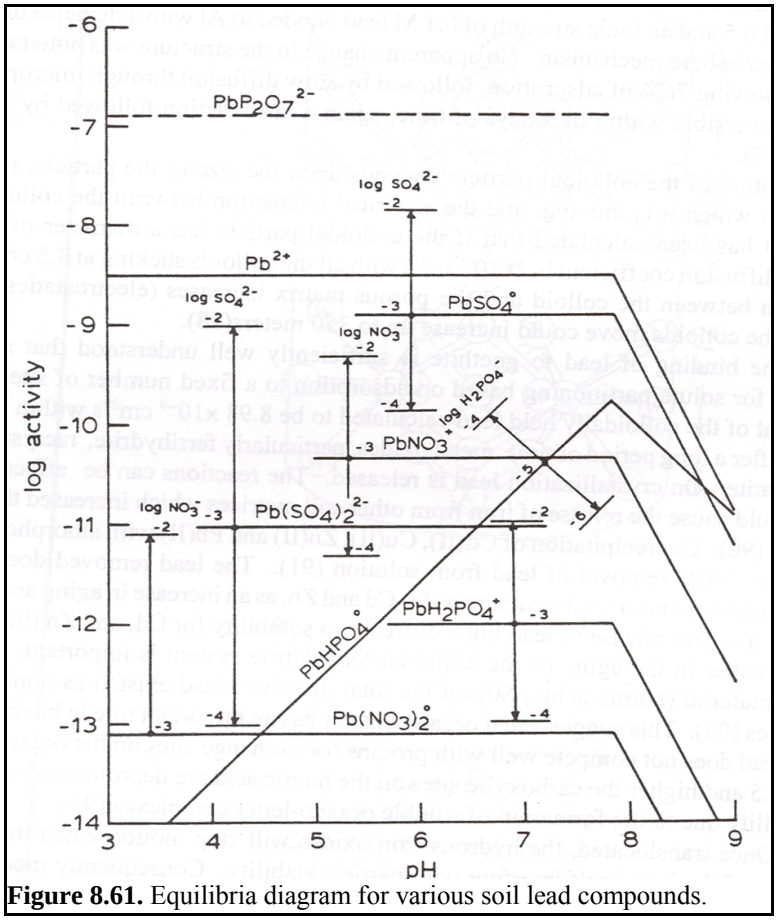

Figure 8.61. Equilibria diagram for various soil lead compounds.

acids tend to be longer and less soluble than fulvic acids. Humic and fulvic materials can chelate metals ions similar due to the high oxygen functionalities on the organic backbone.

Mixed in with the clay and organic material, and water in the channels are various other mineral precipitates, the composition of which depends, again, upon the climatic conditions under which the soil is formed. The soil solution will represent an equilibrium, sometime driven by kinetics of the open ended system, with the solid phase. (Figure 8.61).

Localization Vs Translocation of Lead to Subsoil and Deep Subsoil:

Airborne deposited lead has not been explicitly studied for it's conversion into soil lead but one study from 1999, indicates that most of the airborne lead is of a large particulate size and is filtered into the top of the soil. Once localized it remains localized by rapid adsorption onto insoluble soil surfaces (Mason and others 1999).

The fate of lead in this system is of concern for five possible terminal results. First it is possible that the lead would be transported below the soil to the groundwater. Second, it is possible that lead would remain localized in certain portions of the soil. If the localization process results in a mineral

formed of reduced bioavailability (digestibility) then this would be good. If localization merely means we retain lead in a small particle size, easily soluble form, near the surface of the soil, then this is not good. Third, it is possible that the lead would be transported to growing plants. Fourth, lead can be carried to hands and hence to mouth. Fifth, lead in soils can be carried by foot into homes to contribute to indoor dust.

Mechanism of Localization

Transport of lead to the deep subsoil is generally not observed. Lead remains concentrated within the upper surface (2-5 cm) of the soil (that is, it has a long environmental half-life). The length of the half life is related, again to the insoluble (non-leachable) forms of lead found with common soil anions. Rarely is lead found in the original galena, PbS, form. Instead it is common as sulfates (anglesite) and carbonates (cerrusite). While lead phosphates would be desirable due to their low solubility which would lower digestion, these forms are not common due to the low amount of phosphates in most soils. Figure 8.61 shows an equilibrium diagram for solubility of lead in soils in the presence of various soil minerals. The solubility can be calculated from the typical groundwater solution concentrations of various cations and anions (Table C.7) and the solubility product constants for lead. The amount of lead in the soil solution would be $10^{-8.5}$ M or 0.65 ppb lead where the soil solution lead concentration is controlled by carbonates.

Lead is also retained in the upper surface by ion exchange reactions with either soil organic matter or with clays. Chelation constants for lead by humic material are large enough to have an impact on retention vs mobility in soils (Table D.10). Lead deposited for forests is apparently retained (80%) with organic/particulate matter. The low pH of forest soils allowed the cation of lead to dominate, which in turn allowed lead to be complexed with organic and inorganic large ligands, thus retarding transport of smaller sized lead hydroxides (Wang and Benoit 1996; Wang and others 1995).

The ion exchange retention of lead on a clay can be written as (Farrah and Pickering 1977):

[8.5] $\text{Clay-Na}_2 + \text{Pb}^{2+} \leftrightharpoons \text{Clay-Pb} + 2\text{Na}^+$

The extent of ion exchange of lead on clay has been found to follow an empirical relationship shown in equation 8.5 (Hassett 1974):

[8.6] maximum adsorption
$= 5.34x\ \text{CEC} + 5.36x\text{pH} - 0.0774x\text{P}_i - 34.3$

The maximum adsorption of lead is measured in units of μmol Pb/g soil, where CEC is the cation exchange capacity of the soil in meq/100 g, and P is the amount of phosphate in the soil. The pH effect is due to solubility differences in the soil and due to changes in the cation exchange capacity with pH (Zimdahl and Skogerboe 1977), (Harter 1983).

A typical soil can absorb 112.3 μmol/g or 23,200 ppm as the exchanged fraction. In low ionic strength solutions lead uptake is controlled by the ionic exchange reaction. In these dilute solutions lead is dehydrated in the interlamellar space. Exchange does not proceed well in high salt concentration, where the effect is related to the presence of the divalent vs monovalent cation, that is the clays are collapsed and exchange proceeds slowly (Auboiroux and others 1996).

Mechanism for Mobility

For the most part lead does not move down the soil due the reactions described above. It has been estimated that lead moves 0.5 cm/year when present in a halogenated form. The residence time of lead in the soil is estimated to be 100-200 years (Erel 1998).

Metals can also be mobilized by adsorption onto mobile fractions such as fulvic materials and small oxide based colloids. Lead is adsorbed onto manganese dioxides (McKenzie 1978) and aluminum gels (Kinniburgh and others 1976). The colloid fraction most significant in the soil are hydrous iron oxides. Figure 8.62 shows the adsorption of lead onto the hydrous iron oxides. The sorption increases as the pH increases, as is common for soil constituents. The increase is related to a deprotonation of the mineral surface edges and the beginning of a net negative charge on the mineral. The exchange is fairly weak and can be stalled by competitive ions, such as iron, copper, or cadmium, of even sodium, if the sodium is present at higher levels.

[8.7] $\equiv\text{FeOOH} + \text{Pb}^{2+} \rightarrow \equiv\text{FeOOPb}^{2+} + \text{H}^+$

Pb(II) was not found to be trapped into the interior of the iron hydroxide, although Mn(II) and Ni(II) are. Structural incorporation of Pb with goethite or hematite is low at pH 6 (Ford and others 1997). On Al oxide at pH 6.5 and an ionic strength of 0.1 M lead bonded to Al with a distance of 3.4 Å, consistent with

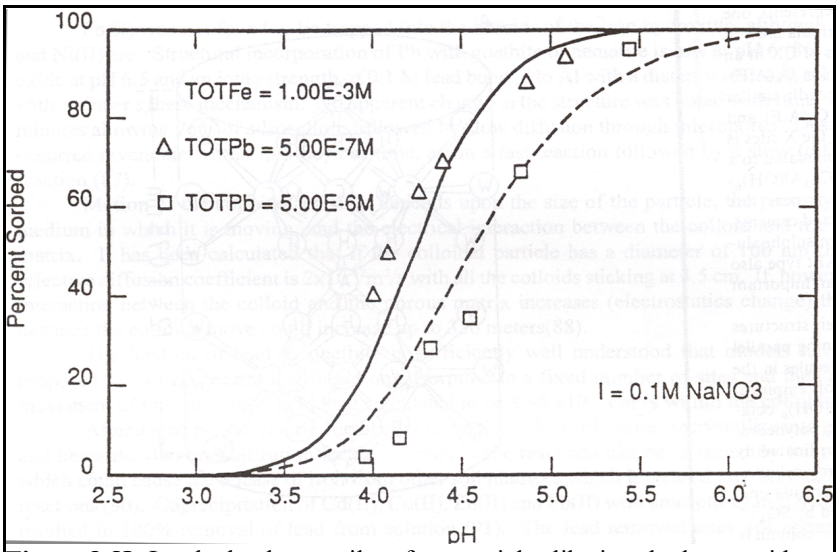

Figure 8.62 Lead adsorbs to soil surface particles like iron hydours oxide. The colloidal particle can then serve to carry lead through the soil matrix.

an inner sphere mechanism. No apparent change in the structure was noted with time, with 15 minutes allowing 76% of adsorption, followed by slow diffusion through micropores. Desorption occurred reversibly within in 3 days of time, again a fast reaction followed by a slow (diffusion) reaction (Strawn and others 1998).

Motion of the colloidal particle depends upon the size of the particle, the porosity of the medium in which it is moving, and the electrical interaction between the colloid and the porous matrix. It has been calculated that if the colloidal particle has a diameter of 100 nm then the effective diffusion coefficient is $2x10^{-12}m^2/s$ with all the colloids sticking at 3.5 cm. If, however, the interaction between the colloid and the porous matrix increases (electrostatics change) then the distance the colloids move could increase up to 350 meters (Liang and McCarthy 1995).

The binding of lead to goethite is sufficiently well understood that models have been proposed for solute partitioning based on adsorption to a fixed number of sites and then a mean movement of the colloidally held lead calculated to be 8.98×10^{-9} cm^2/s within the colloids (Theis and Iyer 1995).

After a long period of time metal oxides, particularly ferrihydrite, recrystallize into goethite and hematite. On crystallization lead is released. The reactions can be affected by temperature which could cause the release of iron from other soil matrices which increased the recrystallization reactions (Martinez and others 1999). Coprecipitation of Cd(II), Cu(II), Zn(II) and Pb(II) with amorphous iron hydroxides resulted in 100% removal of lead from solution (Martinez and McBride 1998b). The lead removed does not appear to be incorporated into the crystal structure as for Cd and Zn, as an increase in aging and thermal treatment results in a higher release of lead but a decrease in solubility for Cd, and Zn (Martinez and McBride 1998a). The presence of organic matter in the aging of the colloidal ferrihydrite system is important. In the presence of organic material (humic acids) 80% of the total dissolved lead existed as nonlabile organo-metal complexes (Martinez and McBride 1999). This suggests that organic matter has an important role in binding of lead. At low pH the lead does not compete well with protons for exchange sites on the organic matter, but at pH values 6.5 and higher the carboxylic sites on the humic acid are deprotonated and lead is increased in solubility due to the formation of soluble organo-letter complexes (Sauve and others 1998).

Once translocated, the hydrous iron oxides will stop motion when the pH and oxidation reactions of the iron itself interfere with particle stability. Consequently models of transport are difficult to monitor as the pH generally decreases with depth (less carbonate to buffer the soil solution) and the redox potential favors reduced forms of Fe and sulfur. The large number of adjustable parameters in the modeling studies (diffusion, sorption to colloid, transport of colloid via diffusion, via convection, precipitation reactions, sorption to fixed mineral components, redox potentials) make modeling difficult. It is suggested that modeling will be most successful when the adjustable parameters are limited to four (Theis and Iyer 1995).

The role of colloidal transport has been implicated with 75% of Pu transported via colloidal material (Champ and others 1982; Newman 1990). These colloids are capable of adsorbing large amounts of material due to their very high surface area (10-500 m^2/g), their small size (10 nm to 450 nm) allowing them to percolate and their concentrations of 20 to 100 mg/L (McCarthy and Degueldre 1992).

Colloids are generated by changes in ionic strength which mobilized sorbed material from larger mineral surfaces, geochemical alteration of primary

materials, precipitation by chemical process. The transport of particles greater than 1 um is governed by gravity, fluid drag, and interfacial forces (Rajagoplalan and Tien 1976). Particles smaller than 1 um can be modeled by Brownian or random walk models. Theory predicts that particles of a diameter of 100 nm would move and stick by a distance of 3.5 cm but if the sticking coefficient is reduced these particles could move as much 350 meters (Liang and McCarthy 1995).

Other colloidal material capable of translocating metals are soluble organic acids which can either chelate or encapsulate ions and prevent them from reacting with the clay ion exchange sites. Low molecular weight fulvic acids are known to move minerals from the upper level of the soil to the lower level. While lead has a fairly high binding coefficient for the ligand sites on the organic material lead does not appear to be translocated efficiently within soils, most likely due to the highly insoluble nature of the precipitates within the soil.

Chapter 8 Problems

1. List the symptoms of lead poisoning beginning with least severe to most.
2. Explain the mode of action of organolead on humans.
3. How long doe sit take for organo lead to circulate after entry?
4. How long does it take the kidney to de-alkylate organo lead?
5. Are all gunshot wounds likely to lead to lead poisoning?
6. What particle sizes are most dangerous for lead inhalation?
7. What are the cilia?
8. What is a normal physiological pH?
9. What is the normal stomach pH?
10. How long does it take to move material through the gastrointestinal track to be observed in urine?
11. If an individual has tibial and cranial bone lead values of 74 and 59 ppm what is the likely symptoms there are to experience?
12. List the blood values of calcium indictive of hypocalceimia, normal values, and hypercalceimia.
13. What are the symptoms of hypo and hypercalceimia and how do they relate to symptoms of lead poisoning?
14. Would lead be bonded in a similar coordination number to calcium in a calcium triggering protein?
15. List three calcium regulators.
16. How many Ca bind to calmodulin?
17. At what point does lead interfere with heme production?
18. Why have ZnPP measurements been phased out?
19. Define edema.
20. Give an explanation for the biological side effects of EDTA chelation therapy for lead.
21. Describe in simple terms why DMSA is more selective for lead than EDTA.
22. What are symptoms of avian lead poisoning?
23. What has happened to the albatross population at Midway Islands?
24. Why do dogs most often present with lead poisoning, as compared, to cats?
25. Which animals are most susceptible to lead poisoning?
26. Why do birds get disproportionately affected by lead poisoning?

Problems Suitable for Chemistry students

27. From the data in the Figures calculate the rate constants for the dissolution of the three different particles sizes.
    a) What order reaction will you assume?
    b) What explains the effect?
    c) Under what conditions might this information be important and what implications does it have for pica?
    e) Would stabilizing lead as a more insoluble salt (suggest one) necessarily solve this problem?
28. What class of chelates bind best to lead?
29. Given a halflife of lead in trabecular bone of 1.2 years calculate the bone concentration in ppmafter 10 years cessation from exposure, if the initial concentration was 74 ppm.
30. Which is the strongest known chelate for lead? Is it selective?
31. Calculate the amount of lead in the kidney after cessation of exposure when the original concentration was 1200 ppm.
32. What would be the predominate species of lead at that pH?
33. Draw GABA and ALA.
34. What is the coordination number of calcium in calmodulin?

Chapter 8: Literature Cited

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