The Toxicity of Cadmium Air Pollution: A Reappraisal

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ABSTRACT

Cadmium, a ubiquitous air pollutant, is increasing in the environment. However, toxicity concerns regarding cadmium are restricted to exposure by ingestion primarily. By re-examining existing assumptions in the light of known cellular actions of cadmium, one can recognize that exposure by air is far more potent and affects all life forms around the globe. By over-emphasizing cadmium accumulation levels, scientists are missing the biologic effects of this highly mobile metal with multiple effects. By altering cell controls affecting weather and temperature, one can hypothesize that cadmium profoundly affects the environment. Cadmium, which concentrates in tobacco leaves and dust, induces stress and enhances stress responses producing injuries in genetically susceptible cells, tissues, organs, or organisms in a variety of ways. Other heavy metals, radon, asbestos, magnetic fields, toxic organics and microbials, which are known to react synergistically with cadmium, have similar effects. By comparing the attributes of a disease like AIDS and the attributes of cadmium in experimental studies, it is possible to build a case for studying and treating this disease as one in which a synergistic effect is occurring between HIV-1 and cadmium. By acting as a biochemical link in psychosomatic processes, cadmium alone and together with other injurious agents can produce the varied injuries associated with disease. Since blocking cadmium solubility in air, supplying depleted nutrients, blocking cell entry or solubility in tissues, and safely promoting cadmium excretion are appropriate ways of treating illness associated with cadmium, the hypothesize that the global bioavailability of cadmium air pollution is having an effect on the environment and human disease needs immediate attention.

Key Words: Cadmium. Air Pollution. Cigarette smoke. HIV-1. Psychoneuroimmunology

INTRODUCTION

The public is concerned about dioxins, pesticides, lead, mercury, asbestos, radon, low level magnetic fields, acid rain, ozone depletion, and global warming. The public is also concerned about the AIDS epidemic, substance abuse and the violence associated with it, cancer, dementia, and other health problems. There are increasing reports of peculiar illnesses associated with fatigue and chronic yeast infections that flourish in immuno-compromised individuals. TB, syphilis, plague, and leprosy--diseases of impaired cellular immunity, that we thought had vanished from our industrial societies--are coming back in small pockets of our land.

With close to 1 in 3 persons likely to experience cancer, 1 in 5 couples infertile, 80% of menstruating women suffering from premenstrual syndrome, and 50% of the world's trees showing pollution damage, it is prudent to consider a pollutant that can be linked to all these problems. The pollutant, scarcely known to the general public, which has the unique qualities to be that key is cadmium.

Cadmium is a very unusual toxic substance contaminating our environment, (Webb, 1979, Mislin and Ravera, 1986, Venugopal and Luckey, 1978). Under certain conditions in animal studies, cadmium leads to cancer, immune suppression, hypertension, and multiple organ failure or dysfunction (Webb, 1979, Foulkes, 1986). After over 50 years of study, scientists know it can be toxic to plants, animals, and humans; but the customary models cannot prove low dose effects. The literature on experimental effects is full of contradictions (Foulkes, 1986). It is abundantly clear in experimental studies that cadmium has many effects because of its bioavailability and similar diameter to calcium and sodium.

A Reappraisal of Assumptions

Recent studies regarding cadmium have shown that existing assumptions that have guided epidemiologic and toxicologic investigations of cadmium toxicity, need to be re-examined and replaced with models that fit the data. These assumptions will be discussed and then a new hypothesis will be presented. This will be followed by a discussion of the sources of cadmium air pollution, with particular emphasis on the cycling of cadmium through the global biomass and its concentration in dust as a significant route of human exposure. Because cadmium has so many effects at a cell level beyond cytotoxicity, these actions will be discussed in the next section. Finally, the hypothesis will be used to consider the possible effects of bioavailable cadmium on the environment and the effects of cadmium on human health. A special discussion of the links between cadmium and the illness AIDS is provided to demonstrate how this hypothesis can be tested using the revised assumptions.

Air versus Food Exposure. Certain assumptions appear to have dominated the thinking about cadmium, limiting the investigation of alternative hypotheses. The first assumption is that the most important source of cadmium exposure is food. Cadmium is a rather volatile substance. Kopp (1986) suggests that the reason for the contradictions in experimental studies on cadmium-induced hypertension may be due to the high rate of hypertension in control animals. This in turn could be explained by a significant air exposure to cadmium in the control animals.

This author has found that 14 month old control animals in a behavioral study of cadmium had elevated levels of hair cadmium and marked variability in weight and organ pathology (unpublished study). The dust in the room where the animals were kept contained 18.9ppm cadmium 9 months after the start of the study while the dust in the breeding room contained 8ppm. This data suggests that volatile cadmium, coming from cadmium treated animal excretions, exposed all animals in the study through inhalation of cadmium concentrated in dust.

Since little attention has been given to the cycling of cadmium in air, it is useful to consider what mechanisms are possible. In a recent study of the effects of sludge application on land (Page et al., 1983), there was no consideration of the possibility that the loss of cadmium from the land could be exposing animals and humans through accumulation in inhaled dust. Studies have shown that 40% of cadmium applied to the land "disappears" (Mislin and Ravera, 1986).

There appears to be little appreciation of the observation made by Beauford et al. (1977) that both cadmium and zinc are transpired from plants into the air. Sludges are being applied to forests (Cole et al., 1983). Because of the acidic soil in forests, the vegetation can be expected to pick up cadmium, a significant contaminant of sludge, and transpire it into the air where it can become very widely dispersed.

The forms in which cadmium travels in air are not known. Both sulfur and nitrogen gases are associated with cadmium (Glooshenko et al., 1988, Mislin and Ravera, 1986). But cadmium is known to accumulate in primitive organisms or bind to their surfaces. Just as radon enters houses in soil microorganisms that concentrate radon daughters, cadmium, which is present in the same phosphors that contain uranium, may also enter homes by this route. Cadmium also becomes concentrated in microorganisms in soil (Kurek et al., 1982).

In-door air concentrates pollutants whose sources are outside. A mechanism that may be responsible for this concentration could be their bioconcentration in dust, a complex substance that is about 60% biological. One of the many substances that could concentrate pollutants is chitin. Chitin in the tiny mites that are the cause of dust allergies is a nitrogen containing polysaccharide which may have an affinity for cadmium. Keratin in hair and spider webs, which is high in cysteine, concentrates cadmium, mercury and lead. Cadmium, but not lead and mercury, has a high affinity for

many of the toxic organics of concern, especially those that contain chlorides such as dioxins. It is necessary to study the impact of environmental pollution sources on housedust to learn about their effects on human health.

Because cadmium is highly concentrated in tobacco leaves, the most important source of indoor air cadmium is cigarette smoke. Cadmium binds to B-12 and does not become methylated like lead and mercury. For this reason lead and mercury can be transferred easily to the fetus but not cadmium which is retained with B-12 in the placenta. The effect of maternal cadmium on the fetus is the induction of fetal mineral deficiency which can have long lasting effects on behavior and development. Passive smoke exposure of infants and children who are generally mineral deficient and absorb toxic metals easily is a very important source of cadmium exposure. Both active and passive smoke exposure need to be considered throughout life to appreciate exposure to this air pollutant.

Dose Response. It is customary to assume in risk assessment that an increasing dose will have an increasing effect. By using doses higher than would be encountered in the ambient environment, it is expected that the risks of exposure can be identified and by extrapolation the effects of lower dose exposure can be estimated. This is another assumption worth questioning. In a study of toxic effects of cadmium on rainbow trout there was no correlation between body concentration and occurrence of mortality (Pascoe, 1986).

Recently, 10nM of cadmium was found to dissolve bone. But 1uM cadmium had only half the effect (Bhattacharyya et al., 1988). Cadmium does not fit the dose response model. Normally one looks for a difference in mean values to show significance. In a study of cadmium effects on natural killer cells, cadmium increased the variability in activation four fold; but, since the mean values were unchanged, its effect was judged insignificant (Stacey et al., 1988). In a rat study, looking at behavior, investigators at Ohio State University found that increasing doses of cadmium did not change the mean values of escape latency in swimming trials. However, increased cadmium did increase the number of perturbations in the data (Wieber, Hothersall, Stewart-Pinkham, unpublished data, see Figure 1). A factor that increases variability with increasing levels is a chaos factor (Gleick, 1987). This behavior needs to be taken into account in designing studies of effects.

Specificity of Response. A common assumption in cadmium risk assessment is that the target organ is the kidney. In fact, all cells, tissues, organs, and organisms which lack protective mechanisms because of genetic factors, nutritional factors, or chronic stress induced by other environmental exposures are subject to injury. While lead has been linked with all disease (US EPA, 1986), cadmium is biochemically capable of causing all disease.

Thresholds. Because of its well documented toxicity in water, thresholds have been established for cadmium in drinking water of 5 ppb. There are controls on levels allowed on land and dumped into water. The level that causes alteration of calcium in the cell membrane is anything above 1 nanomole (Verbost et al., 1989). Effects on daphnia can be found at 1.79 ppb. Toxic effects on fish can be seen at 3.4 ppb. Higher levels are not necessarily more toxic. Cadmium at sublethal doses blocks a later lethal dose.

Correlational studies of cadmium content in soil with human health effects have not been fruitful (Morgan, 1988). It is the bioavailability of cadmium in soil that appears to determine its toxicity to the environment and to human health. Environmental bioavailability is determined by such factors as pH, chlorides, zinc, lead, selenium, iodine, calcium and magnesium.

Risk Assessment. The assumption is made that the way to determine risk assessment is to do large epidemiologic studies to measure exposure, isolating the effects of other confounding variables, in order to prove the specific effect of a variable. Or experimental studies with different doses are done to determine a safe level of exposure. Consistency across studies and a preponderance of evidence are used as additional criteria.

These assumptions are not safe guidelines to use with a chaos factor that increases variability and shows such striking individual differences within species. Moreover, the pollution of the environment is mixed. Many agents of concern are ubiquitous. The lead studies are flawed by a failure to consider the influence of cadmium on elevations in blood lead levels. The studies of low level magnetic fields have also failed to consider effects on cadmium uptake and toxicity. Increased magnetic fields produced by solar flares are associated with lower levels of selenium containing glutathione peroxidase enzyme in red blood cells (Braven and Fisher, 1988), a toxic effect associated with cadmium since cadmium forms an insoluble precipitate with selenium reducing its availability.

It would be a mistake to fail to consider a possible synergy with dioxins which are also ubiquitous and have complex and variable effects. There are very few studies of synergistic effects of cadmium with toxic organics. Those that have been done show impressive increases in toxicity at doses that individually are non-toxic in the system (Stacey, 1987, Khanna et al., 1988).

Environmental Monitoring. Cadmium is volatile (Webb, 1979, Foulkes, 1986). For this reason, one must question why no special technique has been used for measuring cadmium in air, although special techniques are used for zinc, mercury, selenium, and arsenic (US EPA, Municipal Waste Incineration Study, 1987).

It is unwise to assume that low levels of cadmium in air, soil, or vegetation reflect in any way emissions or human exposure. A seven-fold reduction in measured air cadmium (0.0044ug/m^3 in 1981 to 0.0006ug/m^3 in 1986) occurred in Columbus, Ohio (National Aerometric Databank, personal communication Ohio EPA) in the face of rising emissions from a large municipal waste incineration which starting operating in 1983 (Lisk, 1988).

It is, however, possible to determine environmental exposure through biological monitoring. In the United States and Canada, Glooschenko et al. (1988) found increasing levels of cadmium in deer and moose liver and kidneys, especially in environments affected by acid rain.

The advantage of biological monitoring lies in its reflection of multiple environmental processes that affect bioavailability. Levels of acids and chlorides (which increase cadmium solubility), and levels of lead and zinc (which decrease solubility), are pertinent measurable factors that contribute to the actual biologic effects. Lead levels in air have dramatically fallen with the elimination of leaded gasoline (Ohio Air Quality Control, 1986). Zinc levels as monitored in lichens, have also fallen in the last decade (Showman and Hendricks, 1989). The cause of this decline is not known but it possible to hypothesize that cadmium bioavailability could be a cause and that the resulting decrease would increase cadmium toxicity.

Human Monitoring. Using the assumption that the kidney is the target organ, monitoring has been focused on blood cadmium, urine cadmium, hair cadmium, and beta 2 microglobulinuria. All of these factors are correlated to some degree with certain kinds of kidney injury induced by cadmium. Since low dose cadmium in experimental situations does not significantly influence these parameters they are inadequate for assessing cadmium toxicity.

Instead of looking at cadmium accumulation or a single parameter like beta 2 microglobulinuria, it is more productive to consider the possibility that multiple effects are possible in different cells, tissues, and organs in different individuals. Depletion of vitamins and minerals are often found in animal studies. In view of the great variability in response to cadmium, the deviation of any value from the mean found in individuals free of disease with no evidence of stress may provide a realistic guide to biochemical effects occurring in an individual induced by cadmium exposure or stress-induced cadmium release in tissues. Although this approach does not allow one to isolate the effects of cadmium alone, in reality it is much more relevant to assess the synergistic effects, recognizing that an impact on the process may be possible by altering the bioavailability of cadmium.

Cadmium accumulation in biological material generally reflects the presence of metal binding mechanisms which have been induced by exposure. Cadmium levels are elevated in lung cancer and prostate cancer. Cancers induced by benzo[a]pyrene show elevated levels of cadmium (Venugopal and Luckey, 1978). Analysis of highly malignant tumors for cadmium may be a practical way of monitoring cadmium exposure in humans.

A New Hypothesis

By modifying assumptions that are inapplicable in studying cadmium, it is possible to propose and test a new hypothesis regarding the environmental and human health effects of cadmium air pollution. The hypothesis is as follows: Cadmium air pollution is ubiquitous. Its biologic impact is determined by other factors in the environment that affect its mobility and bioavailability. These factors may include magnetic fields and presence of substances that render cadmium insoluble like lead, zinc, selenium, iodine, and calcium. A variety of calcium channel blockers, may block ionic entrance into the cell. By binding to organics, hormones, and microbials, cadmium has access to the cell interior by alternate routes. Multiple defenses protect cells, tissues, organs, and individuals from the toxic effects of free intracellular cadmium. These defenses include metallothionein, glutathione, various binding proteins, and other substances. Cadmium is a stress agent and enhances the response to other environmental stresses-- psychosocial, physical and chemical. Genetic factors, nutritional deficiencies, co-exposure to other toxic agents, and chronic stress predispose particular individuals to harmful effects. These effects can be detected by looking for deviations from mean values of a variety of parameters. By changing atmospheric solubility, supplying deficient nutrients, and bolstering detoxification systems, it is possible to block harmful effects of cadmium on the environment and on human health and partially block the effects of other environmental agents of concern whose effects are augmented by its involvement.

Sources of Cadmium Air Pollution

In considering this hypothesis that cadmium is involved in all problems, it is essential to understand how cadmium moves through the environment and concentrates in in-door air. In a building with cigarette smokers the most important source of cadmium picked up by filters is cigarette smoke. In a building that lacks this exposure, environmental factors affecting bioavailability influence the levels found in dust. What are these factors?

Cadmium becomes a troublesome pollutant when it enters air, water, or soil in a freely moving form. Such movement can occur during production, use, or disposal of cadmium containing products. When garbage, which on the average contains 12 ug/g cadmium, is burned in municipal waste incineration plants, 30% of the cadmium fumes elude electrostatic precipitators polluting the total environment.

Burning coal, oil, and wood pollutes air, water, and soil with different amounts of cadmium. As industrialization increases and the population grows, so does cadmium pollution. Acid and chlorides, which also pollute the environment, free cadmium to move into plants, humans, and animals. In them cadmium can concentrate or move on.

Atmospheric scientists consider trash-burning fumes the most important source of air cadmium in the USA (Mislin and Ravera, 1986). Traffic--with tires, electroplated metal parts, and gasoline as sources of cadmium fumes--is also an important source. The levels of cadmium in leaves of Toronto's urban plants have increased forty times since 1910. Traffic

is considered a major source of the pollution (Mislin and Ravera, 1986).

It is impossible to make sharp distinctions between natural and anthropogenic sources. Volcanoes and ocean spray are natural sources. Release of cadmium in forest fires and transpiration of cadmium from plants are definitely affected by human caused pollution.

All settings--rural, suburban, and urban--have significant sources of air cadmium. Blown dirt, fertilizers, brush fires, home incineration, and wood fires are sources of suburban and rural cadmium fumes.

Cadmium does not settle out around emission sources. In Denmark, 70% of the cadmium deposited on the soil comes from 200 miles away or more (Mislin and Ravera, 1986). Obviously, cadmium pollution is a global problem.

Cellular Toxicity

Around the globe cadmium is capable of moving into cells of all kinds. To understand its effects on the earth as a whole or on human health, it is necessary to understand the many effects occurring in the individual cell. With cadmium, accumulation is not associated with toxicity. Free cadmium ions are causing problems in plasma membranes at 1.6nM (Verbost et al., 1987). The effects associated with low level pulsating magnetic fields mimic those of cadmium (Brodeur, 1989). Since both are ubiquitous it is necessary to consider them both rather than try to tease out the effects of either alone. Hormones enhance cadmium uptake in certain tissues in higher life forms. Dioxins, which are also ubiquitous, may act as carriers for cadmium across certain membranes. Cadmium has a potential for complexing with many kinds of substances identified as dangerous.

Cellular Chaos. Cadmium has two opposing effects. Cadmium enters rapidly growing cells readily. It is present in high concentrations in rapidly growing cancer cells and in algae blooms in the ocean. By altering cell controls it can actually increase growth in these instances; however, in mature cells, it produces free radical induced injury and premature aging.

It is through low continuous exposure from air pollution that cadmium can have the most devastating effect. It is uniquely damaging at very low dose to the lining cells of the trachea (Lag and Hegeland, 1987). At low continuous exposure of the single cell amoeba, cadmium changes cell controls, nutrient uptake, and can modify the genes through mutation. The effects on the amoeba depend on previous nutrition and differ from those of all other toxic agents (Webb, 1979).

Communication Effects. In addition to being an injurious agent, cadmium has profound effects on cell functions by affecting gene expression and influencing the level of free cytosol calcium. It changes in many ways the systems used in intra and inter cell communications (Verbost et al., 1987). A key source of cell communication is the calcium ion. By having the same diameter, cadmium (but not mercury or lead) can slide into slots where calcium belongs, changing the communications. Moreover, cadmium can both increase and decrease the entry of calcium into cells. Blockade of the calcium channel protects cells against cadmium toxicity (Hinkle et al., 1987). But cadmium itself at doses of about 1-10 uM acts as a calcium channel blocker, thereby decreasing its own toxicity. By understanding these biochemical actions, one can better comprehend why cadmium fits the chaos model. It does so by being the factor which biochemically increases variability.

Trace Metal Effects. No other metal pollutant can cross cell membranes as well as cadmium at very low dose levels. Bound to the cell surface or multiple sites inside, it has profound effects on other metal ions. Although a cytotoxic and genotoxic agent, cadmium has an effect at low dose exposure by changing the levels of other trace minerals that control cell functions without inducing direct cell injury. Viruses are also known to have this effect (Oldstone, 1989). Cadmium has a synergistic effect with retroviral induced murine leukemia (Blakely, 1987). It is quite possible that other viruses are working synergistically with cadmium in causing both cytopathic and non-cytopathic effects.

Zinc is a vital metal for the nerves, bones, digestion, and the immune system. One of the things that makes cadmium unique is that it lies directly below zinc in the periodic table. Cadmium can displace zinc from enzymes, both poisoning them and changing their properties. Lead is unable to displace zinc but does displace copper. Cadmium can displace both. It alters the effects of far more enzymes than lead or mercury (Vallee and Ulmer, 1972).

Magnesium is the only ion that is able to displace cadmium and lead (Wills, 1985). Unfortunately, chronic exposure to cadmium by producing stress leads to magnesium losses in both plants and animals. Thus, chronic cadmium exposure makes cells very vulnerable to toxic effects from heavy metals.

Cadmium and Cell Energy. By multiple mechanisms, cadmium has a profound effect on cell energy. In animals, by releasing catecholamines, a surge of energy can be experienced.

Cadmium can form an insoluble precipitate with phosphate, a needed substrate for energy transfer in all cells decreasing cell energy. Cadmium has a rapid direct effect on the myocardium depressing cardiac contractility before depleting ATP. P31 NMR studies show a change in inorganic phosphorus with this effect (Kopp et al., 1986). A cadmium toxic effect in hair cells appears to influence hair phosphorus (Stewart-Pinkham, 1989). This effect occurs in children with decreased listening and achievement test scores. Bacteria with zinc and iron deficiencies, conditions that predispose to cadmium uptake, have a five fold increase in insoluble polyphosphates (Winder and O'Hara, 1962). In other bacteria cadmium detoxification is known to involve the formation of insoluble phosphates (Macaskie et al., 1987).

Cadmium also affects the mitochondria and ATP levels with chronic exposure. Although muscle contains very little cadmium compared to liver and kidney, Toury et al. (1985) found profound effects on mitochondria in all three tissues with membrane degradation, direct inhibition of succinic dehydrogenase, and an indirect effect on both mitochondrial and microsomal cytochromes. Glycogen stores were depleted, as well.

Zinc stimulates the production of metallothionein, a metal binding protein which protects mitochondria from cadmium and other heavy metals. By causing zinc deficiency at low-dose chronic exposure, cadmium increases the chances of low cell energy coming from toxic effects. But cadmium also stimulates the production of metallothionein and other protective substances like glucocorticoids, which by binding cadmium and stabilizing membranes prevent cadmium from exerting a toxic effect even though there is a high dose exposure. It is this behavior that leads to an increase in variability.

Cadmium and the Environment

The deterioration of our environment is a serious concern receiving attention around the world. Many scientists are underestimating the effects of cadmium by over-emphasizing cadmium accumulation levels instead of measuring biologic effects. The issue is not how much cadmium there is, but what it does. Cadmium acts as a stress agent in both plants and animals and may in fact mediate the biochemical responses to stress. Small mobile amounts that affect cell controls can have far reaching effects. Large amounts of insoluble cadmium have no effect. Using this hypothesis, how could cadmium's actions affect the environment?

Acid Rain. Cadmium is one of the few metals that forms an acid in water. In water, cadmium poisons our eco-system in several ways. It lowers its life-giving oxygen content by poisoning the plants that make oxygen. It turns the water into acid, not only directly but also indirectly by fostering acid production in living cells. Cadmium binds closely to the sulfur and nitrogen gases generally associated with acid rain (Glooschenko et al., 1988). In a recent review of the effects of acid rain many features were brought out that appear puzzling and contradictory (Huckabee et al. 1989). Although cadmium was not mentioned in the article, the biochemical actions of cadmium provide a reasonable explanation for the complex effects observed. Acid rain increases cadmium levels in tap water but does not elevate human blood cadmium levels, instead selenium levels fall (Svensson et al. 1987).

Ozone. The destruction of the upper ozone layer has been attributed to chlorine gas formed from chloro-fluoro hydrocarbons. Cadmium binds very closely to chlorides and may play a catalytic role in such reactions. In addition to playing a catalytic role, could cadmium form chlorine gas biologically as well? This could occur if microorganisms use $CdCl_2$ as an electron donor in photosynthesis instead of H_20 (Keeton and Gould, 1986). In the lower atmosphere, cadmium oxide can form increased ozone when it reacts with chlorinated air pollutants.

Greenhouse Effect. Atmospheric scientists are increasingly alarmed by the warming trend. They believe it is caused by increased carbon dioxide formed directly from burning fossil fuel. As yet, no one has considered the fact that cadmium--which is emitted from the same sources-- by affecting plant controls, increases the production of carbon dioxide and decreases the production of oxygen (Lamoreaux and Chaney, 1978).

Plants. Cadmium, but not lead and mercury, is significantly taken up by higher plants. Plants, therefore, should be good indicators of cadmium pollution. It is evident that very toxic effects are occurring in trees. World-wide forest damage has been attributed to acid rain and ozone (MacKenzie and El-Ashry, 1988). These affects are likely to involve cadmium. Recent studies show that even at very low levels of cadmium in air as measured by filters, there is significant uptake by young foliage and subsequent translocation to other parts of the plant (Harrison and Chirgawi, 1989).

If plants are deficient in minerals because of cadmium, ozone and acid rain are even more damaging. Cadmium lowers the resistance of plants to these injurious agents and all kinds of diseases precisely because it induces these deficiencies. By both lowering the resistance of plants to toxic agents and infection and also producing the toxic exposure, a small increase in cadmium multiplies into a very large effect.

Cadmium is uniquely linked to reproductive events in plants and animals. Since 1986 the dramatic increase in seeding of trees has become more marked each year (see Figure 2). Seeding in plants, a common stress response, is an expected response to an increase in cyclic CMP (Chan, 1987). This molecule can accumulate with inhibition of pyrimidine-5'-nucleotidase, the enzyme that controls the cell energy supply (Angle and McIntire, 1982). This enzyme can be inhibited by cadmium and restored with zinc and metallothionein. Currently, because seeding is viewed only as a non-specific response to stress, the association with cadmium has not been made.

To understand the effect of cadmium on plants, it is necessary to know the levels of other metals that can block its effects. The decrease in lead air pollution, which in water vapor decreases cadmium solubility and bioavailability, could be part of the explanation for the increased evidence of tree diseases. Lichens, algae, and moss--which flourish in an oxidative acid environment promoted by cadmium--were inhibited by lead emissions but now grow abundantly on the bark of trees in suburbs by busy streets (see Figure 3).

It is important to recognize that cadmium increases variability. It can act as a growth stimulant. Because the forests treated with sludges grew abundantly, the assumption was made that it was well tolerated. Cadmium, as a stress agent, increases auxin and increases gene products regulated by auxin (Hagen et al., 1988). Auxin stimulates the above

ground biomass. It opens the leaf pores so that cadmium vapors can escape preventing accumulation. An imbalance in auxin and abscisic acid results in a decrease in deep root growth and open pores (Keeton and Gould, 1986), making plants affected by cadmium exceptionally sensitive to drought. Because abscicic acid is responsible for cold resistance and auxin is associated with heat resistance, cadmium exposed plants are also more susceptible to cold injury. In the absence of drought, cold, and other stresses, the vegetation may grow luxuriously but have a shortened life span.

Food. Toxicologists consider food the most important human exposure to cadmium. Yet in Sweden, with the lowest intake of cadmium in food and the lowest body burden, there is the highest incidence of prostate cancer (Kjellstrom et al., 1979). The malignancy of prostate cancer is strongly linked to cadmium content (Feustel et al., 1982). One must conclude that cadmium content in food is not necessarily important but cadmium air pollution is important. But the effects of cadmium air pollution on food value rather than cadmium content may be quite important as well.

There are insufficient facts available to evaluate the effects of cadmium air pollution on the nutrient value of food. In a study of sludge effects, attention to cadmium was focused entirely on the accumulation of cadmium in the food (Logan and Chaney, 1983). But by affecting soil pH, soil micro-organisms, and trace metal uptake into plants, cadmium can cause effects indirectly by lowering the nutrient content of food produced in a polluted environment. Processing food further depletes food of nutrients and may even increase cadmium content from the absorption of volatile fumes. Analysis of cadmium in food may be inaccurate using certain digestion procedures (Cabanis et al., 1988) so cadmium accumulations may go unnoted.

Nutritional deficiencies play a vital role in cadmium toxicity (Webb, 1979, Venugopal and Luckey, 1978, Foulke, 1986). The vitamins, minerals, amino acids, essential fatty acids, and fibers in food greatly modify the toxic effect of cadmium exposure coming from the air. Pesticides and herbicides used in agriculture may synergistically react with cadmium to cause negative effects on food nutrients. These issues have not been addressed. Radiation of foods for preservation may also negatively affect essential fatty acids required to resist cadmium toxic effects.

Weather. By influencing the global biomass, cadmium inevitably affects weather. Cadmium's effects on weather go beyond effects on air temperature through global warming. Cadmium easily moves into the upper atmosphere where it can be carried long distances, before coming down in rain. It affects the growth of algae in the ocean. Some estimate of this effect can be determined from studies of the frequency of antibiotic and heavy metal resistance, pigmentation and plasmids in bacteria of the marine air-water interface (Hermansson et al., 1987). This impact in turn affects water and air temperatures in these regions thereby influencing weather systems. By poisoning plant roots, cadmium can harm plants during droughts; when rain finally comes, soil erosion and flooding occur.

Human Cadmium Toxicity

Acute cadmium toxicity is recognized in humans. It causes flu-like symptoms associated with gastrointestinal and respiratory viral illnesses. Chronic toxicity has generally been recognized only in isolated environmentally contaminated areas like Japan and industrially exposed workers where the frequent absence of a dose response effect has obscured the significance of various studies for scientists unfamiliar with the chaos model (Foulkes, 1986).

Using the hypothesis elaborated in this paper, it is clear that cadmium at ambient levels can be expected to have an effect on all disease. It works in synergy with other agents. Stellman et al. (1988) have found that veterans exposed to a dioxin in "agent orange" have a variety of complaints that overlap with ones associated with cadmium effects in animals. Viruses have also been found associated with a variety of problems that are not generally regarded as infectious (Oldstone, 1989).

Three factors are commonly associated with adverse health outcomes: tobacco use, drug and alcohol abuse, and stress. Each of these factors is linked to cadmium. As mentioned previously cadmium is a major pollutant in cigarette smoke and it synergistically increases the toxicity of nickel (Patai et al. 1988) and dimethylnitrosamine (Wade et al. 1987), two other toxic agents in smoke. What has not been considered is that cadmium or other heavy metals that synergistically increase toxicity could also concentrate in leaf products made into abused drugs like marijuana and cocaine. High levels of mercury are present in cannabis growing around volcanoes in Hawaii (personal communication S.M. Siegel). Cadmium combined with mercury and or lead results in increased histopathology in the kidney (Prasada-Rao et al., 1989).

Studies are available about the effects of cadmium and alcohol. Nation et al. (1987) have found that when rats are exposed to cadmium and stress they develop a preference for alcohol over water. Alcohol promotes zinc excretion thereby increasing cadmium toxicity (Nomiyama and Nomiyama, 1986).

Cadmium is considered a classical stress agent because it increases serum catecholamine levels, glucocorticoid levels, and other endocrine and metabolic changes associated with stress agents (Hidalgo and Armario, 1987). But rather than consider cadmium just one stress among many, it is reasonable to hypothesize that cadmium is the biochemical mechanism by which psychosocial stress can result in all disease.

One mechanism linking cadmium and stress in general would be a synergistic effect of cadmium and glucocorticoids on gene control mechanisms responsible for an over-reaction to any stressful stimulus, psychosocial, physical, such as low level magnetic fields, or chemical, such as cocaine or cadmium itself.

The support for this hypothesis is found in the following studies. Emotional stress caused by physical restraint in

rats causes extremely high levels of zinc and metallothioenin to accumulate in the liver (Hidalgo et al., 1986). Cadmium has forty times the affinity as zinc for binding to the steroid binding site on DNA (Freedman et al., 1988). Cadmium has been found to increase 35 fold the protein synthesis and secretion of a gene product (Dickerson, 1987). Glucocorticoids increase cadmium uptake into liver cells and by themselves are not strong stimuli for metallothionein synthesis. The evidence is suggestive that cadmium augments steroid mediated gene expression.

What constitutes proof? Since one cannot show the effect of cadmium on dysfunction by looking at cadmium accumulation, one must look instead at the multiple attributes of an illness and compare them to the attributes of cadmium. If the attributes of the disease closely fit what is known about cadmium in experimental work, one is justified in approaching the study and treatment of the disease as if cadmium is a significant factor. The successful treatment of the illness by 1.compensating for deficiencies induced by cadmium, 2. forming insoluble cadmium complexes with iodine, selenium, or other compounds or 3. fostering its safe excretion with chelating agents would provide additional evidence that cadmium is a causative factor.

To see in some detail how this approach could be used, it is instructive to consider the effects of cadmium on the manifestation of AIDS, an illness associated with all disease--premature aging, multiple cancers, multiple infections, auto-immune disorder, multiple organ failure and death.

Cadmium and HIV-1 Infection. Cadmium is a stress agent. Stress hormones promote the viral replication of HIV-1 (Marhan et al. 1986). Cadmium binds to the tat protein involved in viral replication of HIV-1 (Frankel et al. 1988). Because T cells lack metal binding proteins, they are particularly susceptible to toxic effects of cadmium (Koizumi et al. 1987). T-cells in mice have decreased viability with cadmium exposure (Fuzinaki, 1987). The presence of p24 antigen in blood is highly correlated with beta-2 microglobulins (Jacobson et al. 1989). Increased levels are found in patients with cadmium exposures, viral infections and hematologic malignancies. Imuthiol, sodium diethyldithiocarbamate, an immune modulator, which is also a cadmium chelator, inhibits the progression of HIV infection (Caraux et al. 1988). Its clinical effects are similar to zidovudine (AZT), an inhibitor of HIV replication. Susceptibility to cadmium and HIV-1 infection is associated with major histocompatibility antigens (Lawrence, 1985, Jeannet et al. 1989).

Infections. There are several ways that cadmium can contribute to opportunistic infections. By depressing multiple cell nutrients, cadmium impairs cell mediated immunity needed to resist the opportunistic infections that occur in these patients when they become immunocompromised.

Pharikal et al. (1988) considers vitamin C deficiency a metabolic marker of a cadmium toxic effect. Other nutrients depleted by cadmium and stress such as B-12, zinc, selenium, and vitamin E may be important as well (Beisel, 1981). B-12 deficiency is associated with increased susceptibility to TB, a disease of impaired cellular immunity (Chanarin and Stephenson, 1988). Lethal pneumocystis carinii pneumonia, the most common cause of death in AIDS patients, is associated with markedly elevated lactate dehydrogenase enzyme (Lipman et al. 1988). This enzyme is readily released from the liver in the presence of zinc deficiency and cadmium toxicity (Nomiyama and Nomiyama, 1986).

Cadmium in the low dose released by stress may act as a growth stimulant for the bacteria, fungi and protozoa that cause infections by promoting a favorable environment. Virulence may be associated with cadmium resistance of these organisms. Bacterial plasmids associated with heavy metal and antibiotic resistance control cell membrane pumps that extrude cadmium, as well as other heavy metals (Silver et al. 1989). In a study of mycobacterium avium, plasmids were associated with virulent strains (Fry et al. 1986). When incubated with 1 mM of sodium ascorbate, penicillin resistant staphylococcal aureus lost their plasmids and their penicillin resistance (Amabile-Cuevas, 1988)

Endocrine Disorders. Cadmium can cause multiple endocrine abnormalities. Primary hypogonadism is found in 70% of male patients with AIDS with low testosterone levels (Croxson et al., 1988). Testicular toxicity is a very common cadmium effect at doses that do not produce liver or kidney toxicity in animals. In toads, cadmium inhibits testosterone synthesis by inhibiting 17-beta hydroxysteroid dehydrogenase (Gosh et al. 1987). At higher doses cadmium causes hemorrhagic necrosis by affecting blood vessels resulting in ischemia.

Neuropathy. The effects of cadmium on the brain (Gulati et al. 1987) are very similar to experimental models of neuropathy caused by B-12 deficiency (Metz et al. 1987). Multiple neurological problems compatible with changes found with B-12 deficiency (Lindenbaum et al. 1988) are described in patients with HIV infection (Dalakas et al. 1989).

Birth Defects. An embryo toxic effect has been described for HIV infection involving facial features. Important viral cadmium interactions enhancing aberrations in rat embryo cells have been described by Zaskhina et al. (1977). The effects of cadmium are on the facial prominences in hamster embryos (Gale and Horner, 1987).

Dilated cardiomyopathy is associated with cadmium toxicity (Smetana et al. 1987) and HIV infection (Himelman et al. 1989). It is possible to go on and on finding a parallel between every finding associated with HIV with a finding of cadmium in animal studies. If one abandons the inapplicable criteria for proof that have dominated toxicology, the evidence is compelling that cadmium, a known immunosuppressant, and HIV virus together are responsible for AIDS. Sodium N-benzyl-N-dithiocarboxyl-D-glucamine is an excellent safe chelator for cadmium in animals (Jones et al. 1988). This and many other non-toxic strategies could be used in binding and inactivating cadmium to prevent the progression of this disease.

Cadmium and Disease Mechanisms

What about the other illnesses that are of concern? It is possible to show that key disease mechanisms are indeed associated with cadmium toxic effects. A central event in the sick cell is the development of increased free cytosol calcium. This occurs at levels just above 1 nanomole of cadmium through competitive inhibition with calcium for the calcium ATPase pump (Verbost et al., 1989). Cadmium has 1,000 times the affinity for the site. Many other cell mechanisms are involved as well.

Auto-immune Effects. Auto-immune toxic agents bind to cell surface sulfhydryl groups and promote oxidation. Cadmium and mercury (but not lead) have these properties (Lawrence, 1985). Low dose exposure to cadmium induces anti-nuclear antibodies in mice (Ohsawa et al., 1988). This disease process is associated with the production of leukotrienes which produce inflammation. These substances have a tripetide composed of gamma-glutamylcysteinylglycine. The tripeptide by itself is glutathione, one of the first lines of defense against toxic effects of all kinds. Poly(gammaglutamylcysteinyl)glycine is associated with cadmium resistance in plant cells (Jackson et al. 1987). Currently, unidentified environmental factors are considered to be the inciting agents in human auto-immune diseases.

Free Radicals. Free radicals are identified in many human disease processes. Low levels of cadmium in tissue (<1.0ug/g) can result in dramatic reductions in the anti-oxidant defense system (Jamall and Sprowls, 1987). Low levels of superoxide dismutase and increased lipid peroxide levels were found by Shukla et al. (1987) in different areas of brain with cadmium administration.

Carcinogensis. Multiple factors affect carcinogenesis. Genetic mutations, failure of DNA repair, changes in microsomal enzymes, changes in intracellular calcium, changes in plasma membranes, changes in basement membranes are effects observed in carcinogenesis (Flamm and Lorenten, 1985). Radon, asbestos, and toxic organics are associated with increased cancer risk. But the carcinogenicity of these agents are all increased with cigarette smoke, a very important source of cadmium air pollution.

All the effects associated with carcinogensis are associated with cadmium. The substitution of cadmium and other mutagenic agents like nickel or cobalt at the zinc coordination site in the finger loop domains is considered a mechanism for metal carcinogensis (Sunderman and Barber, 1988). Nocentini (1987) found that cadmium impaired DNA repair and that zinc had a protective influence. Selenium, an effective cadmium blocker, blocks chemical carcinogensis (Ip, 1981). Cadmium has been shown in several studies to influence intracellular calcium, plasma membranes, and basement membranes. The resistance of cancers to anti-tumor agents such as adriamycin is associated with the development of metallothionein, making them cadmium resistant (Imura et al. 1989).

Reproductive and Endocrine Effects. Cadmium concentrates in endocrine organs and causes both benign and malignant tumors in these tissues (Webb, 1979). As mentioned above cadmium is toxic to the testicle. It is also toxic to the prepubertal ovary. The result of these two effects is infertility. Cadmium is very toxic to pregnant animals, inducing a stress that could lead to miscarriages or fetal damage without accumulating in the fetus. By causing rapid sexual maturation and affecting pituitary mechanisms, increased fertility can also be expected. The opposing effects would result in no change in birth rate. An increase in endocrine tumors in animals and reproductive failure in humans was found with low level pulsating magnetic fields (Brodeur, 1989). It is very reasonable to consider the possibility that cadmium effects could explain the potency of magnetic fields.

Cadmium affects males and females differently. In women the cadmium content of the adrenal at autopsy is five times that of males (Takac & Tatar, 1987). It is possible that adrenal insufficiency from a cadmium toxic effect on the adrenal gland is responsible in part for chronic fatigue syndrome. Estrogen affects the uptake of cadmium into cells (Nishiyama et al. 1988). Hormone fluctuations in the non-pregnant state could play a role in premenstrual syndrome. The increase in breast cancer recently noted in young women taking birth control pills deserves careful attention with respect to synergistic effects of estrogen and cadmium on breast cancer.

Birth Defects. There has been a dramatic increase in birth defects in the last 15 years (CDC, Congenital Malformations Surveillance, 1988). The birth defects that are increasing are identical to ones produced with cadmium and with zinc deficiency (Keen and Hurley, 1987), an expected effect of chronic low dose cadmium exposure with or without alcohol which induces zinc deficiency, a possible basis for fetal alcohol syndrome. Pregnant women with a fetal neural tube defect had significantly lower leukocyte concentrations of zinc and selenium (Hinks et al., 1989).

Nutritional Deficiencies. Nutritional surveys identify several nutrient deficiencies in various populations. Consideration has not been given to the possibility that various deficiencies could be induced by cadmium toxic effects. The marked variability in response of individuals to cadmium may reflect the marked variability in need for nutrients. Not only is the necessary daily allowance of nutrients variable for different individuals, but it varies in the individual. Exposure to a pollutant like cadmium exaggerates the variable need.

Hypertension is a condition easily produced in certain animals under specific dietary conditions with chronic low dose exposure (0.1-1ppm) to cadmium (Tomera and Harakal, 1988, Schroeder et al., 1965, Perry amd Erlanger, 1974). So it is interesting that Salonen et al. (1988) recently found lower levels of vitamin C, selenium, and linolenic acid in adults with higher blood pressure readings. Low dietary calcium and zinc levels were found in individuals with hypertension by Harlan et al. (1985). All these nutrients are depleted by cadmium and /or protective against cadmium toxicity.

Implications

Studying an air pollutant that moves and doesn't settle out around a point source is difficult. It is possible to measure emissions with some accuracy and measure substances like acids that increase mobility and substances like lead, zinc, selenium, and iodine that decrease mobility. But by looking for significant correlations between accumulation of cadmium and toxic effects, the world's scientists have overlooked the actions of cadmium.

Using a new hypothesis--that the presence of multiple nutrient deficiencies or free radical injury caused by cadmium, in the presence of environmental exposure or stress-induced mobilization of cadmium from stores, indicate cadmium toxic effects--it is possible to identify low dose cadmium toxic effects with environmental decline and disease processes. This hypothesis has major implications for the study and treatment of disease. Support for this hypothesis lies in its congruence with observations that have already been made. The hypothesis suggests that many more observations need to be obtained that have not been considered because of limiting assumptions.

Cadmium is not necessarily and often not solely the responsible agent. Viruses, dioxins, and low level magnetic fields have been found to have effects indistinguishable from cadmium. These interactions need to be studied. By studying the interactions of cadmium, magnetic fields, organics, and infectious agents, it may be possible to understand disease processes and identify persons at risk and block toxic effects in those individuals affected. Cadmium also increases the carcinogenicity of such agents as radon and asbestos. This hypothesis needs further study in order to arrive at cost-effective solutions to environmental problems.

Further studies are urgently needed to explore the implications of this hypothesis in diseases such as HIV infection and cancer. By recognizing that acids and chlorides have far more potent affects than contributing to acid rain and ozone depletion, environmental control may be implemented more rapidly and more effectively.

The world is like an organism. Changes in the atmosphere are being observed by astronauts. The role of the bioavailability of cadmium in the atmosphere in creating these changes needs serious consideration by all individuals concerned about environmental impacts and human disease.

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Figures:

Figure 1. Escape latency of Long Evans male rats fed varying amounts of cadmium in drinking water. An increase in environmental exposure to cadmium is associated with increased pertubations.

Figure 2. The marked increase in seeding of trees is a likely effect of a "fertility" substance that increases when cadmium inhibits the enzyme pyrimidine-5'-nucleotidase, the same enzyme that controls the cell energy supply in animals.

Figure 3. Lichens grow abundantly in environments with low lead and slightly higher cadmium. By lowering host resistance, cadmium makes trees become susceptible to drought and disease of various kinds. Acid rain enhances the uptake and toxicity of cadmium. Because aluminum accumulates in cells from a cadmium toxic effect and not necessarily cadmium, attention is drawn to aluminum.