Metabolism of Trace Metals in Man

Volume I
Developmental Aspects

Editors

Owen M. Rennert, M. D.

Wai-Yee Chan, Ph. D.

Metabolism of Trace Metals in Man

Volume I
Developmental Aspects

Editors

Owen M. Rennert, M.D.
Wai-Yee Chan, Ph.D.
Department of Pediatrics
University of Oklahoma
Health Sciences Center
Oklahoma City, Oklahoma

CRC Press, Inc.
Boca Raton, Florida

Library of Congress Cataloging in Publication Data

Main entry under title:

Metabolism of trace elements in man.

Bibliography: p.
Includes index.
1. Trace elements—Metabolism—Age factors.
2. Trace elements—Metabolism—Genetic aspects.
3. Trace elements—Metabolism—Disorders. I. Rennert,
Owen M. II. Chan, Wai-Yee. [DNLM: 1. Trace elements—
Metabolism. Qu 130 M5871]
QP534.M47 1983 616.3' 99 83-2704
ISBN 0-8493-5798-5 (v. 1)
ISBN 0-8493-5799-3 (v. 2)

Direct all inquiries to CRC Press, Inc., 2000 Corporate Blvd., N.W., Boca Raton, Florida, 33431.

International Standard Book Number 0-8493 5798-5 (Volume I)
International Standard Book Number 0-8493-5799-3 (Volume II)
Library of Congress Card Number 83-2704
Printed in the United States

PREFACE

The importance of trace metals in human health and normal development is receiving more and more attention. As a consequence of advancement in analytical techniques and sophisticated instrumentation in the past two decades, there has been a rapid expansion in biomedical research on trace elements. An increasing number of trace elements have been found to be essential for life processes. Pronounced alterations in trace metal concentrations in tissues or body fluids have been frequently observed in response to certain clinical conditions such as infection, stress, malignant diseases, hormonal changes, etc. Changes in trace metabolism during development are gradually being investigated and identified. Teratogenic effects of specific deficiency or excesses of trace metal are becoming an increasing concern to developmental biologist and pediatricians. New human and animal mutants with abnormal metal metabolism have been reported in recent years. The study of trace metals no longer constitutes a small subdivision in nutrition. Its importance is significant to modern nutritionists, biochemists, molecular biologists, developmental biologists, geneticists, environmental scientists, pediatricians and other clinical disciplines.

A vast literature exists dealing with trace metals and a number of outstanding monographs deal with the biological, biochemical, or clinical effects of a specific trace metal or trace metals in general. However, newer aspects of trace metal research, i.e. the developmental aspects and genetic implications, have not been systematically discussed in any existing texts. The present two volumes will summarize the present status of research in these areas and serve as milestones for future development in these areas of trace metal research.

THE EDITORS

Owen M. Rennert, M.D., is Professor and Head of the Department of Pediatrics, Chief of the Section of Genetics, Endocrinology, and Metabolism, Professor, Department of Biochemistry and Molecular Biology, and Director of the Program in Human Genetics in the Departments of Biochemistry and Molecular Biology and Pediatrics at the University of Oklahoma Health Sciences Center, Oklahoma City. Dr. Rennert is also Chief of the Pediatric Service of the Oklahoma Children's Memorial Hospital, Oklahoma City.

Dr. Rennert received his M.S. (Biochemistry) and M.D. from the University of Chicago. He completed his internship and residency and a postdoctoral fellowship in biochemistry at the University of Chicago as well.

During his military service, from 1964 to 1966, Dr. Rennert was a Senior Surgeon with the U.S. Public Health Service and concurrently held the position of Research and Clinical Associate at the NINDB, NIH, Section of Pediatric Neurology of the Public Health Service, Bethesda, Maryland. Returning to the University of Chicago in 1966, Dr. Rennert worked as an Instructor and as Chief Resident (1966 to 1967) and as an Assistant Professor (1967 to 1968) in the Department of Pediatrics. From 1968 to 1977, Dr. Rennert was on the faculty of the University of Florida College of Medicine, Gainesville, in the Departments of Pediatrics, Biochemistry, and Neuroscience, and from 1970 to 1978 was Head of the Institutional Division of Genetics, Endocrinology, and Metabolism and Director of the Sunland Training Center. Dr. Rennert has been in his current position since 1977.

Dr. Rennert is active in numerous professional societies whose interests include clinical research, pediatrics, and biochemistry and has served as Chairman, Co-Chairman, and Recorder at conferences of the Cystic Fibrosis Foundation, the American Association of Clinical Scientists, the Society for Pediatric Research, the American Pediatric Society, and the Gordon Conference on Polyamines. He was Vice-President Elect of the American Association of Clinical Scientists in 1980, and is currently on the Editorial Boards of the *American Journal of Clinical Research* and *Annals of Clinical and Laboratory Science.*

Dr. Rennert has contributed to over 200 publications. His current research interests include growth and differentiation in humans, the role of trace metals in growth and differentiation, and the fundamental processes by which trace metals affect growth and differentiation in humans.

Wai-Yee Chan, Ph.D., is an Associate Professor in the Department of Pediatrics and the Department of Biochemistry and Molecular Biology at the University of Oklahoma Health Sciences Center, Oklahoma City. He is also Co-Scientific Director, Trace Metals Laboratory of the State of Oklahoma Teaching Hospitals, and a Consultant in Medical Service to the Veteran's Administration Medical Center, Oklahoma City.

Dr. Chan received his B.Sc. with First Class Honors in Chemistry from the Chinese University of Hong Kong. He received his Ph.D. in Biochemistry from the University of Florida, Gainesville and was a Postdoctoral Fellow in Biochemistry at the University of Oklahoma. Dr. Chan has been affiliated with the University of Oklahoma since 1977.

Dr. Chan is active in numerous professional societies whose interests include clinical research, nutrition, biochemistry, and pediatrics. He is a national committee member of the Council on Pediatrics and the Council on Trace Metals of the American College of Nutrition. In recent years, Dr. Chan has been invited to participate in conferences held by the Cystic Fibrosis Foundation, the NIH, Ross Laboratories, annd the Hospital for Sick Children, Toronto, and has served as the American Delegate to the First U.S.-China Bilateral Conference on Protein in Biology and Medicine and as Coordi-

nator to the Recent Advances in Protein Biochemistry Symposium sponsored by the Chinese University of Hong Kong and the Hong Kong Biochemical Society.

Dr. Chan has contributed to numerous publications in his field of interest and has presented papers to meetings of the American Society of Human Genetics, the Association of Clinical Scientists, the American Pediatric Society, NATO ASI, the Southern Society for Pediatric Research, and the American College of Nutrition. In addition, he has conducted seminars at the University of Florida, the Oklahoma Medical Research Foundation, the University of Oklahoma, the Shanghai Institute of Biochemistry of the Chinese Academy of Science, Shanghai, and the Institute of Basic Medical Science of the Chinese Academy of Medical Science, Beijing.

Dr. Chan's research interests include trace element metabolism in development and diseases, polyamine metabolism in animals, molecular mechanisms of genetic diseases (Menke's Disease, Wilson's Disease, Cystic Fibrosis), lipoprotein metabolism in mammals, and lysosomal hydrolase metabolism.

CONTRIBUTORS

James M. Bates, Jr.
Research Assistant II
Department of Pediatrics
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

Michel Bourel, M.D.
Professeur de Clinique Medicale
Hôpital Pontchaillou
Rennes, France

Wai-Yee Chan, Ph.D.
Associate Professor
Department of Pediatrics
Department of Biochemistry and Molecular Biology
University of Oklahoma Health Sciences Center
Co-Scientific Director
Trace Metals Laboratory
State of Oklahoma Teaching Hospitals
and
Consultant
Medical Service
Veteran's Administration Medical Center
Oklahoma City, Oklahoma

David L. Donaldson, M.D.
Assistant Professor
Department of Pediatrics
University of Oklahoma
Health Sciences Center
Oklahoma Children's Memorial Hospital
State of Oklahoma Teaching Hospitals
Oklahoma City, Oklahoma

Gunther L. Eichhorn, Ph.D.
Chief, Laboratory of Cellular and Molecular Biology
Chief, Inorganic Biochemistry Section

Roland M. Leach, Jr., Ph.D.
Professor of Poultry Science
The Pennsylvania State University
University Park, Pennsylvania
National Institutes of Health
National Institute on Aging
Gerontology Research Center
Baltimore, Maryland

M. Duane Enger, M.D.
Deputy Division Leader
Life Sciences Division
Los Alamos National Laboratory
University of California
Los Alamos, New Mexico

Lawrence C. Erway, Ph.D.
Associate Professor
Biological Sciences
University of Cincinnati
Cincinnati, Ohio

J. K. Griffith, Ph.D.
Genetics Group
Los Alamos National Laboratory
University of California
Los Alamos, New Mexico

Jack Hegenauer, Ph.D.
Associate Research Biologist
Department of Biology
University of California at San Diego
La Jolla, California

C. E. Hildebrand, Ph.D.
Deputy Group Leader
Genetics Group
Los Alamos National Laboratory
University of California
Los Alamos, New Mexico

Nina Horn, Ph.D.
Department of Medical Genetics
John F. Kennedy Institute
Glostrup, Denmark

Jeng M. Hsu, Ph.D., D.V.M.
Medical Research Service
Veterans Administration Medical Center
Bay Pines, Florida

Leslie M. Klevay, M.D., Sc.D.(Hygeine)
Research Medical Officer
Research Leader
USDA-ARS Human Nutrition Research Center
Grand Forks, North Dakota

Max Perlman. M.D.
Clinical Director
Neonatal Division
Hospital for Sick Children
Associate Professor
Department of Pediatrics
University of Toronto
Toronto, Ontario, Canada

Ananda S. Prasad, M.D., Ph.D.
Professor of Medicine
Director, Division of Hematology
Wayne State University School of Medicine
Chief of Hematology
Harper-Grace Hospitals
Detroit, Michigan
and
Veterans Administration Medical Center
Allen Park, Michigan

Owen M. Rennert, M.D.
Professor and Head, Department of Pediatrics
Professor, Department of Molecular Biology and Biochemistry
Head, Division of Genetics, Endocrinology, and Metabolism
University of Oklahoma Health Sciences Center
Chief, Pediatric Services
Oklahoma Children's Memorial Hospital
State of Oklahoma Teaching Hospitals
Oklahoma City, Oklahoma

Paul Saltman, Ph.D.
Professor
Department of Biology
University of California at San Diego
La Jolla, California

D. Cristina Sarale, M.D.
Department of Pediatrics
University of Oklahoma Health Sciences Center
Oklahoma Children's Memorial Hospital
State of Oklahoma Teaching Hospitals
Oklahoma City, Oklahoma

TABLE OF CONTENTS

Volume I

Volume II

Chapter 1

FOR THE WANT OF A NAIL . . . TRACE ELEMENTS IN HEALTH AND DISEASE

Paul Saltman, Jack Hegenauer, and Linda Strause

TABLE OF CONTENTS

I. INTRODUCTION

There is a remarkable biochemical unity to all living systems. Too often we dwell upon their differences, gross and subtle, and neglect to appreciate the coherent chemical patterns of life. The familiar rectilinear displays of the elements of the periodic table hanging in every chemical lecture hall and laboratory are seldom associated with flesh and blood, health and disease. Four elements of the 103 on that chart comprise more than 96% of the weight of our body. Water alone constitutes 65%. The covalent bonding of carbon to hydrogen, oxygen, nitrogen, and to itself forges the endless variety of monomeric and polymeric organic molecules common to all cells.

The next most abundant elements of life are mineral salts, including sodium, calcium, potassium, magnesium, chloride, phosphate, and sulfate. These salts are responsible for the maintenance of osmotic balance, the bioexcitability of the membranes of nerves and muscles, and the architectural integrity of skeleton and cells. Thus, 11 of the first 30 elements in the periodic table account for more than 99.9% of the composition of our body. As for the want of a nail, the fabled battle was lost, so, literally and figuratively, for the want of trace amounts of iron, copper, zinc, manganese, cobalt, chromium, selenium, silicon, nickel, molybdenum, iodine, and fluorine, life would not be possible.

As their classification implies, the amounts of these metal ions required by our bodies are extraordinarily small. Their concentrations are measured in parts per million (ppm) or even at times in parts per billion (ppb). These trace elements are absolutely required for proper growth and development of our bodies. The scarcity of any single trace element can lead to major impairment of physiological function, usually characterized by unique and specific lesions but frequently only by slow weight gain, malformation of various tissues and organs, shorter lifespan, and other nonspecific problems. Some elements are present in low concentrations in our body but appear to play no specific biological role. It is difficult to show a specific biochemical activity for aluminum, scandium, or titanium, even though they are relatively abundant on the crust of the earth and are always present in tissue.

If excess amounts of trace elements are ingested and assimilated, serious toxicity can develop. The most critical region is that where insufficient amounts of the metal are in the diet. A hypothetical biological response to increasing concentration of an essential element is represented in Figure 1. There is a broad range over which maximum response is observed. The body seems to integrate the various parameters of uptake, storage, and excretion to provide a metal buffer. When the buffer capacity is exceeded, serious illness may result. It is very difficult to ascertain what are "normal", "necessary", or "optimal" amounts of trace elements present either in various tissues or in our diets. By combining several techniques and criteria, reasonable values can be determined.

Many reviews of trace elements have appeared recently.[1-3] These tend to be rather like "taxonomic treatises" in that they describe each of the essential elements, the amounts required, and their biological roles in plants and humans. Our review concentrates on the metabolism of iron as an example of an essential trace element with which we have had extensive experience. As we examine various aspects of trace elements in general, we will look at iron in particular and also cite parallel experiments for other trace elements which reinforce the unifying concepts that we believe provide the foundation for understanding trace element metabolism.

II. BIOLOGICAL ROLES OF TRACE ELEMENTS

Trace elements play three essential biochemical roles. In close association with enzymes, some metal ions are an integral part of the catalytic centers that carry out the reactions of biological chemistry. Working in concert with the protein and frequently with other organic

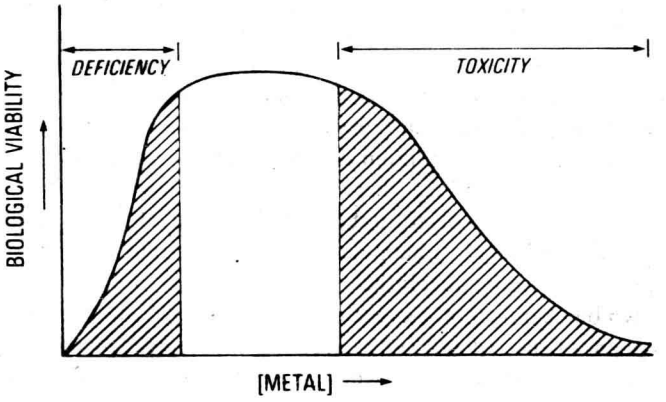

FIGURE 1. Dose response curve for a typical trace element. The biological viability can refer to one or more measures of growth, development, and metabolism. Concentration of metal is in arbitrary units and will vary widely depending upon which metal is investigated and the biological activity being monitored.

coenzymes, the metal attracts the substrate molecule and facilitates its conversion to a specific end product. A second function of some metal ions is to donate or accept electrons in reactions of reduction or oxidation. Such redox systems are an intimate feature of the generation and utilization of metabolic energy by the "burning" of foods in our cells. Chemical transformations of molecules frequently involve redox reactions. The third mode of action of some metal ions is to bind, transport, and release oxygen.

A. Metalloenzymes

Zinc has now been associated with over 90 different enzyme reactions involving carbohydrate metabolism, lipids, and the synthesis of proteins and nucleic acids. Not only does zinc function as a proton donor at the active center, but also serves as a bridging atom linking the substrate to its enzyme. Some zinc atoms are known to impart stability and three dimensional structure to enzymes and their subunits. Manganese is an essential factor for enzymes of carbohydrate and amino acid metabolism. Of particular interest is its participation in the transglycosylation reactions for the synthesis of polysaccharides of connective tissue.

B. Redox Reactions

With a few exceptions, enzymes have iron as part of the active center if they are involved in redox reactions. The participation of iron in the enzyme aconitase, a key step in respiration via the Krebs cycle, is significant. Histidine decarboxylase converts this amino acid to histamine in an iron mediated reaction. In all redox reactions, iron shuttles back and forth between its oxidized and reduced forms, Fe^{3+} and Fe^{2+}, respectively. Iron in biological systems is primarily responsible for the generation of metabolic energy through the oxidative respiration of mitochondria. Both cytochromes and nonheme iron proteins participate directly in the linkage of electron transport to ATP synthesis within the cells. Some biochemical pathways require iron to shuttle electrons, activate oxygen, and substitute hydroxyl groups in the synthesis of essential intermediates.

Copper is in many respects analogous to iron in its redox reactions. There is a facile equilibrium between the oxidized, Cu^{2+}, and the reduced form, Cu^{1+}. In a cooperative mechanism, copper functions with the iron of cytochrome a_3, the critical terminal step in the aerobic electron transport system of mitochondria. Several hydroxylation and oxidation reactions are copper mediated. The Cu-containing enzyme tyrosinase is responsible for

synthesizing the black skin and hair pigment, melanin, by hydroxylation and oxidation of tyrosine. Therefore, the color of some sheep wool can be correlated directly with the copper status of the animal. Lysyl oxidase is involved in the cross-linking and strengthening of collagen and elastin. In the absence of copper, major defects are observed in heart muscle, vascular tissue, and the organic matrix of bone which in turn leads to skeletal abnormalities.[4] The importance of copper enzymes in brain metabolism has been shown for many species. For example, the inability to coordinate nerve and muscle (ataxia) has been linked with a lower level of copper enzymes involved in the synthesis of myelin, the insulating sheath of nerve cells. Copper is necessary to maintain proper concentrations of bioamines such as dopamine, epinephrine, and norepinephrine.

There is no known biochemical redox reaction involving zinc, although zinc is apparently a structural component of the red cell superoxide dismutase. Manganese is an integral part of the superoxide dismutase of the liver, whose activity in preventing oxidative damage to cells by the oxidative free radical called superoxide is under investigation.

C. Transport and Release of Oxygen

The most familiar form of iron is hemoglobin. Its remarkable properties allow it to bind, carry, and release molecular oxygen from the surface of our lungs through the blood and capillaries to all tissues. The chemical properties of iron in heme permit facile association or dissociation of oxygen depending on the concentrations of oxygen and carbon dioxide in the tissues. A functionally equivalent oxygen-binding protein called myoglobin is found abundantly within muscle cells. Myoglobin accepts oxygen delivered by the hemoglobin and brings it into the tissue where it ultimately interacts with the last enzymes in the electron transport system of the mitochondria. A recent experiment has shown that if myoglobin is selectively inhibited in isolated gastrocnemius muscle of the dog, a correlation between muscle performance and the amount of oxygen-binding protein present can be demonstrated.[5]

Oxygen transport and exchange is carried out by invertebrates using the copper protein, hemocyanin. This bright blue respiratory pigment provides O_2 exchange from circulation to tissues. No trace elements other than iron and copper have been related to oxygen transport. Zinc, however, is an integral part of the enzyme carbonic anhydrase, which facilitates gas exchange in blood and tissues by forming dissolved carbonic acid from gaseous carbon dioxide and water.

III. FACTORS REGULATING TRACE ELEMENT METABOLISM

We can simplify our study of the biochemistry and physiology of the trace elements by considering eight categories which describe the management of each element by the body:

1. Availability: In what form is the metal present in the environment and how much is in the diet?
2. Solubility: Is the metal soluble as it passes through the stomach and intestine? Can it form soluble organic complexes?
3. Permeability: Can the metal ion or its organic complex pass the intestinal and other cell membranes? Is its passage regulated? How?
4. Ligand exchange: How rapidly does the metal ion exchange its ligands from one chemical group to another, from a small complex to a protein? Is the metal chemically reactive?
5. Transport: How is the metal carried by the blood to various parts of the body? Bound to a specific protein? As a low molecular weight chelate? As a free ion?
6. Assimilation: What reactions are involved in various cells? Where does the metal ultimately manifest its biological activity? How does the metal become incorporated into the active site of an enzyme?

7. Storage: Can the body "stockpile" the metal as a reserve to be called out when needed? Are there mechanisms to prevent toxicity by removing the metal from a reactive environment?
8. Excretion: Is the excess metal eliminated from the body in the urine, feces, sweat, or by other means?

A. Availability

It is difficult to determine trace metal requirements for humans. Chemical analysis of these elements in cells and tissues led early investigators to correlate diet, deficiency states, and pathological conditions. Frodisch in 1830 demonstrated that the iron content of blood from anemic patients was lower than normal. Purified diets lacking specified elements were fed to rats, mice, and other animals to produce the unique spectrum of pathological conditions that we now recognize as deficiency syndromes. Such investigations recognized the essentiality of iron, copper, zinc, manganese, and many other metal ions. At the same time, many nutritional disorders of natural origin were observed in man and livestock. Both deficiency and excess of various metals under "normal" environmental conditions produced serious health problems and economic losses. Judicious supplementation of the missing metals either to soil or to food resulted in full recoveries. The present state of knowledge is made possible by the availability of radioisotopes of essential elements so that the dynamics and distribution of minute quantities of the elements can now be followed as they move through the body. State-of-the-art analytical methods including atomic absorption spectrophotometry, nuclear activation analysis, and X-ray emission must be employed. Analysts must take scrupulous care to avoid contamination. At the same time, modern biochemistry can elucidate the multiple mechanisms by which metals manifest their action. The use of total parenteral nutrition allows a semisynthetic diet to be delivered intravenously to patients unable to take food orally. Before this technology was fully developed, inadvertent omission of certain trace elements from the formulation produced deficiency syndromes that allowed astute investigators to make direct observations of metal requirements uncomplicated by the variables of foodstuffs, digestive processes, and assimilation.[6]

Iron deficiency is one of the most widespread nutritional problems facing both developing and developed nations. We feel it is also one of the most destructive deficiency syndromes. Its consequences include poor growth, lethargy, lowered work performance, and reduced immune response. The average adult contains 3 to 5 g of total iron. The most available sources of food iron are meats, green leafy vegetables, and beans. In the past, cooking in cast-iron utensils provided a significant quantity of iron in daily diets. As iron was replaced by stainless steel, fluorocarbon coatings, and aluminum, as caloric intakes decreased, and as foods became increasingly refined and processed, contemporary Western diets came to contain considerably less iron than they did in the past. People with insufficient funds to purchase certain nutrient-rich foods, particularly red meats and dark green vegetables, often live on diets which are primarily carbohydrate and fat and provide little if any iron or other essential trace elements. Some vegetarian diets have extremely low concentrations of available metals. Individuals who voluntarily accept such diets must take care that deficiencies are not encountered.

It is difficult to imagine how iron deficiency can be a major nutritional problem when this element is so abundant in the crust of the earth. However, the amounts of iron present in the plants and animals we use as food are small. The U.S. National Academy of Sciences recommends a daily intake of 18 mg of iron to satisfy the needs of 95% of Americans, including menstruating females with increased iron losses. Only from 6-17% of this iron is absorbed. Most food iron is present as protein-bound, nonheme ferric iron. About 30% of the total iron in an average diet is present as iron bound within the hemes present in meats. Both forms are utilized. For centuries man has recognized the importance of adding iron to

his diet. To enhance their strength, Jason and his Argonauts added filings from sharpening their swords to the wine that they drank before embarking on their quests. In a modern folk remedy dating to the Middle Ages, nails were placed in apples and allowed to rust before the fruit was fed to children. By the early 1800s ferrous sulfate was given as a cure for anemia. This simple compound of iron is still one of the most effective therapies for iron deficiency. For many people who take iron pills, it produces gastric upset. When taken in excess it can actually be a fatal poison, particularly for children who steal their mothers' candy-coated iron tablets. Many new forms and compounds of iron have been developed to enrich and fortify our diets. The microscopic colloidal particles of metallic iron used as modern fortificants are probably more effective than the metal filings of ancient times. Complexes of iron with gluconic and fumaric acid have been used for both food supplementation and therapeutic treatments. Injectable forms of colloidal iron dextrans have found limited application when normal dietary supplementation cannot be tolerated. Most baby pigs raised commercially receive an injection of iron shortly after birth. This not only increases their growth, but also makes them more resistant to disease.

Strategies to fortify or enrich food consumed by susceptible populations have met opposition from some physicians who believe that the risk from iron overload outweighs the benefits of supplementation. In a study recently conducted in collaboration with the Department of Education and investigators at the University of Juarez in Durango, Mexico, we added iron and copper to milk in the school lunch of several hundred Mexican children aged 6 to 15. We saw striking improvement in the hemoglobin concentration of the group (Figure 2). Almost every child showed a higher hemoglobin concentration after only 3 months of supplementation. The data showed that the entire population, by definition, was iron deficient because of suboptimal dietary iron.[7] Milk is an efficient vehicle for supplementing children. Although cow milk is a remarkably nutritious food, it does not contain significant amounts of iron or copper. In a perfect world, we will expect everyone's diet to contain proper amounts of necessary trace elements. That possibility can be achieved only by a sound program of nutrition education coupled with effective strategies of fortifying common, available foods.[8]

Our initial interest in iron metabolism was aroused by some curious medical and urban anthropological observations by Dr. Ed Butt, then chief pathologist at the Los Angeles County Hospital.[9] He noted that alcoholics from southern California, New York City, and Paris all died from cirrhosis of the liver; however, only liver tissue from Los Angeles autopsies was heavily loaded with iron. To explain this unusual finding, we investigated the mechanisms for iron uptake by liver and ultimately discovered that low molecular weight complexes of iron enhanced absorption.[10] We showed that the muscatel wine consumed by southern Californians contained iron and sugar which could be converted to a readily absorbed iron-sugar complex during digestion. Whiskey, the beverage of choice in New York, contained neither sugar nor iron. The dry red wine consumed in Paris had iron, but no sugar; the iron was unavailable. Thus, the drinking patterns in various regions gave rise to major changes in iron metabolism. Textbook wisdom at that time held that iron uptake from diets was under a strict feedback control called the "mucosal block".[11] When iron in the body was at a "normal" level, further absorption of iron was decreased or shut off. There are, however, at least three other diseases characterized by inappropriate iron absorption:[12]

1. Bantu natives in South Africa accumulated great amounts of iron by eating a diet of corn gruel cooked in cast-iron pots and drinking a ritual beer brewed in cast-iron equipment. Obviously, the "mucosal block" did not prevent iron from being absorbed. Chemical complexes of iron with sugar in these foods increased absorption and exacerbated the overload.
2. In a genetic disorder called hemochromatosis — a recessive inheritance with compli-

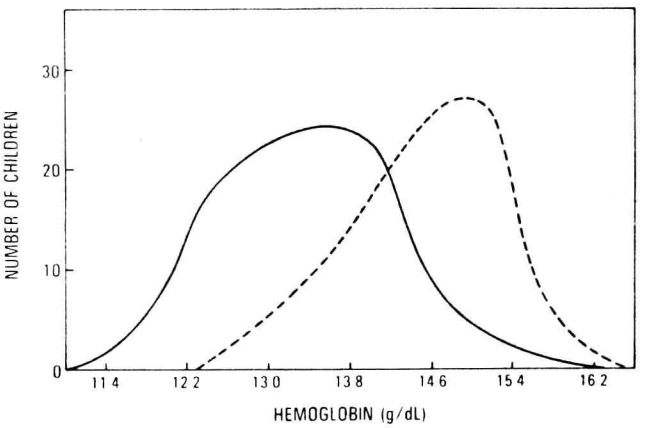

FIGURE 2. Hemoglobin concentrations in control (—) and iron- and copper-supplemented (— —) diets of children from the ages of 7 to 13.

cated linkage — iron from a normal diet is accumulated so efficiently that the liver, spleen, and other tissues literally "rust out". Serious heart disease can result, as well as pancreatic dysfunction and diabetes.

3. Iron overload is also encountered in conditions where individuals cannot make enough functional hemoglobin and repeated transfusions of whole blood are necessary to maintain life. The body eventually destroys transfused red cells, then reclaims and stores the iron. Ultimately, the iron given as blood to maintain life is the "poison" that destroys it. The physician faces a dilemma. Only by chemically removing excess iron using chelation therapy can transfusions be continued.

The normal adult human contains about 80 mg of copper. Overt dietary deficiency of copper in humans is rare. Most commonly it is seen in premature infants born in the nutritionally deprived areas of the world. These children are anemic and have poorly developed skeletal structure. Copper deficiency was also seen in the early days of total parenteral nutrition but is now avoided by proper supplementation. The toxicity of excess copper is rare. Sources of this metal are shellfish, organ meats, nuts, and legumes. Recent studies indicate that contemporary American diets may contain marginal copper.[13]

Since 1924 it has been recognized that copper deficiency plays an important but poorly defined role in iron metabolism.[14] Diets lacking copper, even though they may contain sufficient iron, can lead to anemia by depressing red cell formation. In the absence of copper, iron is stored in the liver and little is incorporated into hemoglobin.[15] Some investigators have claimed that the plasma protein, ceruloplasmin, is required to mobilize stored iron. However, Wilson's disease patients (see below) lack this protein but have normal iron metabolism. The relationship between copper and iron remains a biochemical mystery.

The diverse and essential functions of zinc depend upon a mere 2 to 3 g of the metal in our adult bodies. The best food sources are shellfish, muscle meats, and nuts. Whole grains lose much of their zinc in milling and refining. Fruits and nonleafy vegetables are relatively poor dietary sources. Human milk has less zinc than does the cow's, but neither is a particularly rich source of the metal. Marginal zinc deficiency has been observed in the U.S., and there is increasing concern that we are not getting sufficient amounts of this metal. The U.S. Recommended Daily Allowance for infants is 3 mg/day, 10 mg for children up to 10 years old, and 15 mg for adults. During lactation and pregnancy even more zinc is necessary for maintenance. The solubility of dietary zinc is affected by the presence of competing insoluble ligands and by other metal ions, particularly Ca^{2+}. Prasad and co-