TRACE ELEMENTS

in Human and Animal Nutrition

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ACADEMIC PRESS INC. • PUBLISHERS
NEW YORK • 1956

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125 East 23rd Street
New York 10, N. Y.

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Library of Congress Catalog Number: 56–6613

PRINTED IN UNITED STATES OF AMERICA

PREFACE

The real purpose of a preface, it has been said, is to break down reader resistance, "to put the reader in the proper frame of mind to approach the reading of the book." Such a purpose has no great appeal to the present author but it may perhaps put the reader in a more sympathetic frame of mind if it is mentioned at the outset that this is a first book: not a first book in the author sense, but in the subject sense. Numerous books have been published on the vitamins but none dealing wholly with the trace elements in human and animal nutrition. This is curious when one considers that the history of the trace elements is as stimulating and as romantic as that of the vitamins; their economic significance is as great or greater; and they lie equally at the root of physiological processes. These points will, it is hoped, become abundantly apparent from the pages which follow. It is true that a small book by Stiles called "Trace Elements in Plants and Animals" was published in 1946 and one by Monier-Williams, entitled "Trace Elements in Food," in 1949, but the former devotes only a few pages to animals and the latter is concerned principally with analytical methods and with toxicological and public health aspects of the trace elements, rather than with nutrition. For this reason the present text can legitimately be regarded as a first attempt to survey the trace elements from the point of view of their nutritional significance to man and his domestic animals.

This book is written for those who plan to specialize in nutrition, or who are already specialists in nutrition. It is not written for those who are primarily dietitians, biochemists, or pathologists, although inevitably there is much in it to interest all three. In fact, it is impossible to treat the trace elements at all effectively without venturing boldly, sometimes even rashly, into the biochemistry of the cell, on the one hand, and into the pharmacology and toxicology of the living body, on the other. The extent of the movement into either field varies with the element. It is governed by no known rationale but rather by the personal interest, knowledge, and predilections of the author. The author's aim has been to present a balanced treatment, to explore as fully as space will allow those facets of any element which throw light on the nutritional significance of that element, and to exclude arbitrarily other aspects which appear to have no such bearing on nutrition. The author has also thought it important to preserve an historical approach, wherever possible. It is felt that this has particular value in a first book, not only because it brings together under one cover much interesting material likely to be lost in a welter of original articles and reviews, but also because in no other way can the methods and approaches of research be revealed and the step-by-step development of knowledge be emphasized for the benefit of the young student and researcher.

The problem of selection of material—of what to leave in and what to leave out—is always a difficult one, but it is especially difficult with the trace elements because of their nature and their ramifications. The author has tried to deal thoroughly with all those elements in which naturally occurring deficiencies or excesses are known, because of their obvious economic importance and interest. However, all trace elements which have been shown to be essential, or which have had nutritional significance ascribed to them, have received attention.

Complete documentation, with authority for every statement made, was considered to be clumsy and unwarranted. Reference is made, nevertheless, to a very large number of original articles and to most of the excellent reviews which have appeared on individual elements or groups of elements. A list of these appears at the end of each chapter. Many authors and editors of journals have readily granted permission to reprint various graphs and illustrations, all of which are acknowledged in the text. The author is indeed grateful for this assistance. It is a pleasure to record, also, the help and encouragement received from many friends and colleagues. In this connection, special mention should be made of Drs. H. W. Bennetts, D. H. Curnow, A. T. Dick, R. C. Rossiter, and E. G. Saint, and Messrs. A. B. Beck, R. J. Moir, and E. Munch-Petersen, who read various chapters and made many helpful suggestions. Any errors of fact or defects in the plan and scope of the book are, however, the author's own responsibility. Finally, it is a particular pleasure to record the debt owed to Miss M. Keane for her care and skill in the typing of the manuscript and in the laborious task of checking references.

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March, 1956

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CONTENTS

CHAPTER 1

INTRODUCTION

I. The Trace Element Concept

Over the last hundred years, and especially in the last thirty years, a steadily increasing number of elements has been found to be constantly present in living tissues. To a few of them, definite biological functions have been assigned. The term "trace elements" was quite understandably applied by the early workers to those elements which occur, or which function, in very small amounts relative to the amounts of the main constituents of the tissues, because of the difficulties then associated with measuring the low concentrations involved and their recognition, therefore, merely as "traces." The term "minor elements" has also gained some acceptance, particularly by plant biologists, to describe these elements. Both these terms have been quite justifiably criticized as misleading, or as having prejudicial implications—the first because it fails to convey the idea of their quantitative significance and the second because it suggests for them a minor, or less important, role compared with those elements which occur, or are required, in larger quantities. Several alternative names have been suggested. The terms "oligo-element" or "oligo-metal" (oligo coming from the Greek "oligos," meaning scanty) have been used in the French literature for some years, and the terms "micro-element" or "micro-nutrient" have the impressive support of several international conferences. None of these latter terms, however, appears to have made a great deal of headway, in spite of their greater descriptive accuracy. The name "trace elements" is retained in this book because of its historical associations and its continued general acceptance by most active workers in the field.

Nearly every element has been found to occur in living tissues by one method or another, at some time or another. Spectrochemical methods, because of their convenience, specificity, and accuracy, in skilled and critical hands, have been particularly useful in the detection and estimation of a series of trace metals in biological materials under a variety of conditions. They have, in fact, played a very important part in giving useful leads in the investigation of several naturally occurring nutritional problems in animals, to which reference is made in the appropriate chapters which follow.

One of the earliest of these general spectrographic studies was that of Dutoit and Zbinden (6) who found Ag, Al, Ca, Cu, Fe, K, Mg, Mn, Ca, P, Si, Ti, and Zn in all samples of human blood examined, and Co, Cr, Ge, Pb, Ni, Sn, and Sr in many of them. Rb and Li were subsequently added to this list. In the same year Wright and Papish (14) published a spectrochemical study of cow's milk. They found milk to contain, in addition to the elements already known (namely Ca, Mg, K, Na, P, Cl, Fe, Cu, Mn, and I), the following elements in minute concentrations: Si, B, Ti, V, Rb, Li, and Se. Subsequently Ba, Sr, Cr, Mo, Pb, and Ag were added by other workers. These early findings have been substantially confirmed and extended by improved spectrochemical methods and by the use of the highly refined and sensitive colorimetric and catalytic methods which have been developed with such success by modern analysts. As a result, it has been established that, in addition to the so-called major elements, C, H, O, N, S, P, Ca, K, Na, Cl, and Mg, which normally occur in relatively high concentrations, the following elements, Fe, Cu, Mn, Zn, I, Co, Mo, Ni, Al, Cr, Sn, Ti, Si, Pb, Rb, Li, As, F, Br, Se, B, Ba, and Sr, are constantly present, usually in low but very variable concentrations, in the tissues and fluids of higher animals and plants, whereas other metals, such as, V, Ag, Au, and Ce, are frequently or occasionally present. The members of these latter groups are the elements designated the "trace" elements, although there is no reason to believe that others will not be added to the list.

Within this group a small number of elements exists for which an essential physiological role has unequivocally been established, and there are several others which have had physiological significance ascribed to them, based on highly suggestive but not yet conclusive evidence. Of the 22 elements listed in the first group in the preceding paragraph, only the first 6, namely Fe, Cu, Mn, Zn, I, and Co, have been conclusively shown to be nutritionally essential for the higher forms of animal life, although there is some justification for including Mo, F, Ba, and Sr among the essential trace elements. Similarly, only seven of these trace elements, namely Fe, Cu, Mn, Zn, B, Si, and Mo, have been definitely established as essential for the life of higher plants. For certain of the lower forms of plant and animal life vanadium must be added to this list. It is apparent, therefore, that important qualitative differences exist in the trace element requirements of plant and animals. If the term "trace element" is restricted to those elements which are known to be nutritionally essential, then it must be given a rather different interpretation according to whether it is meant to apply to plants or animals. Plants apparently do not require iodine or cobalt, although these are invariably present in plant tissues, and animals have not so far been shown to require boron or silicon, although these trace elements are also normally present in animal tissues. These qualitative differences in the trace element requirements of plants and animals, as well as the considerable quantitative differences which exist both within and between plants and animals, have great practical significance, as is emphasized in Chapter 13.

The small proportion of the total trace elements constantly present in plant and animal tissues which can at present be described as definitely essential should not be taken as an indication that the rest are merely accidental contaminants. That this number of essential trace elements is small could be a reflection of the great technical difficulties imposed by the extraordinarily low concentrations involved, especially as it is only comparatively recently that many of the vitamins essential to growth studies with the trace elements have become available in pure form. It is only within the last few years, also, that such a new and promising technique as the use of radioactive isotopes of these elements has become really effective. It may be that living tissues have developed a passive tolerance to the presence of some of these elements, due to their constant occurrence in the soils, foods, waters, and the atmosphere with which the organism is constantly associated. Even a consistent concentration of certain elements in particular organs or tissues, however teleologically tempting or useful as a stimulus to further investigation, cannot be taken as evidence that the element in question performs some specific function, since such a concentration may merely mean a higher tolerance, or a greater chemical affinity, of one tissue or organ compared with that of another. Nevertheless, it seems highly probable as more highly purified, nutritionally adequate, diets are developed and as physiological and analytical techniques improve, that some at least of these "accidental" trace elements will be found to have essential physiological functions in the tissues. It should not be forgotten that a few years ago copper, zinc, manganese, and cobalt were generally regarded as merely interesting contaminants.

The essential trace elements are frequently classed together by nutritionists, much as the vitamins are classed as a group by these workers. There is no more real physiological justification for this with the trace elements than there is with the vitamins, because almost the only characteristic which they have in common is their ability to function in small quantities. Even in this respect they differ markedly in their quantitative requirements by plants and animals, and in the levels in which they normally occur in living tissues, so that it becomes difficult to draw a clear line between those elements which can legitimately be classed as

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trace elements and those which cannot be so classed. For instance, iron is considered a trace metal by some writers and not by others. It is certainly required by animals in significantly larger quantities than the other trace elements and it occurs in the body in relatively high concentrations as part of the hemoglobin molecule. On the other hand, it functions also as a constituent of a number of oxidative enzymes, in a manner similar to copper, and is intimately related to copper in its metabolism. Moreover, in many body fluids and tissues it does not normally occur in concentrations which are as high as those of another acknowledged trace element, zinc. For these reasons it is included among the trace elements in this text. Even if iron is excluded from the present considerations, however, large quantitative differences remain. Thus the requirements of mammals for copper are many times those for iodine or cobalt and the concentrations of zinc in animal tissues are many times those of manganese, and so on. An idea of the magnitude of some of these differences can be gained from an inspection of Table 1, in which typical concentrations of the six essential trace elements in normal human blood are presented.

TABLE 1

TYPICAL CONCENTRATIONS[a] OF ESSENTIAL TRACE ELEMENTS IN NORMAL HUMAN BLOOD

Element	Whole blood	Serum
Iron	50,000	80–100
Zinc	700–900	300
Copper	100–120	100–120
Manganese	12–18	4–6
Iodine	8–12	5–6
Cobalt	–	0.8

[a] Measured in μg. per 100 ml.

Some of the trace elements to which no definite functions have yet been ascribed occur in the blood and tissues in concentrations significantly higher than those of the essential trace elements. Bromine and silicon are examples of such elements, as is evident from the data given in Chapter 12. Another example of great interest is the alkali metal, rubidium. Rubidium has been found to occur in most animal and human tissues and organs, including fetal tissues and milk, in fairly constant proportions amounting to no less than 20–40 p.p.m. on the dry basis (12). No attempts to find out if these appreciable quantities of this element serve any useful or essential function within the tissues appear to have been made.

II. The Development of Knowledge of the Trace Elements

Although a great deal of our knowledge of the significance of the trace elements in animal physiology has been accumulated in the last thirty years—in fact, since the classical demonstration by E. B. Hart and his colleagues of the essential nature of copper in mammalian nutrition in 1928 (9)—interest in certain aspects of these elements dates back for over a century. The presence of copper in the oxygen-transporting hemocyanin of mollusks was first recognized in 1847 (8); iron was shown to be a part of the hemoglobin molecule in 1886 (15); iodine was found by Baumann (1) a few years later to be concentrated in the thyroid—although this element had been used empirically in the treatment of human goiter as early as 1820 (4); zinc was shown to be present in the respiratory pigment of the snail, Sycotypus, in 1905 (11); vanadium was demonstrated in the blood pigment of sea squirts in 1911 (10); and the series of early investigations on cell respiration and on iron and oxidative processes which began with Claude Bernard in 1857 (2) pointed the way to the discovery of metalloenzymes and to metal-enzyme interactions in catalysis.

During this early period, also, the universal presence of a range of elements, in minute quantities, in plant and animal tissues and in the soils on which the plants feed, was established. Many of these early studies are now known to have been quantitatively misleading, because the analytical methods then available were rarely equal to the task of estimating accurately the extremely low concentrations involved and because the ease with which contamination can occur was not generally appreciated. Nevertheless, these "distribution" studies served the very useful purpose of drawing attention to the possible significance of many elements previously disregarded and gave the necessary stimulus to physiological and nutritional investigations designed to ascertain their function, if any, in living tissues.

Interesting and important as these studies were, advances in our understanding of the role of the trace elements were exceedingly slow until two different types of investigations began—investigations which bear a striking resemblance, in their method of approach, to those which have been so successful in illuminating the significance of the vitamins in animal physiology and of the trace elements in plant physiology. These are (*1*) the investigation of various naturally occurring diseases of man and animals, widely separated geographically, which were shown to be due to a dietary deficiency, or excess, of a particular trace element and (*2*) the investigation of the effects on animals of highly purified or specially constituted diets deliberately designed to have an abnormally low, or high, content of the trace mineral under study.

Outstanding examples of the first type of investigation are (a) the clear demonstration, early in this century, that lack of iodine in the foods and waters of certain regions is the primary cause of endemic goiter of man and farm stock; (b) the revelation, in the 1930's that cobalt deficiency in the soils and pastures of particular areas is the cause of a group of wasting diseases of sheep and cattle; and (c) the demonstration, in the same decade, that excessive intakes of molybdenum from certain pastures are responsible for a severe scouring condition in cattle. These are, of course, considered in some detail in subsequent chapters. The considerable scientific effort which was concentrated upon the solution of these and similar types of "field" problems, and the spectacular results achieved, were very potent factors in the development of a new knowledge about the nutritional significance of the trace elements. A great deal of light was shed upon the ways in which these elements function in the animal body. Soil-plant-animal interrelationships were given added meaning and significance, especially as the soil deficiencies or excesses primarily responsible for the disease conditions in animals sometimes affected plant growth or health as well as plant composition. New and improved methods of estimation of great delicacy and precision were developed in response to the urgent need to trace the distribution of the elements concerned in soils, plants, and animal tissues. The importance of trace element deficiency problems was found to extend far beyond the disease conditions which gave the initial stimulus to the investigations, by the disclosure of the widespread occurrence of more subtle, milder forms of deficiency, less dramatic in their manifestations, but often of greater economic importance. Further, the vital significance of a proper balance of minerals in the diet was revealed by the discovery that a number of these dietary disorders resulted not merely from a deficiency or excess of a single trace element, but from a deficiency or excess conditioned by the extent to which other elements, nutrients, or special factors are present in the diet.

In the second mode of approach, involving the use of highly purified or specially constituted diets with small laboratory animals, the motivating philosophy was the desire of enquiring minds to learn whether this or that trace mineral serves any useful function in the animal body. Although lacking the stimulus and resources which stem from economic need, these investigations have been equally fruitful and were responsible for the original demonstrations of the essential nature of copper, manganese, and zinc in mammalian nutrition. Many of the early studies with purified diets, especially those of the great French school led by Gabrielle Bertrand, and of J. S. McHargue in Kentucky, during the 1920's, were inconclusive because the diets employed were generally lacking in essential vitamins, so that the animals made little growth or survived for only short periods, even when supplemented with the element under study. Not until vitamin research had advanced sufficiently to enable diets to be devised low in the element in question, but adequate, or reasonably adequate, in other respects, was rapid progress made in this type of study. Outstanding in this respect was the Wisconsin school, led by the late E. B. Hart. Not only were the researchers of this school extremely successful with purified diets, but in the decade following the demonstration of the relation of copper to hemoglobin production in the rat in 1928, they pioneered the use of whole milk, or of diets composed largely of milk, in trace element studies. Milk, because of its palatability, its richness in many dietary essentials, and its natural deficiency in iron, copper, and manganese, has proved to be an invaluable tool to nutrition workers interested in the trace elements.

The two approaches to the study of trace elements, outlined above, were at first distinct and unrelated, but they have tended to merge in recent years, each contributing to developments in the other in a manner similar to the merging of pure and applied research in the related field of vitamin research. Studies of naturally occurring deficiencies or toxicities in man or farm stock have provided new stimuli for the further investigation of the mode of action of trace elements in laboratory animals by disclosing new and often unexpected functions within the body, and laboratory studies with small animals have been fruitful in drawing attention to the wider significance of certain elements in field problems previously inexplicable. Such cross-fertilization in ideas and techniques, examples of which are given in the chapters that follow, has been a potent factor in increasing our understanding of the nutritional significance of a great number of these elements.

Within the last few years a new and powerful weapon, the "tracer" isotope, has been added to the nutritional physiologist's armamentarium. Radioactive isotopes, with a suitable half-life and a high specific activity, are now available for a wide range of elements in amounts and at a cost suited to most biological needs. With the trace elements this has proved to be a development of tremendous significance, because essential investigations of absorption, excretion, distribution, and combination within the tissues were in some cases impossible, and in all cases difficult, by conventional methods. The value of radioactive isotopes has been shown most convincingly with iodine, whose metabolic movements defied accurate appraisal for many years, and with iron, whose peculiar mechanism of absorption and complex intermediary metabolism have only been revealed by the use of radioactive isotopes of this element. With other trace elements, radioactive isotopes have not yet proved of such outstanding value, although there is little doubt that they will do so as more research is undertaken with them and as techniques improve.

III. Mode of Action of the Trace Elements

It was pointed out earlier that the only characteristic which the trace elements have in common is their capacity to function in small quantities. It is this capacity which indicates that they must act as catalysts involved in hormone or enzyme systems, either as constituent parts of the molecules of hormones, vitamins, enzymes, or coenzymes, or as enzyme activators. In fact, as Green (7) has said, ". . . enzymic catalysis is the only rational explanation of how a trace of some substance can produce profound biological effects." Many examples of trace elements functioning in these ways are now known. Iodine has been shown to be an integral part of the thyroid hormone, thyroxine or triodothyronine, and cobalt of the vitamin, B_{12}; iron and copper are known to be irreplaceable components of the molecule of several oxidative enzymes; zinc is present in carbonic anhydrase, manganese in arginase, and molybdenum in xanthine oxidase and nitrate reductase. In addition, many trace minerals have been shown to function as catalysts for a range of more or less purified enzymes *in vitro*.

These findings leave little doubt that the trace elements function as activators or as catalysts within the living cell and that they lie at the root of living processes. At the same time it is necessary to avoid the rather specious clarity which frequent repetition of such a statement tends to engender. The metal ions, which include many of the trace elements, appear to act in two different ways in enzyme systems. They may be an indispensable part of the protein, from which they can only be dissociated with difficulty. Examples of such are the iron complexes of the "heme-proteins," the cobaltic complex of vitamin B_{12}, and the zinc and molybdenum enzymes mentioned in the preceding paragraph. In these cases it would be better, as Williams (13) has suggested, to describe the function of the metal ion, which is highly specific, as one of activation, rather than of catalysis, of an enzyme reaction. The metals may also act in a manner similar to their action in nonenzymatic catalysis. In these cases, as with the peptidases and the phosphatases, the metal ions are readily dialyzable from the enzymes, which then become somewhat reduced in activity, and the catalysis has a relatively low metal-ion specificity. In neither case, however, can a clear exposition of the way in which these elements function yet be given. Moreover, with the latter group especially, most of the studies have been carried out *in vitro*. Enzymatic catalysis in these circumstances may not be applicable to *in vivo* enzyme reactions, although it is difficult to imagine that they are totally unconnected.

In the earlier stages of the trace element era, investigators tended to concentrate upon the reaction of the whole organism—upon such gross effects as growth, appetite and live-weight changes, reproductive performance, and the like. These were obviously necessary and important and are still so, but they do not readily illuminate the mode of action of the element in question. Subsequent investigations have, however, moved successively and successfully down the scale of organizational complexity from the whole organism to organs, tissues, cells, cell particulates, and finally to individual components of the matrix of enzymes, coenzymes, and inorganic cofactors within the cell. These have proved increasingly revealing in respect to trace element-enzyme relationships but, unfortunately, many of the studies of enzymatic changes in the tissues and fluids of living animals suffering from various trace element deficiencies have, as yet, proved very disappointing. Changes in the concentrations or activities of those enzymes or hormones with which the particular trace element is known to be associated have been demonstrated under these conditions with some elements, notably iron, cobalt, copper, and manganese. But frequently marked retardation in growth and profound clinical changes have been observed in the deficient animal well before any reduction in the amount or activity of the enzyme or enzymes concerned can be detected. This is particularly outstanding with zinc, as is shown in Chapter 7. These findings do not, of course, denigrate the trace element-enzyme relationship, but they indicate that the functions of these elements in living systems extend far beyond our present understanding and that these functions are more subtle and more complex than can be appreciated at the present state of knowledge.

Whatever future research may hold in this respect, it nevertheless seems clear that the trace elements constitute such a small proportion of the structural make-up of plants and animals that they must function as catalysts. Bertrand has put forward the interesting hypothesis that they have played a significant part in evolution by increasing the number of chemical reactions within the cell and the consequent elaboration of morphological structures, physiological functions, and biochemical potentialities. In more emotive language, he suggests that the living organism, both plant and animal, is "a kind of oligarchy in which the masses,

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