Keynote Speech - Frontiers in Trace Element Research

Henry A. Schroeder, M.D.[1]

A very important international symposium on "Trace Elements and Brain Function" was held at the Nassau Inn, Princeton, New Jersey, October 24-26, 1973. Dr. C. Pfeiffer, Program Chairman, in his preamble to the program wrote:

"The most challenging area of medical research for the last decade has been the area of neurophysiology, especially that which pertains to the neuropathology seen in psychiatry. A group of pioneers in this field have found that biochemical mechanisms can explain many of the functions and malfunctions of the central nervous system. Imbalances of trace element metabolism and altered function of metalloenzymes have been found in the schizophrenias, the epilepsies, and hypoglycemia. The goal of this meeting shall be to bring together those actively working in this field to answer questions which have been previously posed and to formulate the questions for tomorrow's research. A secondary goal shall be to call attention to the wealth of data demonstrating the importance of trace element metabolism in normal brain function. Since mental illness is still the most prevalent medical disorder today, the knowledge that can be obtained from this meeting and its research will affect our society and its medical care in the future."

We are pleased to publish in our Journal Over the next few issues some of the papers which were presented.

The keynote speech was delivered by Henry A. Schroeder, M.D., a long-time pioneer in the field relating trace elements to human nutrition.

A. Hoffer, M.D., Ph.D. Managing Editor

Dr. Pfeiffer, Dean Gordon, Members of the Symposium, Guests, Ladies and Gentlemen:

I am highly honored to be invited to give the keynote speech at this symposium, although this honor must be shared with Dr. Tipton. She gave this subject a sound and basic start by discovering what trace elements were in the body and where, which varied geographically round the world and which did not, and which ones accumulated with age, by analyzing 40 organs and tissues of over 400 human subjects for 36 elements, some 600,000 analyses. Her monumental work will not soon be repeated, if ever.

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This symposium may be a milestone in the field of trace elements, and it is about time it happened. We have been intrigued for many years with the overt effects of certain metals on the nervous system when accumulated in large amounts: copper in Wilson's disease, manganese toxicity showing Parkinsonism, lithium in manic states, mercury in erethism, alkyl mercury in cerebral deterioration, alkyl lead and tin, and lead poisoning. Overt toxicity, however, is not an all-or-none phenomenon; it is always preceded by recondite toxicity which may go unrecognized under a variety of symptoms. Is it possible that some of the common diseases of the brain, the major psychoses for example; are examples of recondite metallic toxicity or deficiency in predisposed individuals? Or some of the rarer hereditary diseases, such as amyotrophic lateral sclerosis and myotonia?

It is my purpose tonight to try to point out the potentials for discovery in several disciplines in which trace elements are involved.

Biochemistry

Twenty years ago I was discussing this subject with a biochemist who was also a Nobel Laureate. She advised me not to study in this field, as there were over a thousand enzymes known and only a very few were metalloenzymes or were metal-activated. Today there are many, and the list is increasing annually as analytical techniques and indices of suspicion improve. I must admit, however, that only 16 zinc enzymes, 12 copper, 16 cobalt, 20 manganese, one chromium, four molybdenum, 30 iron enzymes, one selenium enzyme, and no vanadium or nickel enzymes have been found in the mammalian body up to now. Undoubtedly there are more, considering the body burdens of some of these catalytic elements. Magnesium activates about a hundred, mostly for ATP or ADP energy exchanges. There are a great many enzyme inhibitors involving metals, and eight elements specifically antagonistic to essential ones. This subject requires further exploration.

Microbiology

All primitive organisms require manganese, iron, copper, zinc, and some need boron, cobalt, molybdenum, and vanadium. Many antibiotic drugs are chelating agents. Could the action of some antibiotics be due to binding an essential metal in a strong chelate?

Isoniazid —isonicotinic acid hydra-zide— and its derivative marsalid act on the tubercle bacillus to bind copper at the membrane, probably making it unavailable for growth of the organism. Penicillin is a metal-binding agent. So are a number of other potent antibiotics. To my knowledge, Eugene Weinberg was the first to study this possibility. Although most antimicrobials are chelating agents, not all chelating agents are antimicrobial. Not all have the requisite structures to penetrate the cell to reach the enzymes involved in growth. Furthermore, when a chelating drug is antibiotic, its action can often be suppressed by excess of the metal bound. Tetracycline is inhibited by iron and magnesium on both gram-negative and gram-positive bacteria.

Weinberg also showed that the amount of a metal, manganese, sufficient for growth and reproduction of a bacteria was not sufficient for optimal function, in this case production of an antibiotic. Weinberg's Principal can be applied to all living things, including mammals; that is, optimal function or health depends on adequate supplies of trace elements, and marginal supplies are accompanied by ill-health.

All of the common antitubercular drugs appear to bind copper and are inhibited by an excess of copper in the environment. Likewise, all of the antibacterial agents are involved in chelation, in one way or another. The metalloenzymes within the cells which are bound are not known.

Host-parasite reactions are influenced by trace metal imbalances, be they viral, bacterial, or mycotic, in plants and animals. Penetration of viruses into host

cells is mediated by the divalent cations magnesium and calcium or, in some cases, by strontium, barium, or manganese. Zinc and iron are necessary for virus synthesis, and the level of zinc is critical. In fungal infections too much zinc enhances growth, and zinc-binding agents are used topically to control skin infections. 8-hydroxyquinoline was used in World War II to mould-proof jungle equipment. Eight known bacterial toxins act through metal ions; iron, calcium, cobalt, or zinc are necessary for such toxins as anthrax, plague, diphtheria, and infections by **E. coli,** an anaerobe, a mould, and two plant pathogens. Defense of the host against a number of infectious agents is usually increased by iron and decreased by copper or, in some cases, manganese or cobalt. Cobalt has been reported to increase immunity.

This is a fertile field, but today most medical students are unaware of it.

Pharmacology

A great many ordinary drugs are chelating agents. In 1954, I spent several hours with John Bailar, going through the Merck Index and listing probable metal-binding agents from their formulae. It was most intriguing to match chelating strengths of drugs with their late and bizarre side effects, such as collagen disorders, liver damage, arthritis, leucopenia, and anemia. This property appears in **some** people when any synthetic drug is given for long periods of time. It has not been described in patients given naturally occurring substances chronically, such as digitalis, quinine, morphine, cocaine, ephedrine, hormones from animals, and plant extractives. Hydralazine disease, which mimics lupus erythematosus, is prevented and reversed in animals by manganese. The monoamine oxidase inhibitors in general share the ability to bind copper, and it is theoretically possible that evidence of collagenous abnormalities and even medial degeneration of the aorta with rupture might result from long term copper depletion resulting from their use; such changes are seen in turkeys depleted of copper. Copper is necessary for the integrity of elastin.

We do not understand the mechanisms of late toxic reactions to drugs, but they deserve "scrutiny from this viewpoint.

A biguanide used as an oral antidiabetic agent binds trivalent chromium with a log K2 of 12.02; another has 13.95. Data on the other three oral agents are lacking. Could it be that these agents act by mobilizing chromium from tissue stores and releasing it at the site of action, much as aspirin transports copper from blood to cells?

I have long wanted to team up with someone like Martell and give him a list of active drugs so that he might determine stability constants on the essential metals. We all know that no chelating agent is specific for one metal. What all of us do not realize is that the introduction of a chelating drug into the body results in a competition of the agent with metals bound to enzymes and other proteins more or less tightly. EDTA causes an outpouring of zinc —and has caused acute zinc deficiency in large doses—although copper and nickel are more tightly bound by it. Obviously zinc in tissues is available for chelation and other metals less so. The Perrys showed this 14 years ago. However, knowledge of binding strength of drugs might pinpoint mode of actions. "Chelating Agents," published by the Chemical Society of London, is irritatingly deficient in what one wants to know about drugs.

Medicine

The startling revelation that all antihypertensive agents not acting on nerves were metal-binding was what started us in the trace element field in 1951; that and an abstract of Isabel Tipton's reporting large amounts of cadmium in the average American kidney. These drugs were azide, thiocyanate, nitroprusside, and we added hydralazine, BAL, and EDTA—a weakly-acting drug. Many years later we discovered that cadmium given to rats in doses larger than 0.1 ppm in the diet

elevated blood pressures and in larger amounts produced the clinical picture of hypertension; that human beings dying of hypertension had increased amounts of cadmium or an increased ratio of cadmium to zinc in their kidneys; and in rats with cadmium hypertension removal of some of the cadmium reversed the hypertension. Removal was accomplished by finding a chelating agent with a higher affinity for cadmium than for zinc, loading it with zinc and injecting it. This material, sodium zinc cyclohexane diamino-tetraacetic acid, is almost unique as it has a stability constant for cadmium of 19.88 (log K2), and for zinc of 19.32, which are probably higher than those binding- some cadmium in the body. We believe that this agent removes cadmium from blood vessels, leaving zinc; we know that it removes some cadmium from kidney and liver. It has had limited success in man, is nontoxic, and is ideal for lead poisoning. Thus one serious disease, moderate hypertension, of which 23 million Americans suffer, has been defined by discovery of the action of an abnormal trace metal. The human data have been confirmed and cadmium has also produced hypertension in rabbits and dogs. As a side-light, all commercial laboratory feeds contain cadmium, and it is likely that all experiments on hypertension begin with animals having a slight degree of cadmium hypertension. Normal blood pressure of our cadmium-deficient rats is about 82 mm Hg.

Atherosclerosis is a disease involving plaques in the arteries, elevated circulating cholesterol, and decreased glucose tolerance (but not necessarily overt diabetes). Deficiency of chromium has reproduced this disease in rats, and it is prevented by dietary chromium Chromium is necessary for both glucose and lipid metabolism and will lower serum cholesterol even in rats fed cholesterol. A large majority of Americans, but not foreigners, have low levels of chromium in their tissues, and some are deficient. Those dying of coronary occlusion —atherosclerotic heart disease—had virtually no chromium in their aortas. Feeding patients chromium has restored glucose tolerance and lowered blood cholesterol in about half the subjects. The active form of chromium, a low molecular weight complex called the glucose tolerance factor, has not been synthesized or obtained pure, although we have been waiting eight years for it. When it is found, it will probably be active in atherosclerosis, which most Americans have and half die of. Just why it is so slow in coming remains a mystery, with all the enormous sums spent on much less important research.

This glucose-tolerance factor may turn out to be important in the control of adult onset diabetes, although chromium salts are not. We have given chromic acetate and other forms of chromium to a small group of diabetics for five years. Each time we started it, glucose tolerance fell for six weeks or more, then rose to its previous level. Inconstant effects were also observed on serum cholesterol. The ability of the body to make the glucose-tolerance factor is limited and is probably absent in diabetics. This is a potentially rich field for exploration for glucose mobilizes chromium, and if sugars contain none, chromium is lost in the urine.

The American diet is marginal or deficient in chromium, as this metal is largely removed from grains, fats, and sugar by refining. It is also marginal in zinc. In institutional diets from 28 cities, Murthy has analyzed for zinc and cadmium. In every city but one, the mean intake of dietary zinc was much less than the new F.D.A. Recommended Daily Allowance, or 15 mg, being 7-11 mg, and in only a few cases do the maximal levels found approach or exceed that figure of 15 mg. We have yet to find a diet with 15 mg of zinc, although some of Tipton's diets approached or exceeded that amount. One can conclude that institutionalized patients are likely to have marginal levels of zinc. When we know that 80 percent of the zinc is removed from the grain and 98 percent

from sugar during refining, and that alcohol has no zinc, we can see that our major sources of energy are zinc deficient.

Zinc deficiency has the following known results:

1. Slow growth. Zinc is required for synthesis of DNA, RNA, and protein.
2. Slow wound healing. Post-traumatic and postoperative patients get no zinc. Probably delayed healing of fractures.
3. Lowered tolerance to alcohol (probable). Alcohol dehydrogenase is a zinc enzyme. Probably cirrhosis of the liver.
4. Tendency to infections. Unhealthy animals and plants have poor defenses.
5. Tendency to high blood pressure. Zinc interferes with absorption of cadmium.

Oral zinc therapy represents a major therapeutic breakthrough in ischemic vascular disease. Zinc dilates the blood vessels distal to an atherosclerotic plaque, and circulation in a leg can be restored at a local blood pressure so low as to make surgeons reach for their saws. Even gangrene is no longer an indication for mandatory amputation. The action is rapid, a few weeks. I have seen ischemic cyanosis of the toes disappear and pulses return in three days after zinc therapy was begun. Zinc is often a miracle drug in Berger's disease. Reynaud's disease and even angina pectoris may respond to zinc. It heals indolent ulcers of the legs. It* probably acts on blood vessels by displacing cadmium, which is a constrictive agent.

Zinc also restores the sense of smell and taste in hyposmia and hypogeusia. It can be useful in intestinal malabsorption.

We must emphasize that low zinc aids cadmium absorption. And that cadmium, once in the body, may never leave it.

Among the other cadmium-zinc disorders is probably pulmonary emphysema which is associated with pulmonary hypertension. Cigarette tobacco contains about 1 ppm cadmium, and the burning tobacco is hotter than the boiling point of cadmium. A pack a day may provide 2-4 ug to the body burden of 38 mg. In time this adds up to a lot, 33 mg in 30 years. Cadmium workers lose their sense of smell and taste and suffer from emphysema. They are not hypertensive as a rule for a little cadmium is hypertensive but a lot is not, causing renal damage.

Hereditary copper- and iron-storage diseases are well known and need not be described. Cotzias and we have long toyed with the idea that hereditary manganism resulting in Parkinson's disease may exist, for poisoned miners show Parkinsonism. This has not been proven; it requires extensive analysis of several areas of the brain. Manganese deficiency may exist in man for other mammals require much larger amounts than man gets, perhaps 10 to 25 times as much. Manganese may be involved in glucose metabolism. These aspects deserve study.

Two metals have recently been discovered to be essential for mammals, vanadium and nickel. Their actions deserve study.

Lead is everywhere in this modern society. Each year the average car spews out 2 kg of lead from its exhaust into the environment. Whereas lead is not highly toxic, like cadmium, the enormous amounts around make it so. It is in road dust and house dust and street dirt — and in the glaciers of North Greenland. Children get it not so much from eating lead-based paint as from sucking their dirty fingers, toys, and dropped lollipops. At present, one-quarter of several hundred thousand children tested and living in cities have blood levels at the borderline of toxicity.

Although overt toxicity in children occurs—several hundred cases a year in New York City—with the well-known result of brain damage, convulsions, and sometimes death, as with all toxins there are large areas of subclinical toxicity, if we were only to look for them. One such is hyperactivity, so common in the classroom, for which amphetamines, strangely enough, are used with good

results. Another is found in institutions for retarded children, where a certain proportion have had lead poisoning, often undetected. Likely enough, some slow learners have it. Much work remains to be done, but prevention involves removing lead from gasoline and giving up our jack-rabbit starts.

The adult disease has not been described, although 5 percent of men and 2 percent of women have higher blood levels of lead than considered safe. Nervousness, irritability, fatigue, and headaches are well-known symptoms of automobile drivers. This syndrome needs describing.

The results of feeding each of 31 elements in low doses to thousands of rats and mice for life have shown the following to be toxic in respect to growth, life span, longevity, cancers, and pathological lesions as well as reproductive abnormalities. Very toxic: Selenite, methyl mercury (5 ppm). Toxic: cadmium, lead, beryllium (in dusts), antimony. Slightly toxic: germanium, tin, titanium, scandium, gallium, yttrium, indium, tellurite, barium, tungsten, chromium (VI). Nontoxic: vanadium (essential), chromium III (essential), nickel (essential), zirconium, niobium, molybdenum (essential), fluorine, arsen ic, aluminum, boron, tellurate, inorganic mercury. Carcinogenic: selenate (strong), rhodium and palladium (weak). These studies are nearly finished.

The elements which accumulate with age in man are: titanium, aluminum, chromium in lungs, arsenic, probably selenium, cadmium, tin, beryllium, and lead. Titanium and aluminum are natural air contaminants. The large subject of the geochemistry of disease is hazy and ill-defined.

Soft drinking water in cities is associated with higher death rates from arteriosclerotic heart disease than is hard water. This association holds in the United States, Great Britain, Canada, Sweden, the Netherlands, and South America. We have recently evaluated this Water Factor by a statistical analysis of 35 constituents or qualities of municipal water in 94 U.S. cities. Langelier's Index of Corrosion stood out, the more corrosive the water, the higher was the death rate. No trace metal measured was especially important. We believe that the toxic metal comes from the pipes in houses, dissolved by soft water standing overnight and being ingested with the morning coffee. It is probably cadmium or antimony, or some contaminant of pipes and solders. In England, people living in soft water areas had higher blood pressures, higher blood cholesterol levels, and higher resting heart rates than did people drinking hard water; the British are recommending that cities with soft water harden it. This subject deserves further study.

Ophthalmology

What is the function of the large amount of zinc, 7-12 percent in the tapetum lucidum of the vertebrate eye? What is the function of the large amount of copper, barium, and strontium in the choroid and iris? They must have some physiological action.

Obstetrics

The developing and growing fetus demands essential elements from the tissues of the mother and may deplete her of chromium, manganese, iron, copper, and zinc. Therefore, pregnant women need luxus quantities of trace elements in their diets.

Pediatrics

The growing child needs proportionately more trace elements for good nutrition than does the adult. Although born with concentrations larger than adults, they are depleted within a few years.

Surgery

As no zinc is fed to postoperative, burned, and traumatized patients on intravenous fluids, and as trauma causes urinary losses of zinc, healing is probably slowed in most cases. Attention to this

little detail could shorten convalescence.

Orthopedics

Bone healing is probably increased by zinc, and again convalescence might be shortened by feeding zinc and perhaps other essential metals.

Gerontology

Most of us will come under this specialty eventually, and there is evidence that deficiency of chromium and zinc is widespread in the aged; perhaps manganese also. Attention to nutrition in terms not only of vitamins but of essential trace elements should be paid in these days of refined foods.

Geotropism

I will now present a flyer for your intellectual amusement. Why plants and trees grow up against gravity and their roots grow down is because of geotropism, a descriptive word. The answer may be found in the work of Lounamaa. The abundant heavy elements, manganese, copper, and zinc are concentrated in the roots, whereas the lighter elements, boron and magnesium, are concentrated in the leaves and twigs. This theory deserves study.

I have given you a sketchy summation of this relatively new discipline. I wish I could be with you. Pandora's Box is open. The rest is up to you. . As Fuller Albright used to say, "Much more remains to be done than has been done "