1. Stress Responses of Children to Cadmium Air Pollution: Implications for Patient Care and Public Policy

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Stress Responses to Cadmium

Introduction:

Cadmium (Cd) is a heavy metal which the young absorb efficiently (Froslie 1985, Foulkes 1989). Newborn babies acquire Cd from cigarette smoke and emissions of as little as one ton of Cd fumes into the air a year (Lagerkvist 1992). Although lead (Pb) was expected to be associated with premature births, maternal blood levels of Cd, not Pb, were associated with preterm births in Sweden and Poland (Fagher 1993). Environmental exposure to Cd was correlated to lower human birth weight in a study done in France (Frery 1993).

With the recent recognition that Cd is a human carcinogen, Nordberg, a Swedish Cd toxicologist, suggests that every effort should be made to minimize exposure to and use of Cd (Nordberg 1992). Given that numerous researchers have found health effects from passive smoke (Shaham 1992-3), which is the most important indoor source of Cd (Landsberger 1993), it is necessary to understand how children are exposed to Cd and how this may affect their health.

Cadmium has been well studied over the years, but its effects are generally not known to physicians, because it has not been linked with human disease. This review article is written to familiarize physicians with Cd: its sources, biochemical basis of its actions, stress effects on children, approaches to detect its effects, and therapeutic strategies that block its effects.

Finally, the implications of these findings for public policy will be presented.

Problem. Although the toxic effects of Pb and mercury (Hg) in infants and children are recognized, there is relatively little attention given to Cd, which is infrequently measured in humans. In aquatic environments Cd is well recognized as a highly potent toxicant whose mutagenic, teratogenic, carcinogenic and toxic level is close to the background level (Lithner, 1989, Muntau. 1992).

Toxicologists have considered the kidney the target organ for Cd in humans (Nomiyama 1992, Bernard 1992) and attention has been directed to consumption of food in nonindustrial exposures. Emphasis has also been directed to effects of Cd alone, so that effects of cigarette smoke have not been attributed to Cd. Using these limitations, there are few recognized cases of human Cd toxicity.

In Columbus, Ohio, hospitalization for prematurity rose abruptly the first year that the large waste incinerator started polluting the air with 1 1/2 tons of Cd fumes in 1983 and that level was maintained. During the next few years, childrens' hospitalizations for tonsillectomies, broken bones, and cancer treatment increased. The use of stimulant medications became more frequent in the central Ohio area (StewartPinkham 1991a). In the same time period medicare expenditures rose faster in Ohio than in other states. Through personal communication with the local hospital, US Treasury,

and local Medicare office, I noticed these various health changes in 1987 and began the studies that led to this and other papers.

These problems were not considered effects of pollution by the local authorities. However, 2 1/2 tons of Cd fumes, together with 70,000,000 kg of toxic chemicals including 25,000,000 kg of solvents and 2,000,000 kg of HCl, were released into the air in Ohio in 1987 (Ohio EPA 1993).

In 1993 there has been a 10% drop in childrens' hospitalizations which may represent some kind of adaptation, similar to that found by Beck (1993) in children exposed to air pollution in Germany. A small improvement in air quality has been achieved in this time. Still the death rate from short gestation/low birth weight has increased from 0.8/1,000 live births in 1987 to 1.4/1,000 live births in 1991 (Vital Statistics of Ohio Annual Report, 1991).

For the following reasons Cd has not been identified as a major human pathogen: 1) air pollution has not been considered a significant source of exposure since it is small fraction of the total exposure, 2) epidemiologic studies (Staessen 1992, 93) have not been helpful in understanding Cd effects on health, and 3) synergistic effects with other polluting chemicals have not been considered.

Cd air pollution has not been considered a factor in adverse environmental effects that have been increasing. For instance, baby salmon from the Baltic Sea are suffering from a high mortality that has been

increasing over the last decade (Norrgren 1993). The ultrastructural studies of the livers of the females that bear the affected fry have the same morphology as that shown by the birds exposed to Cd and an organophosphate (Chishti 1993).

Unfortunately, free Cd coming from air pollution was not considered the source of the toxicity, because low levels of Cd were found in the liver. It is probable that elevated Cd would be found if the gonads were analyzed,
rather than the liver, since different kinds of metal binding proteins occur in these tissues (Whanger 1987). Elevations of Cd were found in the gonads of rabbits experiencing reproductive failure in a contiguous area (Lutz 1993). It is also probable that higher dioxin concentrations would be found in the salmon gonads compared to the liver, a finding in another study (Schell 1993).

The world decline in amphibians (which are very sensitive to toxic effects of Cd through their skin (Vasil'eva 1987)) should be suspected of having Cd involvement. Cd levels in gonads could be determined.

Biological monitoring with lichens or resistant bacteria would be helpful. For example, bacteria isolated from a bleached kraft pulp mill wastewater system contained an altered mix of micro-organisms with increased plasmids and resistance to Cd alone (Fulthorpe 1993). This identifies this dioxin producing process, which is associated with tumors in fish and humans in exposed areas, with Cd pollution.

Scientific Evidence. Risk assessment of toxic compounds is very difficult. Numerous studies have looked for dose response relationships in populations with increased Cd intake and have failed to find an excess of health effects (Thornton 1992, Staessen 1992). Cd blood levels in recent studies have been found to show unacceptable variability (Anglov 1993). There are so many dynamic factors that affect free Cd that blood, urine and hair Cd levels are often not very helpful in individuals.

The mean levels of Cd in blood and urine in Sweden are 0.3ug/L and 0.2ug/g creatinine, respectively (Vahter 1992). Since air pollution is a small part of the total input, but one that seems particularly bioavailable (Froslie 1985, StewartPinkham, 1989), it is not surprising that levels of Cd are helpful primarily in newborns, who have very low levels of Cd. Currently, there are more questions about Cd effects on human health than answers (Tsuchiya 1992).

Given all these confounding factors, can investigators come up with scientific evidence for Cd involvement in human health problems? An approach, combining research findings of molecular biology and tools of clinical medicine, is presented. In most instances, one can find evidences for Cd exposure from environmental sources and passive smoke exposure, co-exposure to physical, emotional, chemical, or biological stressors, nutritional deficiencies, exaggerated responses to stress with psycho-neuro-endoimmune alterations, and genetic suceptibility.

Huge emissions of toxic chemicals are released into the air. In only rare instances are the synergistic toxic interactions with Cd investigated. Since Cd is interactive with many chemicals, the toxicity of these compounds is influenced by the great variety of factors that influence the co-toxic agent Cd. Ecological risk assessment needs to be based on an understanding of molecular mechanisms and some reliable measure of exposure.

Whenever an increase in any toxic compound is found or a highly cytotoxic effect is found, Cd needs to be suspected of playing a role in the increased body burden of the chemical, as well as in the toxicity found. Low levels of Cd may be found the liver of the individual but high levels could occur in the adrenals or gonads together with other toxic chemicals.

While toxic metals of concern like Hg, Pb and arsenic are declining in the sediments (Beaurskens 1993), Cd air pollution is not declining and is probably increasing, based on measurements of lichen Cd contents from 1982 and 1987, which suggest an increase in long distance transport of Cd (Sloof 1991). Cd is capable of having low dose effects interactive with other stressors, identified in cell culture experiments. It is by using these chains of evidence that the case for Cd and chemical toxic effects can be made.

Sources of Cadmium. The most important source of human Cd exposure is indoor air contaminated with tobacco smoke (Landsberger

1993). Tobacco leaves concentrate Cd from the soil and absorb Cd directly from the air. The side stream smoke contains 40% of the cadmium in the cigarettes. It is extremely persistent, because it becomes incorporated into microorganisms (Kurek 1992) which are associated with dust. Cd is virtually not excreted. Cigarette smoke doubles the Cd burden (Elinder 1976). The mother's Cd burden acquired from passive smoke and active smoke exposure is directly proportional to the Cd transferred to the neonate (Nakano 1989).

What has not been suspected by previous investigators (Mislin 1986) is that environmental Cd air pollution is a significant source of Cd exposure. Cd air pollution is readily absorbed by lambs (Froslie 1985). Non-smoking mothers acquire Cd from environmental air pollution and pass it to their newborns (Lagerqvist 1992). In a similar manner with cigarette smoke, Cd from the environment becomes concentrated in indoor air through incorporation into bacteria, fungi, danders, and dust mites.

There are many environmental sources of Cd air pollution (Mislin 1986). Fossil fuel and waste incineration combustion are two major sources associated with human activity. With the increase in global population there is also an increase in fuel combustion which, in turn, releases Cd. Large waste incinerators pollute the air with Cd and HCl, which increases its solubility (Stewart-Pinkham 1991) and toxicity to the respiratory tract (Oberdorster 1992). Municipal sludges applied to

fields increase Cd in soil, increasing levels in plants which can then be transferred to air (Beauford 1977). Animals fed on these plants pollute the soil and water with increased Cd in their manure.

In Japan the level of Cd in human kidneys has increased from 43.95 to 73.47 ug/g in the last decade in spite of a drop of Cd levels in food supplies (Noda 1993). Teenagers have levels approaching those of adults. A recent study (Elinder 1992) reported Cd levels of 5-160 ug/g in the kidneys of penguins living in Antarctica. These studies support the conclusion that Cd air pollution is an increasing problem.

Volcanoes and forest fires are other important sources of Cd air pollution that occur in nature. However, the global Cd air pollution problem may involve more than sources. Wetlands act as a trap for Cd. Living microorganisms concentrate it, so that the water and plants contain very low levels of Cd (Albers 1993). With the decrease in wetlands more Cd can circulate in air.

Rain forests might also trap Cd. Insects can bind Cd in their chitin. Cd levels are unusually high in toxic plants, such as Amanita phylloides. When rain forests are destroyed, the only plants and insects that remain are highly Cd resistant. With the reduction in rain forests, more free Cd could travel to Antarctica, increasing the levels in penguin kidneys.

Cd is so bioavailable that any change in the ecosystem can be expected to influence it. There is much that remains unknown about

its cycling in nature in general and in rain forests in particular. (Table 1)

Cd in food varies with the soil concentration of Cd, which in turn, is affected by air pollution and applications of fertilizers containing as much as 40mg/kg Cd (Muntau 1992). The type and part of the plant consumed also affects Cd levels. Toxic effects of exposure to Cd in whole food are quite minimal compared to air; however, in non-occupational exposures, the major daily input of Cd comes from food (Wagner 1984, Maage 1987). Plants produce protective substances with exposure to Cd (Steffens 1986). These and other substances in plant fibers protect animals exposed to Cd added to their diets.

Processed food, however, contains Cd that volatizes off metals used in the processing (Falandysz 1989). Refined grains do not lose Cd which is in their endosperm, but, do lose the protective vitamins and minerals found in their bran. Rats and mice fed human dietary items absorbed 5-8 times more Cd than animals fed ordinary rodent pellets (Anderson 1992).

Soft water affected by acid rain contains increased levels of Cd (Svensson 1987). The toxicity of exposure in drinking water is strongly affected by other minerals (Dive 1989). Copper can greatly increase the toxicity of Cd.

Cd air pollution affects air, soil, food, and water (Stewart-Pinkham 1990). It is toxic to plants worldwide, depleting nutrients, decreasing the production of oxygen and increasing the production of carbon dioxide,

affecting temperature and weather (Stewart-Pinkham 1990). A high dietary intake of Cd in nutrient depleted food aggravates the toxicity of air pollution. The co-exposure to other metals and organic chemicals increases greatly the toxicity of response in some instances while lowering it in others.

Biochemistry:

Cd has been extensively studied in all life forms (Venugopal 1978, Webb, 1979, Friberg 1985, Foulkes, 1986). Of all the metals it is the most easily absorbed and the most influenced by nutritional factors. It has a high affinity for multiple sulfhydryl groups, but it also binds to so many other compounds that its behavior in complex mixtures is difficult to predict. These varied effects are discussed in this section.

Stress Responses. Cd acts as a stress agent (Hidalgo 1987, Fowler 1992). It activates the hypothalmicpituitary- adrenal -gonadal axis. Since the stress response is adaptive, it is an essential metal for cell function and survival in a changing environment. Prolonged stress or stress at vulerable times of the life cycle can be detrimental.

Stress affects psychological processes and neurological, endocrine, and immune function. Cd affects dopamine, norepinephrine, acetyl choline, and serotonin (Rajenna 1990). Cd stimulates insulin release (Nilsson 1987), pituitary hormones (Cooper 1987), inhibits testosterone (Ghosh 1987), and alters steroid metabolism in the adrenals (Colby 1987). Both Cd and emotional stress decrease DNA

repair (Kiecolt-Glaser 1985, Nocentini 1987). Cd, like other stressors, increases variability in responses by having bidirectional effects that change over time. Effects can be transient (Hart 1986) and result in increased hardiness, if nutrition is adequate.

Although toxicologists generally look for dose dependent effects, Cd has dose independent effects on the immune system in human cell and animal studies that vary with age and species (Borella 1991, Descotes 1992, Daum 1993, Ohsawa 1988, Hertenbach 1988, Fuzinaki 1987). In a large study of children with increased Pb and Cd in their hair, and who were exposed to falling levels of Pb but not Cd, there appeared to be a biological adaptation to the stress of living in the polluted environment; however, the total lymphocyte and T-8 suppressor cell counts were reduced and the palatine tonsils showed altered microbial flora (Beck 1993).

In the blood stream Cd has profound effects on cerebral vessels and the choroid plexus (Valois 1987). It causes spasm of skeletal muscle arterioles, (Zhang C, 1993) and coronary blood vessels (Kisling 1993). This may be due in part to effects on the calcium dependent potassium channel (Stockland 1993). Spasm can cause ischemic followed by reperfusion injury. Cd induces inflammatory changes in the blood vessels of the reproductive system (Copius Peerboom Stegeman 1987,89). In a general catabolic state, or with an overpowering dose, Cd induces multiple organ system failure, at least

partially, through these ischemic effects.

Cd alters the gene expression of several stress proteins, including metallothioneins (MT), a family of low molecular weight metal-binding proteins that can bind Cd and other metals (Fowler 1992). Heat shock, nutrient deficiency, oxygen radicals, and metabolic disruption are some of the stimuli for these proteins. An emotional stress, physical restraint, is the most potent stimulus for MT induction in rats (Hidalgo 1987).

Stressors of various kinds release liver MT increasing Cd levels in the kidney. The blood borne MT is broken down inside the proximal tubule cell. If these cells are not producing sufficient MT to detoxify the free Cd, a toxic effect occurs in the kidney. In this way, toxic influences on the liver produce toxic effects in the kidneys.

The stress response is both potentially harmful and adaptive. Since stress proteins are highly conserved and abundant in prokaryotes and eukaryotes, immune responses against stress proteins can induce auto-immune injury; nevertheless, the stress response provides a first line of defense against infections and cancer transformation (Young 1989).

Gene Effects. With exposure to Cd, organisms or cells increase their production of MT. Cd moves from the cell membrane to the nucleus where it binds to DNA, inducing gene transcription in as little as 4 hours (Fowler 1993). With chronic exposure gene duplications can occur (Maroni 1987). In Cd

resistant cells the transcription of MT can increase 20-40 fold (Sequin 1987).

Mutations can occur at very low dose and can be irreversible because Cd interferes with DNA repair, especially in conjunction with other chemicals (Yamada 1993, Webb 1979), causing both benign and malignant neoplasms. Low concentrations of Cd, as well as Hg, change the structure of the tumor suppressor protein p53 into a "mutant" form associated with tumors (Hainaut 1993).

In aquatic environments, Cd favors the persistence of homozygosity, thereby decreasing genetic diversity (Lavie 1986). It is believed that the homodimer provides more secure binding of Cd. This could provide an explanation for the mild illness in patients homozygous for the 1226G mutation in Gaucher's disease (Beutler 1993), which is currently unexplained.

In humans there are at least 14 genes that have been identified which control the production of MT (Gedamu 1987). A mutation that results in the loss of a charged amino acid at the hinge between the metal binding domains makes it ineffective (Cody 1993).

Starvation, infection, physical stress, inflammation, radiation, endotoxin, glucocorticoids, glucagon, catecholamines, calcium ionophores, estrogen, progesterone, interferons, interleukin-1, carbon tetrachloride, chloroform, ethanol, and alkylating agents are some of the stimuli that activate MT genes (Bremner 1987, Karin 1987). Interferon has been shown to protect cells from DNA

damage caused by Cd (Vasil'eva 1989). Methylation of the MT gene affects gene expression (Bhave 1988). The promoters greatly modify the availability of free Cd.

Cd binds to a metal responsive element in the MT-1 promoter, activating it in Cd exposed and nonCd exposed cells (Anderson 1990), suggesting that Cd plays a role in all stress responses. If all goes well, Cd detoxifies itself. In many experimental studies there are transient effects which later resolve spontaneously (Rajanna 1990, Hart 1986, Copius Peerboom-Stegeman 1987,1989). In China, the chemical oleanolic acid, which is used for treating hepatitis, induces MT only in the liver (Liu 1993). It increases the Cd bound to MT in the cytosol and there is less Cd bound to sensitive membranes and high molecular weight proteins.

Cd concentrates in both the ovaries and testes, increasing with age and exposure to cigarette smoke (Varga 1993) and sensitivity to Cd toxic effects (Shaikh 1993).

Chromosomal disorders associated with increased maternal age, like Down's syndrome, can be suspected of having some connection with Cd. By binding to maternal or paternal chromosomes, Cd can have an effect on genes passed by a specific parent.

Cd also causes dyfunctions, of mitochondria at low dose. It induces heat shock protein 60 in a manner independent of MT induction over a much longer time course of 18 hours (Hiranuma 1993). By affecting the mitochondria) genes it can have a role

in maternally transmitted mitochondrial disorders.

Cd causes apoptosis, a gene regulated cell death, associated with stress proteins (Lohmann 1993). Apoptosis is normal during emryogenesis and rids the body of stressed, infected, and cancerous cells (Wyllie 1987). Apoptosis occurs in cells with a fluid membrane which facilitates Cd uptake (Foulkes 1989), with increased intracellular calcium, an effect of Cd on the Ca ATPase (Verbost 1987), and a change in the expression of c-fos and c-myc (Lucas 1991), Cd effects (Jin 1990).

If the stressed cells are in the brain and cause neuronal loss, lasting neuropsychological deficits can occur. If the stressed cells are resistant to Cd, they can persist, leading to chronic viral infections or cancer. Resistance to Cd toxicity has been associated with ubiquitin-dependent proteolysis, suggesting that Cd toxicity is due to persistence of Cdinduced formation of abnormal proteins (Jungmann 1993). As a stress agent, inducing apoptosis and blocking it (Lohmann 1993), Cd can have both helpful and harmful effects.

Cellular Effects. The effects of Cd on cell function are exceedingly complex and intricate, varying with genetic differences, sex, and age (Shaikh 1993). Depending on a multitude of factors, free Cd, not Cd bound to metallothionein, produces toxicity both directly and indirectly through its many actions on phosphorylation of proteins and injurious effects on cell membranes and sensitive organelles (Sharma 1992, Webb 1979).

Cd increases free radicals, promotes lipid peroxidation, and depletes anti-oxidants (Ochi 1987, Pharikal 1988, Mukhopadhyay 1988, Morselt 1987). Cd affects ion transport through membranes (Kim 1988, Verbost 1987, Bevan 1989, Kopp 1986), energy availability through mitochondrial function (Toury 1985, Jamall 1987, Muller 1988), detoxification through microsomal enzymes (Alary 1989), intercellular communications by affecting cell adhesion in epithelial cells (Prozialeck 1991), and many cell signalling functions by affecting intracellular calcium (Verbost 1987), inositol polyphosphate, and protein kinase C (Smith 1989).

Glutathione confers resistance to Cd in some circumstances (Ochi 1988). Although transiently depressing cellular glutathione levels, Cd can increase glutathione as part of an adaptation to its presence. Glutathione in the liver appears to increase HMG-CoA reductase, the enzyme that increases the level of cholesterol and triglycerides in the blood (Kim 1992). In the rat Cd induces heme oxygenase in the liver, has no effect on the kidney, and inhibits it in the testis. Glutathione suppresses the induction of heme oxygenase (Sunderman 1987). Highly tissue specific effects are frequently found with Cd.

With Cd's ability to enter the cell through many channels and to affect many cell reactions that occur with stress responses, it is reasonable to consider Cd both a first and second messenger for the stress response, that is highly conserved in nature.

The induction of MT to bind free Cd is one of the ways to terminate the stress response so that the cell can return to normal housekeeping function.

Cell Adhesion. Cd absorption is much greater in the basolateral compartment, than in the apical compartment, in studies of renal epithelial cells (Prozialeck 1993). Cd also reduces the tight junctions that connect polarized lining cells (Prozialeck 1991). These two properties have implications throughout the body.

In the kidney, the leak is associated with proteinuria. In kidney problems, induced by lo~v dose Cd, the excretion of Cd is zero; because it diffuses into the cell through the basolateral membrane. Only with a slough of cells does urinary Cd excretion go up.

In the liver, thiol oxidizing agents decrease tight junctions, resulting in decreased bile acid excretion and cholestasis. This can lead to oxidative hepatocellular injury (Ballatori 1989).

With absorption of Cd from air, effects may occur directly on the vasculature. In a study of vascular endothelial monolayers, Cd caused detachment of cells, cell injury, and inhibition of cell proliferation, needed to re-epithelialize. All these effects were blocked by zinc (Zn) (Kaji 1993). In the presence of Zn deficiency, the tight junctions are lost and this breaks down the blood brain barrier, allowing Cd uptake into vascular lining cells, decreasing nutrient transfer to the brain, and allowing toxic chemicals to directly affect brain

function.

Permeability of the intestinal lining cells affects the uptake of Cd from food and water. A marked increase in gut permeability follows burn trauma (Epstein 1991). With stress induced permeability of the GI lining, Cd is able to enter the intestinal cell, decreasing nutrient transfer to the serosal side (Sakata 1988, Coppen-Jaeger 1989).

In this circumstance the level of Cd in food becomes a significant factor. In a Finnish study on heavy metals in grains, wheat had the highest level of Cd with 42ug/kg (pasta was 79ug/kg with a range of 26-182ug/kg, but it is also high in selenium). Rye was 26ug/kg, corn 18 ug/kg, rice 10ug/kg and oats 2 ug/kg (Tahvonen 1993). It is possible that some food sensitivities may be mediated by absorption of Cd but only with stress induced GI permeability.

Micro-organisms with plasmids have efficient Cd pumps that can increase local Cd levels adjacent to lining cells (Nies 1992). It is possible that friendly bacteria, like lactobacillus acidophilus, which have a beneficial effect on bowel function, do not increase Cd levels at the epithelial interface. By interactions with stress, foods, and microorganisms, Cd directly depresses nutrient absorption from the GI tract.

As an air pollutant, Cd can affect the permeability of the respiratory lining cells. Local overgrowth of bacteria with plasmids can cause a breakdown of tight junctions. Cd paralyzes the cilia, causes slough of the cells (Lag 1987), and increases inflammatory cells

(Boufreau 1988, Hart 1988, Damiano 1990, Webb 1979). The HCl from waste incineration and the CdO from all sources creates CdC12, which causes the most inflammation (Oberdoester 1992).

A breakdown in cell adhesion affects skin. Plasmids in microorganisms can increase local levels of Cd. Many skin disorders are aggravated by stress and occur in a setting of multiple nutritional deficiencies, detoxification abnormalities, and microbial overgrowth.

Nutrient Depletion. By getting into the GI lining cells, Cd is able to cause multiple nutritional deficiencies. Zinc (Zn), magnesium (Mg,) selenium (Se), iron (Fe), and copper (Cu) are all affected by exposure to Cd. In a study of the trace element composition of food consumed in 24 hours by Swedes, Mg, Zn, Cu and Se were deficient (Abdulla 1989). It is possible that this is a response to Cd exposure in food sources. By causing deficiencies in both humans and their food supply, Cd makes it difficult to overcome deficiencies solely by eating food. The current diets in the western world, though high in calories and protein, produce multiple nutritional deficiencies, especially in a stress situation.

When Cd is injected into the peritoneal cavity of rats it causes a negative Ca balance with loss of Ca in the feces more than the urine (Mei 1993). Oral doses of Cd in nonpregnant Ca deficient mice caused an immediate and significant fecal excretion of Ca from an early direct

effect on bone. (Wang 1993). By causing bone resorption in a Ca deficient, vitamin D deficient, or estrogen deficient state, Cd causes loss of Ca and osteoporosis.

Cd exposure affects the entire anti-oxidant system. Vitamin C is depleted by Cd exposure (Pharikal 1988). Stress causes vitamin E depletion in the brain and spinal cord. Vitamin C, an extracellular antioxidant, protects vitamin E, a membrane antioxidant, from oxidation. Cd and Se form an insoluble compound. Se depletion affects glutathione peroxidase enzyme, Cu deficiency affects superoxide dismutase, and Fe deficiency affects catalase: all antioxidant enzymes.

B-12 is lost from muscle during stress (Bhatt 1987). B-12 deficiency affects microsomal detoxification, increasing interactive effects with other chemicals (Korsova 1989). The entire B complex is needed in greater quantities in stress situations. By acting as a stress agent Cd induces depletion of the B complex. The interactions of the various B vitamins on cell metabolism are exceedingly complex, differing in different tissues. For instance, vitamin B6 deficiency increases glycogen content of muscles but not of liver of rats (Okada 1991), increases Mg losses in the urine (Turnlund 1992), and slows axonal conduction velocity secondary to defective myelination, allowing the deficiency to be detected by brain stem auditory evoked potential (Buckmaster 1993).

Niacin as NAD, protects DNA from oxidative strand breaks (Zhang

JZ 1993), so a deficiency would have a cancer promoting effect. Riboflavin deficiency inhibits the oxidation of fatty acids and leucine (Nagao 1992). Many genetic conditions alter requirements for B vitamins.

Zinc deficiency prevents the mobilization of vitamin A from the liver. Cd also depletes the retinol binding protein, which can make supplemental vitamin A more toxic. Some of the effects of Cd are identical to those of vitamin D deficiency (Toury 1985). With Mg and phosphate depletion vitamin D resistance occurs. Cd forms an insoluble precipitate with vitamin K, phosphate and iodine. By generating lipid peroxidation, Cd destroys essential fatty acids and increases the need for them in the diet. Cd also has direct effects on lipid metabolism (Gulati 1987).

Intracellular potassium deficiency occurs with stress. This can transiently increase the plasma levels but with Mg losses, hypokalemia occurs.

These depletions do not occur equally in each organ or in every organism. The tremendous individual variation in response to Cd defies simplistic analysis but it is a very important mechanism of toxicity.

Interactions:

Infectious Agents. Since Cd binds to nucleotides and is absorbed by all cells, it can influence both infectious agents and their hosts. By lowering humeral (Daum 1993) and cell mediated immunity (Ohsawa 1992) and suppressing natural killer cell function (Chowdury 1989), Cd

makes the host susceptible to chronic viral, bacterial, and fungal infections.

Blakely (1987) found that Cd decreased the latency and increased the severity of a retroviral infection causing leukemia in mice. Viruses can change the distribution of Cd in the host. There is increased accumulation of Cd in the spleen and kidneys of mice infected with Coxsackie virus B3 (Ilback 1993). It is possible that viruses that show a great deal of mutagenicity bind Cd to their DNA or RNA.

Not all studies show a negative effect. Depending on timing, Cd can decrease infections with viruses, probably through stimulating apoptosis of infected cells, ridding the body of the virus before it has ever been exposed to the immune cells.

Of all the metals, Cd, at the lowest inhaled dose, increased the mortality of mice co-exposed to S. pneumonia. Pseudomonads, which are used to biodegrade hazardous chemicals, also bioconcentrate Cd. In studies done with mice, pulmonary exposure to "engineered" pseudomonads negatively altered the bacterial flora. No mortality was seen when large numbers of bacteria were orally given, but all animals died in 2 days after nasal challenge with the same dose (George 1993). Since these organisms strongly concentrate Cd, these effects may be due to Cd.

Rats given endotoxin and prednisone died when given Cd, indicating a harmful effect with bacterial infection (Cook 1975). In this experiment, lead actually blocked the toxic effects of endotoxin and prednisone. Staphylococcus aureus

strains, producing toxic shock syndrome toxin-1, are more likely to be Cd resistant than non-producers (Dickgiesser 1987). The toxin in cholera is associated with a plasmid that could be acquired with environmental exposure to Cd.

Aspergillus rhinitis developed in rats exposed to Cd (Rehm 1988). In an area in Poland where human neoplasms and cattle leukemia were found, Se deficiency was associated with the growth of this fungus (Dobrowolski 1993). With supplemental Se the fungus and the cancers disappeared.

With chronic infections tryptophan and serotonin can be converted into quinolinic acid which is correlated in HIV infection with neuropsychologic deficits (Heyes 1991). Cognitive deficits like confusion, poor concentration and memory deficits are very similar to those that are reported in neurological Lyme disease (Logigian 1990) and Chronic Fatigue Immune Deficiency Syndrome (Sternberg 1993). Both Mg (Schurr 1991) and Zn (Kida 1990) at physiologic levels block excitatory effects of quinolinic acid on the N-methyl-D-aspartate receptor in hippocampal slices. By producing these deficiencies Cd can have CNS effects without accumulating in the brain. Hypo-immune fatigue syndromes do appear to be diseases of the stress response to Cd (StewartPinkham 1990).

Cd works together with other disease mechanisms, such as infectious agents and in a setting where nutritional deficiencies, excess sugar intake, high dietary protein, or

insufficient mineral absorption coexist. Cd appears to alter both the host resistance mechanisms and the pathogen, but there is much that remains unknown about these effects.

Metal Interactions. Cd is unique among the metals in having so many metal-metal interactions (Blazka 1992). Metals activate enzymes that control many cell signalling processes. Cell signalling is a major focus of research but attention is not generally directed to the effects of metal ions (Alberts 1989); fortunately, some studies are available that elucidate their effects.

Zn and other ions, including Pb, can block Cd binding to the cell surface receptor which is associated with phospholipase C activation and inositol turnover (Smith 1989). A guanine nucleotide binding protein is involved. These proteins have a selenocysteine (Whanger 1987) which may be the binding site for these metals. This system is linked to Ca mobilization and protein kinase C activation. These events play a role in such stress responses as platelet activation and aggregation and neutrophil activation.

Inhibition of a Zn metalloprotease, neutral endopeptidase, which breaks down met-enkephalin, formyl-met-leu-phe, and substance P, increases the potencies of the inflammatory peptides (Shipp 1991). Cd readily inhibits peptidases and plays a role in neutrophil activation, and is a good candidate for the physiologic inhibitor of the enzyme that degrades inflammatory peptides.

Calmodulin and protein kinase

interact in combination with cholinergic stimulation of prostaglandin E2, a substance that is involved with Cd stimulated bone resorption in conjunction with cyclic-AMP and Ca as a second messenger (Miyahara 1992).

Just as Cd acts as a stress agent, Zn and Pb can block Cd induced stress reactions. In water and air Pb and Cd at certain doses block each others toxicities. The Pb in gasoline increased atmospheric Pb levels in this century, reaching a peak in 1970 and falling to the level it was in 1900 at present. Cd levels in air, which have the greater toxicity, have not declined and have been made more toxic by the reduction of Pb in air. Similarly, cigarettes, which in the past contained Pb from air pollution, are more toxic with unopposed Cd.

Oral Pb, however, increases Cd uptake by 20% (Endo 1993). This explains the ability of Pb to induce MT in the liver when it is given orally but not when hepatocytes are exposed to it (Bracken 1987). Ingestion of Pb can also increase Cd levels in the brain (Lockett 1986). This is similar to low dose Cd administered orally. High doses of oral Cd do not go to the brain but instead go to the liver and kidneys. At 25 ppm, Cd causes bone resorption in the presence of Ca deficiency, an effect not seen with 5 ppm Cd or 25 ppm Pb (Wang 1993).

Several studies show that Cd and mercury (Hg) bind to different sites yet both can promote acute stress responses (Ghosh 1993) and interfere with DNA repair. Hg can also activate phospholipase C (Jung 1990). Hg can displace Cd from

binding proteins (Funk 1987), leading to an increase in free Cd which could then produce the effects attributed to the Hg added. In one study Hg caused an 11% reduction in Cd uptake and no effect on efflux in kidney cells (Endo 1993). In another study Hg inhibited the uptake of Cd and also enhanced its efflux in liver cells, an effect not seen with Zn, Cu, or Fe (Blazka 1992). Effects of metals on Cd can be organ, tissue, and cell type specific.

Glutathione stimulates the extrusion of Hg but not Cd, so that in spite of tighter binding to MT, Hg excretion through the urine is greater than Cd excretion (Foulkes 1993). High urinary excretion of Hg, coming from the release of Hg from amalgam fillings, was found in women with hormonal disorders and alopecia (Gerhard 1992). It would be a mistake to assume the hormonal disorders were caused by Hg, just because of the high urinary excretion. Cd could cause the hormonal disorders, and Hg excretion could involve Cd stimulation of glutathione in the kidneys of these patients.

Copper(Cu) can also displace Cd, and its toxic effects are also those associated with Cd. But Cu like Zn can competively inhibit Cd uptake (Endo 1993, Blazka 1992). Excess Zn causes Cu deficiency. Cu deficiency causes loss of pancreatic acinar cells in the rat through apoptosis (Rao 1993), resulting in malabsorption. The molecular mechanism, which is unexplained, could involve Cd.

Fe can also competitively block the uptake of Cd into the rat hepatocyte (Blazka 1992), but it is not

as effective as Zn. The interactions of Cd and Fe are complex and vary with age of the host and oxidation state of the Fe. Oxidized Fe increases the
toxicity of Cd (Sakata 1988). Since Fe metabolism is greatly influenced by Cu, Cu deficiency induced by Cd strongly affects Fe transport. Excess Se intake inhibits Cu and sulfur metabolism, making the organism more sensitive to Cd toxicity, even though a low dose of Se blocks Cd toxicity.

Of all the metals Cd can enter the cell most readily and move to the nucleus to alter gene transcription. The glucocorticoid receptor is a receptor for steroids, thyroid and vitamin D. The unactivated receptor is located in the cytosol. After activation it moves to the nucleus where it binds as a dimer with Zn binding fingers. In the glucocorticoid DNA binding domain Cd has 40 times more affinity for the metal binding site than Zn (Freedman 1988). It is quite possible that it activates the receptor, and travels with it to the nucleus and binds to the DNA.

Nuclear factor-kappa beta is released from its inhibitor with protein kinase C activation and travels to the nucleus to induce expression of interleukin-6 and tumor necrosis factor alpha. Cd could be involved by activating protein kinase C or moving with the nuclear factor to bind to DNA, activating the transcription of these acute phase proteins.

Just as Cd can take the place of Zn, Cd can also take the place of Ca and bind to its sites. Cd has 1,000 more affinity for the Ca ATPAse than

Ca, inhibiting the enzyme, thereby, blocking the extrusion of Ca from the cell (Verbost 1987). A very related protein, CdATPase, is induced in bacteria exposed to Cd to extrude Cd from the cytoplasm, preventing it from having a toxic response. Cd can also bind to calmodulin in place of Ca. It binds to glutamate in the "calcium" finger.

Mammalian cells contain a Ca(2+)-dependent endonuclease which is a necessary step in apoptosis. Zinc inhibits this process, depending on the free Ca2+ concentration. It appears that a balance between Zn and Ca regulates this process (Lohmann 1993). Cd alone stimulates the endonuclease, replacing Ca2+, and is more inhibitory than Zn in blocking apoptosis. This ability to take the place of both Zn and Ca and to have higher potencies than either ion, helps explain the highly divergent effects that it can produce.

Vitamin D and extracellular Ca deficiencies increase Cd toxicity but an excess of oral Ca, by blocking stomach acid and the absorption of Mg and zinc, can have a detrimental effect. Extracellular Ca, unfortunately, potentiates the vasospasm induced by Cd through the Ca sensitive potassium channel (Zhang 1993).

Most Cd ions enter a cell through the voltage sensitive Ca channel, which is blocked by chemical Ca channel blockers, Cd, itself a Ca channel blocker, and Mg. It is possible that a minority of Cd ions, by binding to cell receptors and moving with them to the cell nucleus, serve as second messengers in stress

responses.

Commonly supplemented single nutrients, like Ca and Fe, which can both block Cd to some degree, by having an inhibitory effect on other essential minerals, can be detrimental, especially when Mg, Zn, Cu, and Se are deficient in food.

Organic Chemicals. Air pollution is always mixed. Toxic organic chemicals released into the air, like volatile organics, chlorinated organics, and pesticides, have a synergistic effect with Cd. In ultrastructural studies of the liver and kidneys of birds exposed to 100 ppm CdC12 and later exposed to an organophosphorus compound (a single dose of 240 mg/kg methylbromofenvinphos), there were striking toxic effects with swollen mitochondria, lysosomal bodies, and myelin figures in the liver, irregular foot processes and thickening of the glomerular basement membrane in the renal corpuscles, and severe damage to the proximal tubule cells, including damaged nuclei with a dilated envelop in just 24 hours (Chishti 1993). Minor effects were found with exposure to either chemical by itself.

Animal protein can accumulate excess pesticide concentrations when the animals are exposed to Cd, reared in stressful environments, and exposed to pesticides in their food (Leonzio 1992). The human consumption of the food containing pesticide is, in turn, more toxic when the human is stressed and exposed to Cd air pollution. Elevation of pesticide levels are associated in women with fewer conceptions and more frequent abortions (Gerhard

1992).

Chemicals that are drugs of abuse and addiction greatly enhance Cd's toxicity. Alcohol interactions with Cd have been studied (Nation 1988) which show a decrease in toxic effects. In acute studies one does not develop the nutritional deficiencies that can occur with long term human use. It is clear from the previous discussion that alcohol, a solvent upsetting liver function and depleting nutrients, especially Mg and Zn, would have an adverse reaction with Cd. Cocaine induces intracellular Mg deficiency in the brain (Altura 1992), making it more sensitive to quinolinic acid and Cd.

Any chemical known to have toxic effects on liver or kidney can be suspected of having an interaction with Cd. Co-exposure of hepatocytes to Cd and chloroform has a toxic effect (Stacey 1987). It is likely that all anesthetics could react in some way with Cd.

Non-steroidal anti-inflammatory drugs were found to cause lipid peroxidation in the liver microsomes during oxidative metabolism (Yokoyama 1993). A toxic dose of acetaminophen in the liver releases Cd, an effect that can be blocked with caffeine (Gale 1987) which depletes glutathione. N-acetylcysteine, which increases Cd excretion, also blocks acetaminophen toxicity.

Cephaloridine, a beta lactam antibiotic, causes liver toxicity as measured by elevation of plasma sorbitol dehydrogenase activity (Kays 1992). Since chronic Cd exposure depletes Se, the drug exposure can

cause more harm. With Se deficiency decreasing kidney glutathione peroxidase activity by 78%, cephaloridine has a more pronounced nephrotoxic effect with increased plasma urea, increased kidney weight, and excretion of urinary enzymes, all Cd toxic effects. Se deficiency had no effect on liver toxicity caused by cephaloridine.

Effects are not limited to the liver and kidney. Co-exposure of Cd with other chemicals can produce a heightened effect on teratogenesis or carcinogenesis (Yamada 1993, Saxena 1986, Wade 1987). With Cd's wide range of biological action, it is likely that many idiosyncratic reactions to pharmaceuticals involve the drug induced uptake into a critical site causing a toxic effect in conjunction with genetic susceptibilities, nutritional deficiencies, or co-exposure to other toxic agents.

Many commonly used drugs interact with one or more actions of Cd that result in beneficial effects. Anti-inflammatory drugs block actions mediated through prostaglandin E2, anti-histamines block Cd effects on mast cells and hypothalamic histaminergic neurons, which release histamine through actions of G proteins, phospholipase C, and intracellular Ca mobilization (Knigge 1990). Anti-calmodulin drugs block the low dose stimulatory effects on calmodulin. Many different drugs block phospholipase C activation. Calcium channel blockers block Cd uptake by cells and prevent its toxic effects (Hinkle 1989).

At a concentration of only 10-8 M Cd sulfate inhibits the hydrolysis

of diltazem, a calcium channel blocker by 40%, the lowest dose effect of the chemicals used (LeBoeuf 1987).

Pharmaceuticals do not restore nutritional deficiencies and may increase toxicity when metabolized, resulting in undesirable side effects. Often a drug will have both beneficial and harmful effects. Cimetidine can block a Cd stimulated increase in stomach acid; but, if used chronically, it will decrease Mg and Zn absorption, rendering cells more sensitive to Cd inhalation from cigarette smoke or environmental sources.

carcinogenesis. Carcinogenic doses of Cd induce oxidative stress while impairing cellular defense mechanisms against such stress (Koizumi 1992). It is evident that co-exposure to a variety of chemicals result in this carcinogenic state (Yamada 1993). By altering cell metabolism, Cd fosters cell proliferation (Stewart-Pinkham 1991a). The cell surface receptor activated by Cd (Smith 1989), interacts with oncogenes. Cd is known to increase the expression of two oncogenes c-myc and e-jun (Jin 1990). C-myc is associated with aggressive tumors. Cd also alters the tumor suppressor protein p53, eliminating its suppressant effect on cancers in a variety of tumors (Hainaut 1993).

In a situation of Zn deficiency, which always accompanies stress, there is inhibition of DNA repair, which is also significantly associated with carcinogenesis (Nocentini 1987). In any stress situation which results in a loss of tight epithelial junctions, either in the GI tract or in the

vasculature, Cd is taken up by these lining cells and the transfer of nutrients is inhibited, compromising the cellular defenses.

Moreover, Cd effects on the primary tumor may allow shedding of tumor cells into the blood and the breaks in the vascular lining allow metastatic cells access to tissue. In many cell culture systems Cd at certain doses increases cell proliferation. By providing Se, some cancer blocking herbs block the uncontrolled growth of cancer cells stimulated by Cd.

Air pollution with Cd can make cancers resistent to cancer treatments. Tumors resistant to radiation and chemotherapy are resistant to Cd and may contain an overexpression of the MT gene. Overexpression of MT in primary invasive ductal carcinoma of the breast is associated with metastases which are resistant to anti-cancer drugs and radiation and have a poor prognosis (Schmidt 1993). It is possible that the resistance blocks apoptosis. Over-expression of heat shock protein 60 in ovarian cancer is associated with resistance to cisplatin therapy and a poor prognosis (Kimura 1993). In this study the researchers did not find an induction by Cd but they evaluated the cells at 4 hours. Hiramura et al (1993) found that induction by Cd of this protein was maximal at 18 hours after exposure.

Anticarcinogenesis. Although low doses can be carcinogenic, especially in combination with other chemicals, high doses can induce apoptosis. As a stress agent Cd can

kill chemically or spontaneously initiated cancers of the lung, liver, and blood in rats (Waalkes 1991,1992). Lung tumors induced by chemical exposures in humans are inhibited in individuals who are heavy smokers. Unfortunately, they generally suffer from other toxic effects from Cd exposure. Cancer fighting herbs like red clover have an elevated amount of Cd. It is possible that the Cd content plays a role in the anti-carcinogenic effect. (Table 2)

Stress Responses in Children:

Studies relating Cd effects to critical periods of child development of concern to pediatricians follow.

Fetus. Cd can stress the fetus through affecting the mother's nutritonal status, the placenta, and the onset of labor and delivery, and by inducing malformations.

Pregnancy. Low maternal albumin is associated with increased maternal and fetal complications (Mukherjee 1984). This suggests that in these pregnancies increased levels of free Cd are affecting liver function (Wan 1993). A significant increase in blood Cd does occur during pregnancy, leading to an increase in kidney Cd due to mobilization of liver Cd (Chan 1993).

Supplemental Zn and Mg, which are helpful in blocking Cd effects, have both been found to decrease morbidity and mortality in both the mother and the fetus (Kynast 1986, Spatling 1988). Zn therapy in low Zn status pregnancies associated with protein malnutrition, celiac disease, inflammatory bowel disease, diabetes, alcoholism, and

treatment with diuretic drugs, reduces the frequency of premature birth, placental ablation, perinatal death, and post-maturity (Jameson 1993).

Maternal age affects pregnancies. Cd increases in the ovary in a linear fashion from ages 30 to 60 (Varga 1993). Cd is more toxic with nutritional deficiencies that occur with successive pregnancies (Whelton 1988). Although the placenta is a barrier for Cd during most of gestation (Webster 1988), the presence of Cd decreases the transfer of vital nutrients to the fetus (Danielsson 1984, Kuhnert 1987). Decreased Zn levels during gestation can suppress immune function throughout life and can cause life long emotional lability in animal studies (Keen 1987).

Toxemia is readily produced with low dose Cd exposure in some experimental animals (Webb 1979). Chisholm (1987) suggests increased Cd absorption and decreased maternal MT could be the problem in toxemia.

A means of recognizing pre-eclampsia has been developed which uses an exaggerated response of the platelet to arginine vasopressor (Zemmel 1990). Antioxidant depletion was found in preeclamptic pregnancies by Davide et al. (1992). Since Cd can affect platelets (Pezzi 1987) and deplete anti-oxidants, it is possible the platelet test could identify women in need of Cd blocking strategies.

In epidemiologic studies of effects of smoking there is an increased risk of having an ectopic pregnancy if the mother currently smokes or recently has smoked at the time of conception (Stergachis 1991).

Placenta. Cd can be extremely toxic to the placenta (Levin 1987). Wloch (1992) found that pregnant rats exposed to intragastric Cd on days 7-19 and sacrificed on day 21 showed decreased Mg dependent ATPase activity and increased acid phosphatase activity in the fetal part of the placenta. He observed multiple enzymatic deficits when no morphologic effects were observed (Wloch 1992b).

Placental changes found in smokers are the same as those found with Cd exposure alone (van der Velde 1983). In an experimental study, increased placental glycogen, decreased fetal liver Zn levels, and reduced neonatal thymic weights, but no change in fetal weights or birthweights, were found (Hazelhoff 1987).

Birthweight. Cd combined with nutritional deficiency contributes to low birth weight (Kuhnert 1987a,b) and the negative health consequences associated with it. Many studies have found an association with maternal cigarette smoking and low birth weights. In a large study in Shanghai, China, exposure to paternal smoking caused an average reduction of birth weight of 30 gms (Zhang J 1993). In normal appearing Cd exposed embryos, the total cellular, neuroepithelial, optic assembly, otic vesicle, limb bud, and cardiac mesenchyme volumes were lowered (Lanning 1987).

The relationships are not simple or direct in human studies.

Calcifications in the placenta were associated with a 472 g lower birth weight in newborns with the highest quartile of hair Cd compared to the lowest quartile. In the absence of calicfications the average weight difference was 122g, but the absolute levels of the hair Cd were higher (Frery 1993). In a study of women exposed to Cd and nickel no effect of Cd was found on the placenta or birth weight in the occupationally exposed workers. A statistically significant effect was found for smoking, however (Berlin 1992).

Malformations. Human chorionic villus tissue exposed to CdC12 produces heat shock proteins. Embryo cells do not respond to Cd even though they do respond to heat shock. Maternal exposure to Cd results in increased heat shock proteins in the mouse embryo, especially in neuroepithelial cells (Honda 1991). Teratogenesis can be induced by Cd without physically entering the fetus.

Congenital malformations are the leading cause of death in children in the USA. Cd is the most toxic of all the metals studied in the chick embryo (Gilani 1990). Cd toxicity on pre-implantation zygotes can be blocked by Zn, manganese and Ca (Yu 1988). In studies with frogs, Mg blocked Cd induced teratogenicity.

Doses of Cd and lindane that are not teratogenic alone are so when given together (Saxena 1986). Nethylmaleimide increased Cd uptake into the blastomere (De 1993). By inducing apoptosis Cd could delete fetal tissue, producing malformations. Thalidomide, a sulfur containing

compound, may have caused malformations in this way. The bendectin controversy could be settled by determining if it caused an increased uptake of Cd into embryonal cells. Cd reacts synergistically with caffeine in producing recombinations during meiosis in yeast (Sorg 1988). Certainly mothers with nutritional deficiencies are at risk of having affected children if they smoke cigarettes, drink alcohol, take drugs, or even consume caffeine or eat pesticide laden fatty foods. Breathing polluted air makes these effects worse.

Cd, alone, can cause spinal cord defects and exencephaly in animals (Webb 1979. Lanning 1987).

Recently, Se and Zn deficiencies were found in women who gave birth to children with spinal cord defects (Rinks 1989). Severe Zn deficiency was found in an 18 year old Turkish woman who delivered 2 anencephalic stillborns. After 5 months of supplementation with 22 mg of elemental Zn she conceived and subsequently delivered a normal full term infant (Cavdar 1991). In a case control study of paternal smoking in Shanghai, China, the odds ratio for anencephalus was 2.1, for spina bifida 1.9, for pigmentary anomalies of the skin 3.3, and varus/valgus deformities of the feet 1.8. There were usually multiple rather than isolated malformations (Zhang 1992).

Infancy. The leading cause of death in the first year of life is sudden infant death syndrome (SIDS) in the USA. In a recent study done in Sweden in which the base rate of

SIDS was 0.45 deaths/1,000 births in non-smoking homes, smoking 1-10 cigarettes doubled the rate of SIDS and smoking 10-20 cigarettes in the home tripled the base rate (Haglund 1990). Deficiencies of the microsomal G-6PD system have been found in a number of SIDS deaths in other studies (Burchett 1989). This is an enzyme that Cd can easily block (Vallee 1972). In a recent conference in Sweden passive smoke exposure, sleeping position, and a chronic hypoxic state associated with a vulnerability of the immune system and the CNS were considered important etiologic factors (Lagercrantz 1993). Clearly, all these mechanisms could be mediated by a vulnerability to Cd toxic effects.

The measles virus is strongly affected by cellular immunity, as is HIV-1 (Oldstone 1990). There are many reasons to suspect that HIV infection is influenced by Cd (Stewart-Pinkham 1991). In children suffering from Kwashiorkor, the hair level of Cd is extremely high from the release of Cd from binding proteins in the liver. Malnourished children are also those who die easily from infection.

Cd is the most toxic metal to the respiratory epithelial cell (Lag, 1987). It paralyzes the cilia and causes necrosis of the cells at 10 uM levels. With its ability to react synergistically with viruses, one must suspect that Cd could play a role in the pathogenicity of respiratory syncytial disease in infants. Intratracheal administration of Cd produces bronchiolitis in animal studies (Webb 1979).

Celiac disease is a disease beginning in infancy that appears to be increasing. It is associated with a combination of **DQ HLA** class II alleles in over 90% of cases in Europe (Tighe 1993). Sensitivity to Cd is associated with major histocompatibility antigens. When gluten is ingested by celiac patients their serum zinc level drops to half the normal level (Statter 1990), making them very susceptible to toxic effects from environmental Cd. Sensitivity of DQ A1.0501 and DQB1.0201 to Cd could easily be determined.

Childhood. Zn deficiency (Keen 1987) and chronic low dose Cd administration (Smith 1985) to neonatal animals causes life long changes in their behavior. Children with emotional lability find their environments more stressful and perpetuate the cycle of toxicity. Since the highest concentration of Zn occurs in the hippocampus, exposure to a metabolic antagonist of Zn like Cd can be expected to cause attention and memory problems.

Very low birth weight babies grow up to have problems with behavior, motor clumsiness, and lower IQ (Sommerfelt 1993). In this study 16/27 were exposed to passive smoke. Attention deficit disorder with hyperactivity was more characteristic of boys than girls in this group.

It is noteworthy that with the dramatic fall of Pb in air and in blood there has been a concomitant rise in the use of stimulant medications for attention and behavioral problems (Safer 1988). In recent animal studies, Pb and Cd when given

together were found to antagonize effects produced when each was given alone (Nation 1989). The low dose Pb in the atmosphere coming from gasoline could have had an antagonistic effect on environmental Cd in the past. Yet mild elevations of blood lead, by denoting a Cd toxic effect, identify children with learning and behavioral problems and ingestion of lead increases Cd absorption (Stewart- Pinkham 1989a).

Another major source of morbidity and mortality is injuries. By decreasing the mechanical strength of bone, depleting antioxidants, and depleting essential nutrients associated with healing, it takes less trauma to produce a serious injury. Mild concussions might not be associated with prolonged morbidity if there were more intracerebral Mg and vitamin E to block the oxidative stress evoked by trauma.

Asthma is increasing in severity and mortality. Passive smoke increases the incidence of asthma and its severity. Cd is very toxic to the respiratory lining cells and can cause an irritative cough which can provoke bronchospasm. It also can cause edema, increased mucous, inflammation, and bronchospasm. Inhaled heparin which can block exercise induced bronchospasm could bind Cd and thereby block this stress induced condition. Se and vitamin E prevent the oxidation of thiols, which results in down regulation of the beta-adrenergic receptor (Doelman 1990).

Adolescence. Cd is toxic to the prepubertal ovary and can cause sterility in animals (Rehm 1988). It is also toxic to the testicle and interferes with testosterone synthesis (Parizek 1956). In a survey of rabbits showing a fall in population in Germany, the only abnormal finding was an elevated content of Cd in the ovaries and testes (Lutz 1993).

Estrogen increases the uptake of Cd into the liver, kidneys, and mammary glands. Since Cd binds to the metal binding site of the steroid binding site of DNA (Freedman 1988), it can be expected to have a modulatory role on steroid mediated cellular control processes. As a stress agent, it can foster early pubertal development with the risk of early pregnancy. The use of oral contraceptives increases Zn excretion (Stauber 1988), thereby, enhancing Cd toxicity.

Violent children have dominated the news lately. Violence is one behavioral manifestation of stress. Cd exposure in dogs caused violence and aggression (Friberg 1971). Cd makes stressed rats prefer alcohol to water (Nation 1987). Alcohol use is strongly associated with aggression. In studies of addiction, cigarettes are accurately identified as the substance use that later is associated with other more immediately harmful agents.

Schizophrenia has its onset in late adolescence. Brain atrophy is generally found with CT scan. In a recent study, the left hippocampus was smaller than the right and the lateral and third ventricle were enlarged in monozygotic twins affected by schizophrenia (Suddath 1990). Perinatal insults are also

common in these patients (Nasrallah 1990).

Cd is extremely toxic to the neonatal brain (Webb 1979). It induces ultrastructural changes in the cerebellum (Murthy 1987). Since stress and hormones appear to play a role in the precipitation of psychosis, it is reasonable to suspect Cd involvement. In a recent multi-element analysis of the frontal cortex, temporal cortex, and basal ganglia in schizophrenic patients, investigators found a striking reduction of brain Zn (Corrigan 1990). There were smaller reductions in Cu, iodine, and Mg and an increase in Ca. These are Cd toxic effects.

Patient Assessment for Cd Toxic Effects

Historical Assessment:

Present Illness. A multiplicity of complaints and the presence of many stressors including temperature change, chemicals or drugs, infectious illness, noise, malnutrition, and psychosocial stress are alerting signs that a host could have increased susceptibility to prevailing levels of Cd air pollution. Cd causes all the symptoms of allergy. It is essential to inquire about exposure to passive smoke at home and in other care giving environments.

Medical History. Maternal age, nutritional deficiencies, miscarriages, history of fever in the first trimester, and exposure to cigarette smoke, volatile organic fumes, drugs, cocaine, alcohol, caffeine, or stress are relevant. Pre-or post- term delivery, large or small

for gestational age, birth weight, multiple births, high birth order, prolonged labor, jaundice of the newborn, and stressed condition at birth are all pertinent.

Symptoms of stress in infancy such as colic, sleep problems, and frequent respiratory or GI upsets are significant. Serious illnesses, hospitalizations, broken bones, or multiple congenital anomalies should be noted.

Family History. Cd is linked in animal studies to hypertension (Perry 1974, Tomera 1988), heart disease (Kopp 1986), cancer (Foulkes 1986, Wade 1987), neurobehavioral effects (Nation 1989, Smith 1985), and degenerative diseases of various kinds (Webb 1979, Foulkes 1986). Since Cd can have generational effects through alteration of genes, it is important to note active or passive smoke exposure in parents and grandparents.

Psychosocial History. Shyness may increase stress levels. Exposure to violence, either actual or from videos or TV, needs to be noted. Physical and sexual abuse can cause Zn and Mg deficiencies by producing chronic stress states. Significant losses through death or divorce must be noted. Happiness and family support are protective. Life style choices, like regular exercise instead of watching TV, enjoyable hobbies, and interests may determine whether an exposure will have a toxic effect or not.

Environmental History. Farm exposures to fertilizers and pesticides, exposure to lawn chemicals, insect destroying chemicals, and volatile

fumes, such as in plastics processes, welding, or electroplating, should be noted. An attached garage allows more car fumes to get trapped in the house. Dry-cleaned clothes are a pollutant. Out gassing from new houses that are tightly built can be problematic. Living in a dusty environment or one with a great deal of animal danders or molds can be toxic. Living in close vicinity to heavily travelled roads and highways with significant truck traffic is a risk. Wood stoves, kerosene heaters, and carbon monoxide fumes from fires pollute indoor air.

Diet History. A 24 hour recall of all food and beverages is necessary. A diet high in sugar, salt and fat impairs Ca absorption, thereby increasing Cd toxicity. A diet high in aluminum (which is in melted cheese) can also enhance Cd effects by impairing Ca metabolism. A diet low in fiber, especially if it is associated with constipation, will increase Cd absorption. A diet high in commercially produced animal protein and fat will contain increased levels of pesticides. A diet high in organically grown plant food, high in fiber, with moderate protein, some from animal protein, will minimize Cd uptake and toxicity. Type of water should be noted. Tap water may have high levels of aluminum, and the chlorine in tap water increases Cd solubility.

Review of Systems. It is possible to elicit a large number of complaints that may occur in the presence of nutritional deficiencies. These often non-specific complaints are further clues that the smooth

functioning of the total organism is imbalanced in some way. By using references, such as the one compiled by Werbach (1993), it is possible to elicit the range of symptoms noted to be associated with various vitamin and mineral deficiency states.

It is important to note exposure to drugs or supplements. Children with bloating and gas often have poor stomach acid and have an overgrowth of microbial organisms in their upper GI tract. Stomach acid is essential for the absorption of Mg and Zn. Acid blocking drugs and Ca supplements may block Zn, Mg, and manganese absorption. Iron supplements can lead to a drop in Mg and Zn levels (Newhouse, 1993). Oral contraceptives cause Zn and Mg deficiencies (Stauber 1988, Newhouse 1993).

Physical Exam:

An accurate and complete physical exam is essential in understanding the complex manifestations of Cd operating in the developing child.

Bones. Cd has important effects on bone (Bhattacharyya 1988, Miyahara 1992, Wang 1993), affecting chondroblasts and osteoblasts (Dohi 1993). Any deviation in growth, such as a large or small head, facial abnormalities (Gale 1987), or congenital defects, can be a clue.

Cd decreases the mechanical strength of rat bones (Ogoshi 1989). Mg (Boskey 1992) and Zn (Xu 1992) deficiencies also decrease mechanical strength of rat bones. Bone changes occur in premature infants with Cu

deficiency , including multiple fractures and subperiosteal new bone formation and enlarged costochondral junctions (Schmidt 1991).

Zn or B-12 deficiency can have a stunting effect on growth (Graham 1991). In animal studies Zn deficiency causes bone effects similar to vitamin D deficiency (Xu 1992).

BEENT. Cd has immune modulatory effects which can affect viral, bacterial and fungal infections. Antibiotic resistant organisms generally show Cd resistance (Riley 1989), a property that requires exposure of the organism to increased free Cd (Nies 1992). Enlarged tonsils, enlarged cervical nodes, an irritation of the nasal passages or conjunctivae are important indicators of exposure to Cd air pollution (Beck 1993). Canker sores, geographic tongue, fissures in the tongue, excessive tongue coating, atrophy of the taste buds can be looked for. Recurrent aphthous stomatitis can occur with 131, B2, and B6 deficiency (Nolan 1991).

Zn and Se deficiencies have been found in Finland to occur in children with dental caries. Caries may also indicate an overly sugary diet which interferes with mineral absorption. Silver amalgam fillings release Hg with chewing. Hg and Cd have complex interactive effects (Gerhardt 1992, Ghosh 1993, Daum 1993).

Skin. The skin is very sensitive to toxic effects, nutritional deficiencies, immunologic abnormalities, and microbial overgrowth. Mottling, or pallor unassociated with anemia could be an

effect of Cd on arterioles. Heat, cold, or perspiration can be noted. Pigmentary anomalies were frequently found in a case control study of paternal smoke exposure in China (Zhang 1992). One can find dry skin, white lines in the fingernails, scaly dry elbows or knees, parakeratosis, and the presence of chronic viral or fungal infections or parasites. Hy po pigmentation of the skin and hair is associated with Cu deficiency (Schmidt 1991).

Neurological. Cd produces locomotor dysfunctions in rats that vitamin E can block (Ali 1993). Zn deficiency and Mg deficiency can make the brain over-reactive to excitatory stimulation. A child, who on exam seems overly responsive to stress, showing fearfulness and passivity or highly emotional and resistant behaviors, is a stressed child.

Many soft neurological signs could be indicators of a neurologic effect. A delay in visual motor integration skills has been identified in children with elevated Pb and Cd levels in the hair (Stellern 1983). Attention deficit disorder appears to have the neurochemical abnormalities that Cd is capable of producing (Rajanna, 1990, Stewart-Pinkham 1989a). A highly reactive autonomic system can suggest Cd toxic effects. There may be a deviation of BP from the mean or reflexes may be increased or decreased.

Laboratory Assessment:

There is no single test that can detect the wide range of effects that Cd can influence. In addition to

direct effects, Cd can produce effects by inducing multiple nutritional deficiencies. The detection of these interacting effects guide therapeutic interventions.

Blood Tests. Plasma levels of fluorescent lipoperoxides would estimate effects of free Cd, taking into account the summation of all interactive effects. Lipid peroxides in the blood are maximal with B6 deficiency and stimulation by promoters like Fe and Cu (Ravichandran 1991). Fluorescence can be seen by examining a fresh drop of blood with dark-field microscopy. In addition this allows one to see aggregation of platelets, activation of the WBC, acute inflammatory changes, crenation of RBC's [which indicates Mg deficiency (Freedman 1992)], eosinophilia (a Cd effect), and level of fat in the blood. The presence of motile bacteria in a non-ill patient indicates GI permeability, which increases Cd absorption, and lack of clearing by blood phagocytes.

Sera antioxidant activity, used by Davidge (1992), measures a Cd effect on nutrient depletion. Other tests are needed to determine effects on immune function, endocrine function, bone, liver, kidney, and blood elements.

Cadmium. Current methods of analysis are so variable between labs that blood Cd levels may not prove helpful except in the newborn (Anglov 1993). In a study of blood Cd the levels could vary fourfold in an individual during a day (Vahter 1992), so a single level would be

difficult to interpret.

In a study of premature births, maternal blood Cd was significantly higher (Fagher 1993). It would be appropriate to measure blood Cd levels in stillborns, prematures, and neonatal deaths as well as in organs, especially adrenals and gonads, when autopsies are performed.

Elevated blood Cd levels were found in mice with progressive spontaneous lymphatic leukemia (Kaszubkiewicz 1989). It would be reasonable to measure blood Cd in circumstances where beta-2 microglobulin levels are elevated (Stewart-Pinkham 1990).

Lead. Blood Pb has a linear correlation with the toxic effects that Cd can cause. Pb is stored in bone and does not cause bone resorption (Wang 1993). The toxic effect of free Cd increases blood Pb by increasing GI absorption or bone resorption (Stewart-Pinkham, 1989b).

CBC. Deviation from mean values is frequently encountered in a CBC. Cd can cause hemolysis by directly interacting with the membrane proteins (Yang 1993). It can also stimulate erythropoiesis increasing above normal the hemoglobin and hematocrit (Hogan 1992). By inducing Mg deficiency, cells are more susceptible to free radical injury with crenation, lipid peroxidation and hemolysis (Freedman 1992). Cu deficiency also reduces antioxidant defenses and interferes with the maturation of hematopoietic cells (Hirase, 1992). Cd can produce all the manifestations of Fe deficiency anemia (Sakata 1988).

Cd is taken up by platelets

(Pezzi 1987). It is possible that by measuring the Cd level in platelets, one could estimate the level of free Cd entering the blood. Cd has many effects on leukocytes (Webb 1979). A low neutrophil count might indicate Cu deficiency (Schmidt 1991). Sometimes this is associated with anti-neutrophil antibodies (Higuchi 1991). A high neutrophil count might indicate an acute stress response. Inflammation is enhanced with B6 deficiency (Lakshmi 1991). Stress responses can occur with the stress of drawing the blood and may not reflect a steady state condition of toxicity. A low lymphocyte count suggests immune suppression and possible Zn deficiency (Ohsawa 1992).

Chemistries. In animal studies acute Cd stress causes the appearance of c-reactive protein, acute phase proteins and a reduction in serum albumin and acetylcholinesterase (Ghosh 1993). In hepatocyte culture Cd exposure for 20 hours lowers the secretion of albumin and the recovery is slow after the Cd is removed (Wan 1993). This occurred without release of lactic acid dehydrogenase enzyme (LDH).

An elevation of the LDH occurs readily as a toxic effect of Cd in the presence of Zn deficiency (Nomiyama 1986). A low LDH does not mean an absence of a Cd effect, but it could indicate a block in processing of the enzyme to the cell membrane which, in turn, could be associated with Mg deficiency. With both processes occurring, the value could be entirely normal. Serum Zn and serum Mg levels could be measured but these metals are also

difficult to evaluate since serum levels are not well correlated with tissue levels (Werbach 1993, Graham 1991). High levels of the metals in blood could reflect losses from tissue that will cause high urinary levels and eventual depletions.

There are extensive studies of nutrient deficiencies in animals (Graham 1991). Studies of Cd effects in fish are comprehensive (Fu 1989). Using these sources one can gather some evidence for hormonal changes,and specific vitamin and mineral deficiencies. These alterations are acting with Cd and may be a key to correcting the imbalance.

An elevation of alkaline phosphatase may signal the need for more vitamin D, but it also can be a direct toxic effect of Cd, alone or associated with Cu deficiency. Low levels of the SGOT and SGPT may reflect Mg deficiency or low levels of BI and B6 (Borghi 1991). Elevations of these enzymes may indicate low anti-oxidant levels resulting in liver injury from Cd toxic effects. Low levels of Ca and potassium are often seen with Mg deficiency. In premature infants a low phosphorus can be found with Mg deficiency and vitamin D resistance (Paunier 1992). B6 deficiency is also associated with vitamin D resistance (Klimova 1991). It is possible that the low phosphorus is a Cd toxic effect in this instance.

Both low and high levels of cholesterol and triglycerides can occur with Cd. Cd alters lipid metabolism (Leonzio 1992). It is possible that the increase in cholesterol can be a consequence of Cu deficiency and an

increase in glutathione which is induced in the liver from exposure to Cd. Mg deficient rats have hyperlipidemia and increased oxidation of the VLDL and LDL (Rayssiguier 1993a). Similar findings occur with Cu deficiency (Rayssiguier 1993b). Gebhard (1992) found thyroid abnormalities in women with increased Cd excretion which could increase lipids. Carnitine deficiency is associated with high triglycerides and sometimes high cholesterol. Low levels of cholesterol and triglycerides, can accompany malabsorption or viral infections, two effects that Cd can mediate, also.

Lactic acidosis can be associated with thiamine deficiency (Roll 1991). Elevated carbon monoxide levels can occur from activation of heme oxygenase. High uric acid levels and high ammonia levels are found with Zn deficiency. Virtually any deviation from the mean can be viewed as a direct or indirect effect, suggesting possible intervention strategies to return the host to homeostasis.

Urine. To detect passive smoke exposure one can obtain the thiocyanate/creatinine ratio in urine, a reliable, non-invasive and inexpensive test (Pre 1992).

In the urinalysis one can look for proteinuria and calciuria which can occur transiently in response to Cd (Jin 1987). Kidney stones are associated with Cd excretion (Elliot 1973) and decreased antioxidant levels (Selvam 1992).

Signs of acute renal tubular necrosis could be accompanied by

actually increased Cd excretion. Subclinical tubular dysfunction can be seen at urinary excretions of 2ug/24 hours (Bernard 1993). Alpha 1microglobulin and N- acetyl -beta -Dglucosaminidase were increased in the urine of 30% of individuals environmentally exposed and 39 % of those occupationally exposed to Cd (Jung 1993). In another study of urine proteins, apolipoprotein D, a much more storage stable protein than alpha-1 microglobulin, was well correlated with Cd and could be used as an indicator of its effects (Holmquist 1993).

Hair. Hair analysis is an effective means of detecting Cd exposure and toxic effects (Bergomi 1989, Stewart-Pinkham 1989c). Exposure to airborne Cd was particularly well correlated to hair Cd in newborns (Frery 1993b) and children (Prucha 1987). The levels in children with learning and behavioral problems are approximately double those of unaffected children (StewartPinkham 1989c). Seasonal variation and differences in age and hair color cause the standard deviation to be very high (Wilhelm 1988).

Thirty mineral levels are reported with commercial hair analyses. Deviations from the mean of multiple nutrient minerals in hair are an excellent indicator of stress-induced deficiencies and metabolic alterations. The hair levels do not correlate with serum levels or organ levels. In some instances the levels correlate with intake of nutrients. Hair analysis must be used with other information to be most helpful.

If after an intervention, the minerals approach the mean,the overall balance of the trace minerals has improved.

Therapy

Primary Interventions:

By eliciting a thorough history, performing a complete physical exam, and ordering inexpensive screening tests, a physician can gather the information needed to really understand each patient and his or her presenting problems, at the same time becoming the personal, caring, doctor who creates the rapport needed for a therapeutic alliance. Physicians can use their sophisticated understanding of the complexities of molecular biology to help patients recognize the forces that cause them to become sick and assist them in changing their life style.

Controlling Cd toxicity requires a great deal of individual responsibility. Since its effects on genes are at very low dose and can cause irreversible mutations, every effort must be made to discourage smoking by males and females before childbearing and throughout the years that children are growing up. With the removal of lead from gasoline, cigarettes which used to contain some Pb from air pollution are much more toxic to the airway.

Diet is a key to preventing illness (Leis 1991, Galland 1988). A nutrient-dense diet consisting of fresh fruits, vegetables, seeds, nuts, and fish provides the fiber, vitamins, minerals, antioxidants, and essential fatty acids that can block Cd toxicity, provided it is not moldy or

contaminated with pesticides and plasmid containing microbes.

Breast milk is the ideal food for infants, but deficiencies can develop if their mothers are exposed to Cd fumes. It is likely that Cd can reduce nutrient transfer to breast milk by the same mechanism it decreases nutrient transfer in the placenta and the GI tract.

Cow milk, on the other hand, increases toxic effects (Kello 1977). When a one-year-old child developed Zn deficiency after switching from formula to whole milk (Helm 1992), Cd effects in her GI tract could have caused her Zn deficiency (Kello 1977, Coppen -Jaeger 1989). This effect can be blocked in animals with plant fiber and fish. In children without allergies non-fat dry milk, which is free of pesticides, is an excellent source of Ca and carnitine, provided the diet contains sufficient plant fiber and essential fatty acids.

Psychological interventions are extremely powerful by reducing stress and enhancing healthful mental attitudes. Stories, metaphors, neurolinguistic programming, mental imagery, laughter, and group support can help heal serious mental and physical problems. Qigong, a gentle breathing and stretching exercise, has been used in China for 5,000 years for healing and well-being.

Many stress related disorders are self limited when nutrient depletion is not a problem. Leo Galland (1988), in a popular book for parents, discusses the changing requirements for nutrients from pregnancy through adolescence. Anne McIntyre (1992) discusses the use of

herbs. These strategies will be more effective in conjunction with strict efforts to provide clean air and clean water. See Table 3.

Most children have blood Pb levels below the level that requires chelation. In any given area the level of Pb occurring in healthy children can be used as a base for detecting children who are absorbing Pb excessively or resorbing bone from Cd toxic effects. Inquiries should be made about passive smoke exposure and other environmental sources of Cd air pollution when mild Pb elevations are discovered. Nutritional support, through a high fiber diet and supplemental vitamins and minerals, and psychosocial support, through counselling or education to minimize emotional stress, will bring the blood Pb level down.

In China fortified soft drink powders that provide only 10 mg of Fe, 400 units of vitamin D, 10 mg of Zn, and 30 mg of vitamin C, as well as Ca and riboflavin, prevent and cure Fe deficiency anemia, while preventing rickets and Zn deficiency in preschool children (Chen 1992). A reduction in Fe in children's vitamins, prenatal vitamins, and infant formulas could prevent decreases in Zn and Mg.

The use of fresh fruits and vegetables and nutritional supplements would be beneficial in programs for the poor and homeless, where low income, exposure to passive smoke, and poverty associated psychosocial stress, increase the need for the entire range of anti-oxidant nutrients (Drake 1992). Geological variations may affect the availability

of such key nutrients as selenium, iodine, cobalt, and chromium.

Children with chronic illnesses, genetic diseases, or those who are acutely ill and stressed, need individualized and more aggressive supplementation to eliminate lipid peroxidation and restore anti-oxidant levels (Werbach 1993). Critically ill children and adults are often identified with thiamine (Seear 1992), Mg (Rubeiz 1993) and Zn (Shoji 1993) deficiencies. Total parenteral nutrition solutions contain 12 mcg of Cd per liter (Berner 1989), even though the drinking water standard is 10ug/L in the USA, and the threshold for a cellular effect is 0.1 ugA (Verbost 1987). There have been many reports of Zn (Goldwasser 1981), Cu (Takeuchi 1993), Se (Neve 1985), and thiamine (Lange 1992) deficiencies occurring in the recipients.

Nutrient Supplementation:

Just as there is no single effect of Cd, there is no single means of blocking its effects. Cd is so strongly influenced by nutrients that a comprehensive examination of minerals, vitamins, and other plant and animal derived nutrients is warranted. References and a more complete discussion of nutrient interactions are available in articles and textbooks on nutrition, biochemistry, and natural medicine (Beisel 1982, Werbach 1993, Wills 1985, Pizzorno 1993 updates).

Zinc. Cd, which lies just below Zn in the periodic table, acts as an anti-metabolite of Zn. Zn is an essential ion in blocking Cd toxic

effects. Zn blocks Cd inhibition of DNA replication and repair (Nocentini 1987). It blocks the inhibitory effects of Cd on T cell proliferation (Ohsawa 1992). In animal studies Zn blocks the embryotoxic and teratogenic effects of Cd in an additive manner, suggesting competition at a common binding site (Hartsfield 1992). It is probable that Zn plays a role in reversing GI permeability as well as blocking toxic effects on the vascular lining cells. Zn lozenges can block the toxic effect of rhino viruses on respiratory epithelium (Eby 1984), an effect the previous work suggests is mediated by blocking Cd. Zn has a beneficial effects on skin as well (Werbach 1993). A zinc lozenge supplement of 5 mg a day for infants, 10 mg a day for children, and 15 mg a day for adolescents is a safe level to start with. Very large doses of Zn produce adverse effects by blocking Cu or Fe absorption.

Selenium. Se and Cd form an insoluble precipitate. At a 10(-8) M concentration Se inhibits the growth stimulation of 10(-8) M Cd (Webber 1985). Se has a complex effect on Cd that varies with different organs. It inhibits Cd excretion in the rat but prevents its toxicity (Wahba 1990). Se increases the biliary secretion of Cd in humans (Wei 1989). It is a necessary component of glutathione peroxidase, one of the free radical scavenging enzymes. Both Zn and Se protect the enzyme that changes thyroxine to triiodothyronine from Cd inhibition. G proteins composed primarily of aspartate, glutamate, glycine and lysine contain

selenocysteine which binds Cd. This
is the major Cd binding protein in the testis (Whanger 1987). Se supplementation has complex interactions with sulfur, Cu, and Fe. In Se deficient areas more is needed.
A dose of 50 mcg for young children, 100mcg for 5-10 year olds, and 200 mcg for adolescents is appropriate. Toxic effects occur at 700 mcg a day. When fungal infections are found, increased supplementation is warranted.

Magnesium. Mg is a key mineral in energy formation in the cell. On the electrochemical scale it is the only metal above Cd making it capable of displacing Cd. Mg is also capable of blocking many adverse effects. Mg supplementation blocks teratogenic and embryotoxic effects in frogs in a competitive way (Luo, 1993). Mg blocks the lipid peroxidation effects that Cd can produce (Freedman 1992, Rayssiguier 1993). Mg levels in tissue can increase with exposure to Cd, increasing the Mg requirement. Supplementation is needed whenever constipation is noted. Infants need 100 mg a day, children 200-300 mg and adolescents 400 mg a day. Stomach acid is required for Mg absorption, and also vitamin D, essential fatty acids, and

B complex, particularly B-1. B-6 prevents losses in the urine.

Potassium. Potassium (K) is lost from the cell with stress, displaced by Ca and sodium. It enters the cell membrane with Mg. Fresh plant food is the major source of K in the diet. K, Mg, and Zn are all lost with chronic diarrhea and high urine excretion. Oral supplements

are helpful. Although dangerous when given intravenously, it can be given safely in large doses orally if plant food is not available.

Calcium. Mg and Ca interact with each other, vitamin D, and phosphorus. Extracellular Ca is generally protective against Cd but intracellular Ca increases are part of the stress response that can increase Cd toxicity. Ca supplementation, by buffering stomach acid, can block Mg, Zn, Mn, and Fe absorption which all require stomach acid. The amino acid lysine helps Ca to be retained. Supplementation with Ca at night leads to uptake by the bones. This can be used if dairy products need to be withheld because of allergies. To prevent deficiencies in other minerals it can be taken as a multimineral capsule.

Copper. When Cu is supplemented as a free ion it can enhance lipid peroxidation by displacing Cd from binding proteins increasing free Cd. As a component of superoxide dismutase it is an essential co-factor of a major antioxidant enzyme. It also is an essential metal with many other important enzymes. It is safest to eat Cu in food. When there is clear evidence of deficiency, as in sideroblastic anemia or neutropenia, it can be given cautiously in a dose of 500mcg to 2 mg a day, once zinc has been repleted.

Iron. Fe can also increase free radicals with supplementation. Oxidized Fe increases Cd absorption. As a component of catalase it is a cofactor in a major anti-oxidant enzyme. It is also an essential metal in

hemoglobin and many important enzymes

It is interesting that rather low doses were used in China to cure Fe deficiency anemia. With Cd air pollution, supplementation with 5 mg of iron a day in infancy, 10 mg a day in preschool children, increasing to 12 mg a day in menstruating girls might be safer than current guidelines. Vitamin C increases Fe absorption. By preventing Cd toxic effects on the GI tract with multiple dietary interventions, low dose Fe should be sufficient to meet needs without producing toxicity.

Other Trace Minerals. Cd interacts with all the nutrient minerals including Mn, chromium, and molybdenum. When Mn is supplemented as a free ion it enhances lipid peroxidation, increasing Cd toxicity. As a component of superoxide dismutase, it functions as an anti-oxidant and is protective. It is an essential co-factor in enzymes.

In each individual it is necessary to create a balance with the mineral supplements used to block Cd effects. Many traditional herbal medicines have mineral elements in somewhat different proportions (Cai 1990), thus, by supplying a corrected mix of minerals, the herbs contribute to restoring homeostasis.

Vitamin C. Vitamin C increases tremendously in animals capable of producing it when they are exposed to stress. Vitamin C acts as an anti-oxidant in the extracellular space interacting with vitamin E in the cell membrane to protect its function. It causes staphylococcus to

lose its plasmid which is where Cd resistance and multiple antibiotic resistance is encoded (AmabileCuevas 1988). This suggests that vitamin C depletes the organism of Cd, rendering it Cd sensitive again. It is possible that Cd has this effect on mammalian cells. 100 mg a day in young children and 500 mg a day in older children, with increases during periods of stress, are appropriate.

Vitamin E. Vitamin E protects the brain from Cd induced lipid peroxidation (Shukla 1988). Vitamin E protects membranes from oxidation. Vitamin E succinate which is more water soluble is the most protective against Cd toxicity. Vitamin E in a dose of 5 mg/kg, given intramuscularly to rats for 7 days, blocked the toxic effect of Cd given intraperitoneally at 1 mg/Kg on liver and kidney. Levels of Cd in the blood, liver, and kidney were lower with the co-exposure to vitamin E (Tandon 1992). As a fat soluble vitamin, vitamin E is not well absorbed when cholesterol levels are very low or bile acids are not sufficient. A dose of 10 units per Kg is a safe oral level.

Glutathione. N-acetylcysteine increases Cd excretion and increases intracellular glutathione which protects the cell from Cd toxicity (Ottenwalder 1987, Ochi 1988). Glutathione is particularly protective of lung tissue. When cholesterol levels are high, it would not be a desirable supplement, since in the liver glutathione increases cholesterol. When cholesterol levels are abnormally low, such as during viral infections, it is very advantageous.

Carotenoids. Beta carotene, which blocks singlet oxygen free radicals, is a protective substance that increases in plants with exposure to Cd. Supplementation appears beneficial in health maintenance and stress situations. Because of the tremendous number of free radicals formed in photosynthesis, plants contain high concentrations of antioxidant carotenoids and flavonoids.

Flavonoids. There are a large number of bioflavonoids in plants that appear to exert beneficial effects in stress situations and have particular affinity for particular tissues. The ginkgo tree is very resistant to pollution. Ginkgosides from the leaves are protective to blood vessels, the brain, adrenal, and thyroid glands.

Flavonoids enhance cyclic-AMP related events such as smooth muscle relaxation, inhibition of platelet aggregation, and inhibition of mast cell degranulation. Quercitin, a flavonoid with high affinity for mast cells, inhibits histamine release and acts as an anti-oxidant (Pizzorno 1987).

Myo-inositol-1,2,6- trisphosphate. D-myo-inositol 1,2,6 trisphosphate reverses Cd induced hypertension in rats (Perry 1989). This molecule is derived from phytic acid and may play a role in the protective effect of plant fibers. It reverses neuropeptide Y enhancement of vascular smooth muscle spasm induced by alpha - 1 - adrenergic agonists and angiotensin II (Sun 1992). It has been extensively studied in streptozocin-induced diabetic rats where it acts as an anti-oxidant decreasing lipid peroxidation and

cataract formation and decreasing platelet aggregation and normalizing platelet lipid biosynthesis (Ruf 1992).

Coenzyme Q_{10}. Ubiquinone, coenzyme $Q_{,O}$, is a cofactor in electron transport essential for the production of ATP. In the Krebs cycle it functions with succinate dehydrogenase. Cd does not directly inhibit this enzyme, but in studies of intact animals, the activity of the enzyme falls with Cd exposure (Toury 1985). If tissue levels are low, coenzyme Q, increases the activity of this enzyme. It is conceivable that Cd depletes coenzyme Q,,, increasing the need for supplementation. Coenzyme Q10's many therapeutic functions mirror the dysfunctions induced by Cd (Pizzorno 1987).

Animal Products. Although a vegetarian diet includes many protective substances, meat is also a source of important nutrients. It is the main dietary source of Zn and vitamin A and an important source of B vitamins and essential amino acids. It is also a source of carnitine, which can become deficient in a number of stress states in which liver and kidney function are impaired, toxic effects of Cd.

Vitamins A and D. Some individuals can not convert beta carotene to vitamin A, making an animal source of vitamin A obligatory for health. Vitamin A can be given in huge quantities to children with acute viral infections without toxicity. The cholesterol levels are so low during viral infections that there is a very small absorption of these huge doses. Vitamin A is the prinicipal vitamin associated with toxicity. It is

teratogenic and it can increase intracranial pressure causing headaches. A dose of 2,500 units for infants, 5,000 units for children and 10,000 for adolescents can be given. Vitamin D can be obtained from sunshine, if that is available, the weather permits sun exposure, and skin color does not preclude absorption of vitamin D. The use of sunblocks decreases this conversion. Children with allergies appear to have an increased requirement for vitamin D. When the phosphate level is low there is an incresed need for vitamin D, as in prematures. As much as 400 to 1,000 units of vitamin D may be required.

B-Complex. Vegetarian diets are commonly deficient in the B complex. In stress states the entire B complex is protective (Werbach 1993). Since many B vitamins need to be phosphorylated before they are active, an excess over what the liver can metabolize can flood the receptors with an inactive form causing deficiencies. For B-6, the liver can normally metabolize 50 mg an hour in adults, suggesting that 10 mg an hour would be a maximal dose in infants and 25 mg in children.

Thiamine, a sulfur containing B vitamin requiring phosphorylation as pyrophosphate, is especially important for the heart and CNS. It tends to be required in any situation where Mg is needed. Methionine and vitamin E increase the effectiveness of thiamine (Parkhomenko 1992) and block blood lipid peroxidation associated with vitamin B-6 deficiency, as well (Selvam 1991).

Pantothenic acid, another

sulfur containing B vitamin which is not phosphorylated and has no known toxicity, is considered an essential vitamin in stress situations and deficiency is associated with generalized malaise (Tahiliani 1991). It plays a role in secretion of albumen from the liver. It is also a part of acetyl CoA, a central molecule in cell metabolism.

B-12 blocks the toxicity of carbon monoxide which is increased when Cd induces heme oxygenase enzyme. B-12 affects the monooxygenase system and lipid peroxidation in the liver (Korsova 1989). Folic acid is essential in maintaining methylation reactions. 800mcg are recommended to prevent birth defects.

Lipoic acid, a B vitamin with 2 sulfhydryl groups, protects vitamin C from oxidation. It protects blood vessels from reperfusion injury. Lipoic acid blocks Cd effects in hepatocytes by preventing its uptake (Muller 1989).

carnitine. The initial newborn carnitine level is influenced by maternal carnitine concentrations. Supplemental carnitine can provide a needed nutrient without arachidonic acid, pesticides, or microbial contamination present in commercially produced red meats and dairy products, the best dietary sources of carnitine.

Lysine, a nitrogen containing amino acid, is a precursor for carnitine. If the metabolic pathways are intact, supplemental lysine can enhance the availability of carnitine. Lysine is also beneficial in herpes infections.

Taurine, a sulfur containing amino acid found solely in animal products, is a building block for many amino acids and essential for brain development. Taurine is present in all food from skeletal muscle. Taurine is used in bile formation in the liver and can be converted into methionine and cysteine, two other sulfur-containing amino acids. cysteine is a precursor for glutathione. Methionine is another precursor for carnitine.

Breast milk is the best dietary source of carnitine and an excellent source of taurine. It is also an optimal source of essential amino acids and fatty acids. If the mother is malnourished B vitamins and minerals can be deficient in breast milk.

Essential Fatty Acids. Omega-3 fatty acids are relatively deficient in modern diets (Galland 1988). Fish oils were found to block toxicity of Cd
(Webb 1979). Commercial fish are sometimes contaminated with pesticides. Farm raised fish are low in omega-3 fatty acids. Fatty acids are subject to oxidation making them toxic. Deep ocean fish and carefully produced and stored omega-3 fatty acids from flaxseed or rape seed (canola oil) or marine fish oil are important nutrients for blocking Cd toxic effects. 1 t of cod liver oil a day or 1 T of flaxseed oil is a reasonable supplement for children. Evening primrose oil (EPO) is high in gamma linolenic acid and is very helpful for children with allergies. It can be applied to the skin. A dose of 5001500 mg of EPO is appropriate for children.

Herbal Medicines. Garlic is an

effective blocker of Cd toxicity (Cha 1987). Garlic contains both Se and germanium (Ge) which can detoxify Cd. Ge is found in many healing
herbs used throughout the world such as ginseng, shelf fungus, comfrey, aloe and chlorella (Kidd 1987).

Since the effects of Cd are multiple and non-specific it is not surprising that herbal medicines that can block its effects have a broad spectrum of effects making them essentially panaceas. By having different mixtures of minerals and flavonoids, certain herbs are more effective than others in achieving the balance necessary for homeostasis in particular individuals. Herbalists take these variations into account (Brooke 1992).

There should be a careful study of the mineral content of herbs and the effects of these complex mixtures on such aspects as cell adhesion, lipid peroxidation, and DNA repair in cell cultures subjected to some form of stress plus Cd. This might clarify the molecular basis of their actions, facilitating their appropriate use.

Implications for Public Policy

Public Policy. The atmosphere is a thin envelope which makes the world into a global village. There are no boundaries to air pollution carried by long distance transport. All governments need to act to protect the atmosphere from toxic Cd and chemical air pollution. Emphasis needs to placed on Cd, since it is the most toxic metal in air. As both the first and second messenger of the stress response, it is synergistically toxic with all other

stressors, including many other toxic substances. Biological monitoring with bacteria, lichens, newborn hair levels, or gonadal levels in animals, is more reliable than filters in current use. Elimination of Pb and its replacement with added benzene in gasoline appears to have increased the toxicity of atmospheric Cd but a return to leaded gasoline is not necessarily the answer either since ingested Pb increases Cd absorption.

A broad plan is needed encompassing agriculture, chemical and petroleum industries, manufacturing, and all components of the health industry, especially health education. The effect of these activities on Cd and chemical air pollution needs to be determined and efforts directed to stopping pollution at the source.

There is a growing demand for the use of pseudomonads to breakdown toxic organic compounds. A biological filter using pseudomonads, would concentrate Cd in the organisms, as well. These organisms need to be harvested carefully, so that the Cd can be recycled into useful metals, preventing its release into air where it can have toxic effects. In open areas, those engineered to breakdown hazardous compounds, might be engineered to exclude Cd, so that if they get into the atmosphere they would not be as hazardous. It is possible that certain algae could be used to extract Cd metal from waste waters and stack emissions. Governments could subsidize a scientific agriculture using soil microbes to absorb Cd and "friendly"

microbes to help plants absorb essential nutrients.

By withdrawing subsidies for tobacco and stressful dairy/ meat production, governments would encourage better food choices by allowing these products to become more expensive. Instead subsidies could be given for organic farming, which is quite labor intensive, so that the prices of these healthier foods would fall. By imposing a tax on food and drink of low nutritive value with unhealthy concentrations of nonnutritive chemicals, alcohol, sugar, salt, and fat, governments would obtain more funds to pay for health care, and economic pressures would favor better food choices.

The incidence of smoking needs to go to zero. Factors which could promote this include 1) a high tax on cigarettes, 2) mandatory early education programs in schools to discourage cigarette use, as well as drug and alcohol use, and 3) more emphasis on helping individuals to stop smoking.

An immediate health tax on gasoline, pesticides, lawn chemicals, and toxic stack emissions could be used to reduce their production, or use, and to fund care for those afflicted by them. In 1989 an estimated 864 million kg of toxic organic chemicals were emitted into the air and 434 million kg of pesticides were used in the United States (US EPA 1991, Pimental 1991).

World action to stop the loss of rain forests and wetlands is needed whether it affects Cd or not. Perhaps by recognizing the health benefits of

their protection, the world governments will act more quickly and effectively to save them. It is impossible to reconstruct a rain forest once it has been destroyed. The healing traditions of the indigenous peoples living in rain forests need to be carefully studied as well.

Medical Research. Exposing the world to Cd air pollution is like opening Pandora's box of ills. It will take good science, addressing chaos and complexity, to understand this stress agent and prevent catastrophe.

Cd can be suspected of playing a role in all problems that have been increasing: from respiratory failure in children infected with hantavirus to common allergic sinusitis and asthma.

The new hantavirus carried in the deer mouse, causing adult respiratory distress syndrome, has received recent attention because of its high mortality. It could carry Cd to the lung, producing a toxic effect. If the LDH is elevated, these patients need zinc. N-acetyl-cysteine could increase glutathione levels and pantothenic acid might promote healing, as well as vitamins A & D, and magnesium. Although hantavirus is often associated with kidney disease, the kidneys would be spared if the injury is due to Cd and there is no selenium deficiency in the affected patients.

The deer mouse had a sudden increase in population (Stone 1993), a blastogenic effect from Cd, but currently their numbers have suddenly decreased, a toxic effect of Cd. The Cd levels in deer mouse gonads could be analyzed.

Since Cd acts as a stress agent, biological monitoring of Cd levels in pineal, pituitary, adrenal, and gonadal tissue would be appropriate in patients and species of concern showing sudden increases or decreases.

With Cd there are so many modifying variables and dynamic factors that could influence outcomes, that multiple single subject studies are needed to obtain useful information. This is the proper basis for both clinical medicine and environmental toxicology.

If all research facilities addressed the effects of stress, Cd exposure, and nutrient depletion on the disease processes they were funded to study, much could be learned to help clinicians understand and treat disease.

Sophisticated technology can be used to identify Cd's actions. NMR studies of crabs exposed to Cd show an increase in T2 in the hepatopancreas from an increase in free water (Brouwer 1992). Kopp studied changes in energy with 31P NMR in the perfused heart (Kopp 1986). Mg deficits were found in the brain with 31P NMR as well (Altura 1992).

By exposing dispersed cancer cells to varying concentrations of Cd and evaluating their viability in 24 hours, it should be possible to identify Cd sensitivity or resistance before the administration of radiation or chemotherapy, which might aggravate the condition of patients with resistant tumors. Cd effects on gene expression, such as over-expression of the MT gene or heat shock protein 60

can be used to identify Cd resistance in cancer cells using immunological stains.

Cd could be used therapeutically in cancer treatments to induce apoptosis in Cd sensitive tumors. Anti-sense oligonucleotides complimentary to the messenger RNA coding for MT-II increased the sensitivity of neuroblastoma cells to Cd (Iversen 1992). High doses of vitamin C eliminate plasmids in bacteria which confer cadmium resistance. It is possible that high doses of vitamin C could make cancer cells Cd sensitive as well.

Cd can be used therapeutically in gene therapy to incorporate plasmids and promote gene expression. These attributes could be used in new gene therapies to restore the very malfunctions it may have caused.

Summary:

The young are particularly vulnerable to the stress effects of cadmium and chemical air pollution. Like canaries in a mine shaft, newborn babies of non-smoking mothers, salmon fry, and frog embryos are alerting the world community to the threat of Cd and chemical air pollution. By causing nutrient deficiency, Cd increases reactivity to all stressors at the cellular, vascular, and organ level, affecting all disease.

Birth defects, prematurity, and stress induced physical and mental illnesses are taking their toll on children throughout the world. Eliminating the exposure of children to cigarette smoke and Cd and

chemical water and air pollution will improve health. By incorporating the positive features of traditional medicines with a scientific, molecular basis of understanding disease, physicians can improve patient care by recognizing and treating nutritional deficiencies induced by Cd.

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Table 1.

Sources of Cadmium Air Pollution

Indoors

3. Cigarette smoke
4. House dust, bioconcentration
5. Molds, bioconcentration

Outdoors

3. Waste Incineration
4. Smelters, other industrial processes
5. Fossil fuel combustion
6. Traffic Fumes
7. Fertilizers
8. Dust
9. Volcanoes, forest fires, sea sprays
10. ? loss of wetlands and rainforests

Table 2.

Cellular Effects

Gene Effects

3. Deletion of suppressor genes
4. Alters gene expression
3. Inters with DNA repair
3. Blastogenesis
4. Oncogeneis: increase c-mye, c-jun
5. Apoptosis: anti-cancer effect

Signalling Effects

3. Cell surface Cd receptor, PLC
4. Blocks CaATPase, increasing intracellular Ca2+
5. Through PKC increases NF-kB
6. Calmodulin effects
7. Prostaglandin E2

Ion Channels

3. Voltage sensitive Ca channel
4. Na-H transporter, D-glucose
5. Ca sensitive Cl channel, muscarinic AcCh
6. Ca dependent K channel

Functional Effects

3. Psycho -Neuro- Immune -endocrine modulation
4.

Inflammation and fibrosis

3. Bone resorption
4. Lipid peroxidation
3 Smooth muscle spasm
4 Edema formation
1 Hormonal Effects

Morphologic Effects
1. Blebs, increased volume
2. Changes in pseudopods
3. Accumulation of lipid, myelin bodies
1. Increased golgi
2. Increased free ribosomes
1. Toxic effects on mitochondria

Interruption of Tight Junctions
1. In kidney: proteinuria
2. In liver: cholestasis, injury
3. In respiratory tract: cough, injury
4. In GI tract: leaky gut: decreased nutrient transfer
5. In vascular bed: decreased nutrient transfer, interruption of blood brain barrier, metastases
6. In skin: injury, rash
7. In placenta: decreased nutrient transfer

Nutritional Deficiencies
1. Vit C, E, D, A, K,
2. Mg, K, Zn, Ca, Cu, Se, Fe, Mn, Cr, I
1. B-complex
2. Essential fatty acids

Table 3.

Protective Strategies

1. Clean air
2. Clean water
3. Nutrient dense unprocessed food
4. Stress reduction
   mild exercise
   Increased self-esteem Conflict resolution
5. Endogenous opiates
6. Nutritional supplements based on individual need