VOLUME 2

Trace Elements in Human and Animal Nutrition

FIFTH EDITION

Edited by

WALTER MERTZ

Trace Elements in Human and Animal Nutrition—Fifth Edition

Volume 2

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WALTER MERTZ

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Editions 1–4 were prepared by
the late Dr. Eric J. Underwood

1986

ACADEMIC PRESS, INC.
Harcourt Brace Jovanovich, Publishers
Orlando San Diego New York Austin
London Montreal Sydney Tokyo Toronto

ACADEMIC PRESS, INC.
Orlando, Florida 32887

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
24–28 Oval Road, London NW1 7DX

LIBRARY OF CONGRESS CATALOGING-IN-PUBLICATION DATA

Main entry under title:

Trace elements in human and animal nutrition.

Rev. ed. of: Trace elements in human and animal nutrition / Eric J. Underwood . 4th ed. c1977.
Includes bibliographies and index.
1. Trace elements in nutrition. 2. Trace elements in animal nutrition. I. Mertz, Walter, Date II. Underwood, Eric J. (Eric John), Date
Trace elements in human and animal nutrition. [DNLM: 1. Nutrition. 2. Trace Elements QU 130 T75825]
QP534.T723 1986 599'.013 85-20106
ISBN 0-12-491252-4 (v. 2 : alk. paper)

PRINTED IN THE UNITED STATES OF AMERICA

86 87 88 89 9 8 7 6 5 4 3 2 1

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and Animal Nutrition—Fifth Edition
Volume 2

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Preface

Eric J. Underwood died from a heart ailment on 18 August 1980, in Perth, Australia. During his long, productive career he saw his field of scientific interest, trace element nutrition and physiology, expand from small, isolated activities into an area of research that has gained almost universal recognition in basic and applied sciences and transcends all barriers of disciplines. He contributed to this development more than any other person of our time, through his own research, which laid the foundation for our understanding of the physiological role of cobalt, through his numerous national and international consulting activities, and through his book *Trace Elements in Human and Animal Nutrition*, which he authored in four editions. The book has assumed an eminent place among publications in trace element nutrition, not only as a source of data but because it offered mature judgment in the interpretation of the diverse results. In his preface to the fourth edition, Underwood stated that "the overall aim of the book has remained, as before, to enable those interested in human and animal nutrition to obtain a balanced and detailed appreciation of the physiological roles of the trace elements. . . ." This goal remains the dominating guideline for the fifth edition.

The invitation of the publisher to assure the continuation of the book was discussed in detail with Dr. Erica Underwood and Dr. C. F. Mills, who had been closely associated with the previous editions. Both agreed that a fifth edition was consistent with Eric Underwood's plans and should be considered. There was little question concerning the format. In our opinion, Eric Underwood was one of the few persons, perhaps the last, whose whole scientific career had paralleled the development of modern trace element research, and who had acquired a direct, comprehensive understanding of new knowledge as it emerged. On this basis he was able to evaluate with authority the progress and problems of the field. If the fifth edition was to preserve Underwood's aim of presenting a balanced account of the field rather than a mere compilation of literature, we considered the efforts of more than one author essential. We recognize that the

participation of many authors may affect the cohesiveness of the revised edition, but we believe the risk is minimized by the close past association with Underwood's work and the philosophy of many of our contributors.

The major change in the format of the fifth edition is the presentation of the book in two volumes, necessitated by the rapidly increasing knowledge of metabolism, interactions, and requirements of trace elements. Even with the expansion into two volumes, the authors of the individual chapters had to exercise judgment as to the number of individual publications that could be cited and discussed. No claim can be made for a complete presentation of all trace element research, and no value judgment is implied from citing or omitting individual publications. The guiding principle was to present the minimum of results that would serve as a logical foundation for the description of the present state of knowledge. The inclusion of part of the vast amount of new data published since 1977 was possible only by condensing the discussion of earlier results. We have tried, however, not to disrupt the description of the historical development of our field.

Recent results of research were accommodated by devoting new chapters to the subjects "Methodology of Trace Element Research" and "Quality Assurance for Trace Element Analysis" and by expanding the discussion of lithium and aluminum in separate, new chapters. The first two subjects are of outstanding importance as determinants of future progress. The concern for the quality of analytical data motivated the authors of the individual chapters to review critically and, where necessary, revise analytical data presented in the previous editions. The rapid progress of trace analytical methodology since the mid-1970s has changed what had been accepted as normal for the concentrations of many trace elements in tissues and foods. The new data reflect the present state of the art in trace element analysis, but they may be subject to future revision.

The editor thanks the contributors of this fifth edition for their willingness to devote much time, effort, and judgment to the continuation of Eric Underwood's work.

WALTER MERTZ

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1

Zinc

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I. INTRODUCTION

Over a century ago, Raulin (754) showed that zinc (Zn) is essential in the nutrition of *Aspergillus niger*. Not until 1926 was the essentiality of zinc for the higher forms of plant life clearly established (861,862). Before this zinc had been shown to be a constituent of hemosycotypin, the respiratory pigment of the snail *Sycotypus* (589,590).

Following the original demonstration of the occurrence of zinc in living tissues (509), many investigations revealed the regular presence of this element in plants and animals in concentrations often comparable with those of iron and usually much greater than those of most other trace elements. Particularly high concentrations were reported in serpent venom (189), in some marine organisms, notably oysters (77,828), and in the iridescent layer of the choroid of the eye (969).

The first indications of a function for zinc in higher animals came from the work of Birckner (70) in 1919. Early attempts to demonstrate such a function using semipurified diets met with limited success (63,418,572) until 1934, when Todd and associates (909) produced the first indisputable evidence that zinc is a dietary essential for the rat. Twenty years passed before Tucker and Salmon (911) made the important discovery that zinc cures and prevents parakeratosis in pigs, although Raper and Curtin (753) had previously reported that a combined supplement of cobalt and zinc prevents "dermatitis" in pigs receiving corn–

cottonseed meal rations. Subsequently O'Dell and co-workers (677,678) showed that zinc is required for growth, feathering, and skeletal development in poultry. About this time it also became evident that zinc deficiency can occur in cattle under natural conditions in some areas (215,325,326,510). From an early stage, it was apparent that zinc is of outstanding importance for growth and development. Hurley and Swenerton (424) and Warkany and Petering (953) demonstrated that this applied to prenatal as well as to postnatal development.

The first demonstration of zinc as a constituent of an enzyme, carbonic anhydrase, was by Keilin and Mann (466) in 1939. Today more than 200 zinc proteins are known and several biological roles of zinc have been clarified, including those related to cell replication and differentiation (152,927). However, much remains to be learned about changes in zinc-dependent functions resulting from zinc deficiency and about how these relate to the manifestations of zinc deficiency.

Interest in zinc in human nutrition followed the work of Pories and Strain (724) on the relationship of zinc to wound healing, the observations of Vallee (924) on alterations in zinc metabolism in alcoholic liver disease, and especially the studies of Prasad and co-workers (726,732), which provided the first evidence for the occurrence of nutritional zinc deficiency in the human. This was followed in the 1970s by considerable progress toward clarification of the practical importance of zinc in human nutrition. Highlights included the identification of acrodermatitis enteropathica as a genetic disease of zinc metabolism by Moynahan (647), which was followed by the identification of severe acquired zinc deficiency states (460) and appreciation of the multifarious clinical consequences of severe human zinc deficiency. At the other end of the spectrum, there was recognition that mild nutritional zinc deficiency syndromes occur in North America in the free-living population (362). Observations by Golden and Golden (284) on young Jamaican children recovering from protein energy malnutrition (PEM) demonstrated the clinical significance of zinc deficiency as a component of some multinutritional deficiency disorders and have given further insight into the clinical and metabolic consequences of human zinc deficiency.

While absolute deficiency of dietary zinc is uncommon in animals or humans except under experimental conditions, there is now convincing evidence that a relative deficiency of zinc in the human diet is by no means rare. The importance of food processing (818) and food selection (695) in this context have been documented. While the details remain to be clarified, the even greater importance of variations in bioavailability due to dietary factors that inhibit absorption has been established (682,800). However, further progress toward quantifying these effects of dietary and other factors will be necessary in order to delineate nutritional requirements in different circumstances and to prevent zinc deficiency.

II. ZINC IN ANIMAL TISSUES AND FLUIDS

A. General Distribution

With the exception of some specialized tissues that may contain much higher levels, the concentrations of zinc in most mammalian tissues are in the order of 10 to 100 μg/g wet weight (30–250 μg/g dry weight), with little variation among species (128,302,408,439,540,656,864,870). Typical normal levels of zinc in the principal soft tissues of several mammalian species are given in Table I. Other orders have not been investigated extensively, but levels in tissues of birds (817) are in the same range as mammals, whereas the average zinc content of finfish is lower, ~6.5 μg/g (656).

In the late 1940s, Widdowson *et al.* (982) measured by direct means the chemical composition of the whole body of three adult humans. They found an average zinc concentration of 28 μg/g fat-free tissue. Calculation of total-body content by factorial means, using more recent values for tissue concentrations, yielded a very similar result of 30 μg/g body weight or ~2 g total in an adult male. Kennedy *et al.* (472) estimated an average total-body concentration of 34 μg/g lean body mass, using compartmental analysis of zinc-65 (^{65}Zn) turnover measurements. The whole-body concentration of zinc, on a fat-free basis, is in the range of 20 to 30 μg/g in the rat, cat, pig (870), cow (619), and sheep (302), but is higher (50 μg/g) in the rabbit and mouse (983).

Table I
Typical Zinc Concentrations in Normal Tissues[a]

	Zinc concentration (μg/g wet weight)[b]				
Tissue	Human	Monkey	Rat	Cow	Sheep
Brain	13 (58)		13		12
Heart	23 (99)	22	17 (50)		14
Kidneys	37 (163)	29	50	(84)	25 (103)
Liver	58 (199)	19	31 (113)	(111)	40 (128)
Lungs	10 (50)	19	30	(80)	16
Muscle	42 (170)	24	13 (46)	(129)	30
Pancreas	26 (89)	48	33 (145)		15 (74)
Prostate	120 (650)		223		
Spleen	14 (61)	21	23		33
Testis	13	17	22 (152)	(82)	

[a]Compiled from References 127, 244, 278, 302, 439, 441, 455, 473, 540, 617, and 817.
[b]Values for dry weight are in parentheses.

Dietary intakes of zinc are reflected in the zinc concentrations of some tissues (e.g., blood, hair, bone, testes, liver), but others (e.g., brain, lung, muscle, heart) are insensitive to marked reductions or increases in zinc intakes (46,540,751). Zinc deficiency in the young is characterized primarily by retardation of whole-body growth rather than by lower tissue zinc content. Nonetheless, a reduction in the total-carcass concentration of zinc has been reported in calves (617) and rats (441), and in newborn lambs of ewes fed a low-zinc diet during pregnancy (561). Jackson and co-workers (441) found a marked reduction in the zinc concentration in plasma, bone, and testes, and a smaller reduction in liver zinc, in growing rats fed a low-zinc diet (4 μg/g) over 80 days. Total-carcass concentration was also reduced by 30%. When animals that had received the low-zinc diet for 45 days were subsequently repleted with 30 μg zinc per gram of diet, zinc levels in liver and testes rapidly normalized, but bone, and consequently total-body concentrations were only slowly restored. In an attempt to overcome the effect of decreased food consumption, Flanagan (244) fed growing rats a zinc-deficient diet by gastric tube and was able to maintain growth and health, comparable to that in rats fed a zinc-sufficient diet, for 8 days. In the first 2–4 days, levels of zinc in plasma, pancreas, liver, and kidney dropped rapidly to about one-half to one-third the initial levels. Thereafter levels did not change. Bone zinc concentration showed a gradual decrease over the 8 days and was only slowly repleted, compared with the complete and rapid restoration of levels in other tissues when adequate zinc was given. Miller *et al.* (617) had earlier also suggested that there was an initial rapid reduction in zinc levels in some tissues when calves were fed a zinc-deficient diet. Levels then stabilized and were only further reduced in liver, kidney, and rumen with the onset of clinical symptoms. Kirchgessner and Pallauf (482) found the zinc concentrations of the liver, bones, tail, and whole body to be significantly reduced in young rats depleted of zinc over a 35-day period. In weaned rats depleted of zinc for 10 days and then fed diets ranging in zinc content from 2 to 500 μg/g for 21 days, the levels of zinc in serum and liver increased almost linearly with increasing zinc intakes up to the optimal level (12 μg/g diet). A further abrupt rise in these tissues occurred at 500 μg of zinc per gram of diet. The heart and the testes remain relatively insensitive to very high zinc intakes, but large increases in the zinc concentrations of the plasma, liver, kidney, and spleen have been demonstrated on rats fed a normal diet plus 1000 and 2000 μg of supplementary zinc per gram for 15 days (144). Comparable large increases in tissue zinc, other than in the heart and muscles, have been observed in calves at high zinc intakes (600 μg/g), following the breakdown of zinc homeostatis (873). In pigs fed an adequate corn–soybean meal diet, zinc levels in liver, kidney, heart, muscle, pancreas, and aorta were unchanged by supplemental intakes of zinc up to 500 μg/g diet. At a supplementary level of 5000 μg/g liver, kidney, and pancreas levels increased dramatically, but the zinc concentration in aorta and muscle remained unchanged (400).

B. Zinc in Visceral Organs and Brain

The liver of the adult human contains 100–250 μg zinc per gram dry weight (30–100 μg/g wet weight) (127,439,870). In most other species, reported liver concentrations are at the lower end of this range (408,656,817,864,870,983). Liver levels are affected by the level of zinc intake (45,540,751), and species differences may in part reflect different types of diets. In liver cells the zinc is present in the nuclear, mitochondrial, and supernatant fractions, with the highest levels per unit of protein in the supernatant and microsomes (48,620).

The zinc concentration of the kidney cortex in humans is 176 μg/g dry weight, about twice the level in medulla, 81 μg/g dry weight (128). Cortex zinc has been reported to be five times greater than medulla levels in the rat kidney, with the highest concentrations occurring in the cytoplasm of the cells of the juxtaglomerular apparatus (656). The zinc concentration in the spleen is comparable in most species, about 55 to 65 μg/g dry weight (127,128,864), or 15 to 30 μg/g wet weight (408,540,982). The zinc content of the pancreas is about 25 to 40 μg/g wet weight in humans (127), monkeys (540), and dolphins (408), but the level in pigs is twofold higher (178). Zinc is found in the pancreas mainly in the cytoplasm of the α- and β-cells of the islets of Langerhans, and levels in other parts of the organ are very low (656).

Zinc concentrations do not vary widely in the different regions of the brain, and are on average 13 μg/g wet weight in most species (408,656). In the rat brain, higher concentrations of zinc are associated with the mitochondrial and synaptosomal fractions than with other cell fractions (455).

C. Zinc in Muscle

Because of its bulk, a substantial proportion of the total-body zinc in large species is present in skeletal muscle: 50–60% in adult humans (656) and lactating cows (659).

The zinc concentration of muscles varies with their color and functional activity. A threefold variation in the zinc concentration of eight bovine muscles (899) and a fourfold variation in the same eight porcine muscles (131) have been reported. The mean zinc level of the longissimus dorsi, which is light-colored and shows little activity, was 69 μg/g dry, fat-free weight, whereas that of the serratus ventralis, which is a dark, highly active muscle, was 247 μg/g (131). Such differences are minimal in newborn pigs and develop with the use of the muscles, so that marked differences between red and white muscle were apparent by 8 weeks of age (132). The higher zinc content of the red muscle is situated entirely in those subcellular fractions that are composed mainly of myofibrils and nuclei. At least some of the increase in zinc may be associated with higher levels of carbonic anhydrase III, which is found in large concentrations in highly