Handbook of Vitamins, Minerals and Hormones

SECOND EDITION

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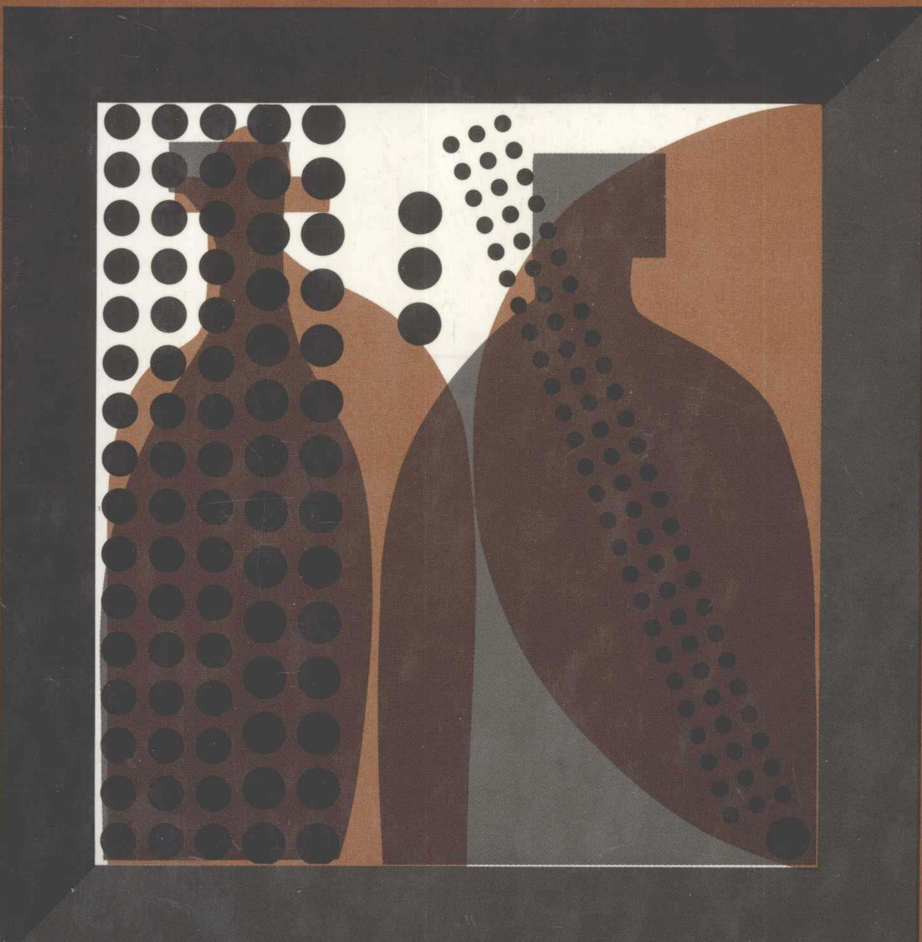

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Introduction

Recent research in tissue culture, physiology, and biochemistry has demonstrated a need for an all-inclusive compendium on minerals as well as vitamins and hormones, as growth factors. In addition, great interest has been generated in presentation of properties of the actual controlling agents which accurately blend all the cellular enzyme systems and organelles to produce a living cell, and, from that, a living multicellular organism. It is precisely in this area of control mechanisms that the minerals, vitamins, and hormones play such a key role, because they are controlling agents.

This book is written primarily from the standpoint of the vitamin, mineral and hormone requirements and contents of individuals of the *human* species. It should be understood that requirements and contents differ from species to species, in general becoming simpler as one goes down the evolutionary scale. For the purposes of this book, a *vitamin* is defined as a biologically active, organic compound, a controlling agent essential for an organism's (human's) normal health and growth (its absence causing a deficiency disease or disorder), not synthesized within the organism, available in the diet in small amounts, and carried in the circulatory system in small concentrations to act on target organs or tissues. A *hormone* is defined as a biologically active, organic compound, a controlling agent essential for normal health and growth (its absence causing a deficiency disease or disorder), synthesized within the organism (human being) in ductless glands which release the agent in very small concentrations into the circulatory system to act on the target organs or tissues.

The chief differences between a vitamin and a hormone seem to be the site of biosynthesis, the types of organic compounds present in vitamins as opposed to the hormones, and some of the modes of action. These differences between vitamins and hormones in essential properties are small compared to their similarities and explain why both vitamins and hormones are combined into one book.

In the light of new evidence, it is becoming difficult to differentiate certain vitamins from some hormones. For example, both vitamin D and niacin are synthesized (but in an inadequate amount) in the human, thus conferring on them a hormonal quality. Similarly, the human requirement for the hormone thyroxine can be partially satisfied by a dietary intake of iodine, and some of the steroid hormones are active in a dietary form, thus giving them a vitamin quality. Moreover, the fat-soluble vitamins (A, D, E, K) show many similarities in biosynthesis, structure, properties and function to the fat-soluble hormones (steroids). Finally, the same molecule can function as a hormone or as a vitamin, depending on the species involved. For example, vitamin C functions as a vitamin in primates because they cannot synthesize it, but it functions as a hormone in cows because they can synthesize it.

We can see that the concept of vitamins and hormones, as defined here, could be extended to all organisms with circulatory systems and would therefore include all vertebrates, many invertebrates, and the higher plants, excepting mainly the lower plants and animals and unicellular organisms. The concept of vitamin is therefore very much dependent on the species concerned. Vitamins seem to have arisen very early in the evolution of life as judged by their presence and requirement in some of the most primitive forms of life known today. Hormones, according to our original definition, however, denote a much later period of emergence, becoming prominent mainly with the evolution of the various animals. They, therefore, reflect a shorter evolutionary history. In view of their primitive nature, vitamins would be expected to have, in general, a simpler structure than hormones, and this is indeed the case, with a few exceptions.

As we compare modes of action of vitamins and hormones, we should compare their chemical structures. The vitamins consist of a fat-soluble series and a water-soluble series. The fat-soluble vitamins (A, D, E, K) consist of derivatives of partially cyclized isoprenoid polymers, somewhat similar to the intermediates in cholesterol (steroid) synthesis. These vitamins seem to act by virtue of their lipid solubility in various cell membranes to affect permeability or transport, and by virtue of their chemical groups as redox agents (A, E, K), as coenzymes or enzyme activators (D, K, A). The water soluble vitamins (B_1, B_2, B_6, B_{12}, niacin, pantothenic acid, folic acid, biotin, C) consist, in general, of derivatives or substituted derivatives of sugars (C), pyridine (niacin, B_6), purines and pyrimidines (folic acid, B_2, B_1), amino acid-organic acid complexes (folic acid, biotin, pantothenic acid), and a porphyrin-nucleotide complex (B_{12}). These structurally diverse water-soluble vitamins act as enzyme activators and coenzymes (B_1, B_2, B_6, B_{12}, pantothenic acid, folic acid, biotin, niacin), as redox agents on enzyme reactions (C, B_2, B_{12}, folic acid, niacin), as nuclear agents (folic acid, B_{12}, C, biotin), and probably as mitochondrial agents (B_2, C, niacin).

The hormones also include a fat-soluble, steroid series (estradiol, progesterone, aldosterone, testosterone, cortisol) which seems to act (1) by virtue of lipid solubility to stabilize and change permeability of the cell membranes, (2) to regulate enzyme activity and membrane polarization, (3) to regulate redox potential, and (4) to affect RNA transcription in the nucleus. The water-soluble hormones consist of a protein series (STH, TSH, FSH, LH, prolactin) which seems to act on the cell membrane to stimulate cyclic AMP production (except STH and prolactin) enzyme activation, and to activate certain genes in the nucleus. The peptide series of water-soluble hormones (insulin, glucagon, ACTH, MSH, oxytocin, ADH, PTH, T4, TCT, and relaxin) acts similarly to the proteins and also has an effect on the mitochondria by T4 and PTH. The amine, water-soluble hormone series (epinephrine, norepinephrine) seems to act chiefly by the cyclic AMP mechanism on the membrane, with consequent enzyme activation. The very extensive role of cyclic AMP as an intracellular mediator of hormonal activity is most noteworthy.

It can be seen that the fat-soluble vitamins and hormones act similarly on membranes, on redox potentials, and as enzyme activators, the only difference being in a demonstrated action on the nucleus by the steroids. Comparison of the water-soluble series of hormones with that of the vitamins again shows a basic similarity in action, the vitamins acting as direct enzyme activators and coenzymes, and the hormones acting as indirect activators via cyclic AMP. Both act on the nucleus but differ in that only some of the water-soluble vitamins have redox properties. Again here, the differences between the two water-soluble series of vitamins and hormones lie chiefly in their differing structures and in some of their properties, such as redox regulation and presence of cyclic AMP intermediates.

The subject of vitamin requirements requires comment. There is now sufficient evidence to indicate that the concept of biochemical individuality has much merit. Thus the recommended allowances as stated in this book (NRC data) should be considered only as average figures, and variations (increase or decrease) of twentyfold or more in individual human requirements may be found, depending on the genetic and physiological state of the individual. Germane to this are the topics of subclinical vitamin deficiencies and megavitamin therapy, i.e., large overdosages of one or more vitamins such as are now being used as treatment of colds and schizophrenia.

The existence of subclinical vitamin deficiencies is extremely difficult to prove without adequate statistical data, but, undoubtedly, if we accept the principle of biochemical individuality, they do exist. In like manner, the use of megavitamins may be helpful to those individuals whose systems for some reason destroy these vitamins rapidly or require these vitamins in large quantity owing to their biochemical individuality. However, in view of the fact that accurate data are lacking, one should treat and use megavitamins as drugs with competent medical advice, being wary of possible unexpected individual toxicity.

A perusal of the miscellaneous section for each factor will indicate to the reader the enormous amount of interplay occurring among vitamins, hormones, and minerals. This includes both antagonisms and synergisms occurring simultaneously among various vitamins, minerals, and hormones. Undoubtedly there exists an optimal set of levels for each factor which, presumably, is that which has been found in "normal" human values. But maximum optimization of levels at "normal" human values has not been proved experimentally; perhaps the human system could run more efficiently at a different set of values. More research is needed to determine this. In any case, optimum amounts and ratios of all vitamins and hormones are important to get full benefits of these agents.

A section is now included on the trace elements and mineral cofactors required for functioning of most coenzyme systems as well as some hormones, e.g., magnesium, iron, copper, iodine, selenium, cobalt, and so on. These trace elements should be present in correct amounts and ratios in any balanced diet containing adequate vitamins.

In relation to requirements, the subject of undiscovered or unaccepted factors should be mentioned. This book has included only those minerals, vitamins and hormones with widespread acceptance. In addition to the 13 vitamins listed here, there are at least another 13 compounds with various acceptabilities as vitamins, plus possibly other vitamins still undiscovered. In view of individual requirements, and the mutual interdependence of vitamins mentioned above, it would still be advisable to rely for one's vitamin requirement chiefly on rich natural sources in the diet, since these would most likely contain the undiscovered vitamins and minerals. However, because of the possible extreme losses of vitamin potency even in our richest dietary sources caused by our present methods of processing, storing, and cooking of food, it would be advisable to consider vitamin supplementation of certain vitamins, especially if one's diet has not been carefully planned.

As far as the hormones are concerned, at least another 23 compounds, in addition to the 23 listed here, are known with various degrees of acceptance as true hormones. No doubt many more remain to be discovered. This book has not listed the insect or plant hormones, because human requirements and levels are being stressed.

Presentation of Data

This book will serve as a ready reference to four major groups of readers, inasmuch as the data for each factor are presented in several separate sections, as follows: "General Information" and "Miscellaneous Information" for the general reader and all other groups; "Medical and Biological Role" mainly for the biologists, physicians, nurses, and pharmacologists; "Chemical Properties" and "Metabolic Properties" for the biochemists and physiologists; and "Nutritional Role" for dietitians and nutritionists. However, it is hoped that parts of all sections will be useful to all the groups. Insofar as possible, the format is similar for all factors for ease of reference. A list of abbreviations is given at the beginning of the book.

The minerals, vitamins, and hormones chosen for coverage in this book are those that have the widest acceptance by the various workers in these fields. Only the most active of the steroid hormones in each category of mineralocorticoids, glucocorticoids, and sex hormones in the human is being covered (out of the 40 plus already discovered).

Chapters on Vitamins, Hormones and Minerals

General Information Section

"Active analogs and related compounds" includes vitamers, isotels, etc.

"Antagonists" and "Synergists" may be the same chemical species but in different concentrations. Interaction at the target site is used as a criterion of antagonism or synergism.

"Sources for Species" (Essentiality) indicates degree of requirement for various species including man. Endogenous = made within organism. Exogenous sources include intestinal bacteria.

Chemical Properties Section

"Reactions" refers to those carried out with standard laboratory conditions and reagents and not under extreme conditions, unless otherwise noted. i.e., heat $\leqslant 100^\circ C$, weak acids or alkalies, reactivity with water, atmospheric or mild oxidation agents, mild reducing agents, bright daylight.

Isolation method gives a typical procedure now in use.

Medical and Biological (Nutritional) Section

This provides, in general, clinical information. Contents of vitamins and minerals are per 100-g edible portion

Antigenicity is defined as the ability to act as an antigen creating an immune response when administered to an organism. Specificity is here defined as the degree of restriction of biological activity to a certain species.

Metabolic Role Section

"Enzyme Reactions" lists enzyme systems affected by the vitamin, mineral, or hormone, organ location, and effects on enzymes, where known.

"Mode of Action" subdivides functions on both a cellular basis (anabolic, catabolic, etc.) and an organismal basis. Anabolic denotes synthetic processes; catabolic denotes degradative reactions and includes most energy-yielding reactions.

Miscellaneous Information Section

"Relationships to other Vitamins, Hormones" attempts to indicate the mutual involvement of both vitamins and hormones in most actions of both groups either together or within the group; similarly for minerals.

"Unusual Features" includes various chemical, biological, and pharmacological features that could not be listed elsewhere.

"Possible Relationships" attempts to draw a parallel between the action of a mineral, a vitamin, or a hormone and its deficiency symptoms.

The tables presented list some of the data already given and some new data in an attempt to indicate fundamental similarities and dissimilarities in structure and function of vitamins, minerals, and hormones.

References are presented in numbered form at the end of sections, and are subdivided into two categories: general and specific. An effort has been made to cite only the latest available handbooks, compendia, journal references, and texts.

Abbreviations

A.A. . . . . amino acid
Absn. . . . . absorption
Acet. . . . . acetone
ACH . . . . acetyl choline
ACTH . . . . . . adrenocorticotrop(h)ic hormone
ADH. . . . . antidiuretic hormone (vasopressin)
Ala. . . . . .alanine
Aldos. . . . . .aldosterone
Alc. . . . .(ethyl) alcohol
Alk. . . . . alkaline
AMP . . . . .adenosine monophosphate
$_c$AMP . . . . . . cyclic adenosine monophosphate
Approx. . . . . .approximately
Aq. . . . . aqueous
Arg. . . . . arginine
Asn. . . . . .asparagine
Asp. . . . . aspartic acid
ATP . . . . adenosine triphosphate

Benz. . . . . benzene
Bio. .biotin
BMR. . . . . basal metabolic rate
CDPG . . . .cytidine diphosphoglucose
CF . . . . .citrovorum factor
Chl. . . . . chloroform
CHO . . . . .carbohydrate
Chromatog. . . . . chromatograph
CMC, CM cell . . . . .carbosymethyl cellulose
CNS . . . . central nervous system
CoA . . . . coenzyme A
Conc. . . . . .concentrated
Conv. . . . . converted
CoQ . . . . Coenzyme Q
Cort. . . . . .cortisol
CRH . . . . . .corticotrop(h)in-releasing hormone
Cys. cysteine

DDT . . . . dichloro-diphenyl-trichloroethane (insecticide)
DEAE . . . . diethylaminoethyl (cellulose)

Defic. . . . . .deficiency
Dil. . . . . .dilute
DOPA . . . . dihydroxyphenylalanine
DPN . . .diphosphopyridine nucleotide
DNA. . . . . .deoxyribonucleic acid

Enz. . . . . enzyme
Ep., Epi. . . . . .epinephrine
Equiv. . . . . .equivalent
Esp. . . . . especially
Est. . . . . .estradiol
Eth. . . . . ether
Ext. .extract

F.A. . . . . folic acid
FAD . . . . .flavin adenine dinucleotide
FMN. . . . . .flavin mononucleotide
FRH . . . . FSH-releasing hormone
FSH . . . .follicle-stimulating hormone
Fluoresc. . . . . fluorescent

GH . . . . .growth hormone (STH)
G.I. . . . . gastro-intestinal
Gln. . . . . glutamine
Glu. . . . . .glutamic acid
Gluc(ag). . . . . .glucagon
Gly. .glycine
GPU . . . . .guinea pig unit
GRH. . . . . growth (somatotrop(h)in) releasing hormone
GTF . . . . .glucose tolerance factor
HCG . . . . . . human chorionic gonado trophin
HGH. . . . . . human growth hormone
His. .histidine
HMG. . human menopause gonadotrophin (mixture of FSH and LH)
HMP . . . . .hexose monophosphate
Hyp. R.F., HRH .hypothalamic-releasing factor (hormone)

Ile. . . . . isoleucine

In. . . . . insulin
Insol. . . . . .insoluble
IRC . . . . ion exchange resin
Irrad. . . . . irradiated
I.U. . . . . .international unit
I.V. . . . . .intravenous

Leu. . . . . .leucine
LH . . . . luteinizing hormone
LLD . . . . *L. lactis Dorner*
LRH . . . . .LH-releasing hormone
Lys. . . . . .lysine

Max. . . . . .maximum
me. . . . . .methyl
Met. . . . . .methionine
Metab. . . . . .metabolism
MIH . . . . MSH-inhibiting hormone
Monocl. . . . . monoclinic
MP . . . . .melting point
MRH. . . . . . . .MSH-releasing hormone
MSH .melanocyte-stimulating hormone
MW. . . . . molecular weight

NAD(P) . . . . nicotinamide adenine dinucleotide (phosphate)
NADPH. . . . . .reduced NADP
Nia. . . . . .niacine
NIH . . . National Institutes of Health
Nor., Norepi. . . . . . . norepinephrine
NRC . . . . .National Research Council

OAA. . . . . .oxaloacetic acid
Oxy. . . . . .oxytocin

P.A., Pant. . . . . . . pantothenic acid
PBI . . . . protein-bound iodine
Pet. . . . . .petroleum
PGA . . . . .pteroyl glutamic acid, folic acid
Phe. . . . . phenylalanine
pI . . . . .isoelectric point

PIH. . . . prolactin-inhibiting hormone
PMSG . . . . .pregnant mare serum gonadotrophin
Ppt. . . . . precipitate
PRH . . . . prolactin-releasing hormone
Pro. . . . . .proline
Prog. . . . . progesterone
Prol. . . . . .prolactin
PTH . . . . parathormone

RBC . . . . red blood cell
Relax. . . . . relaxin
RNA. . . . . ribonucleic acid
mRNA . . . messenger ribonucleic acid

Ser. .serine
Serot. . . . . serotonin
Sl. .slightly
Sol. . . . . .soluble
Soln. . . . . solution
St. . . . . .standard
STH . . . . .somatotrop(h)in (GH)

T3 . . . . triiodothyronine
T4 . . .tetraiodothyronine (thyroxine)
TCA . . . . . tricarboxylic acid (cycle), Krebs (cycle)
TCT . . . . thyrocalcitonin
Test., Testos. . . . . testosterone
Thr. . . . . threonine
TPN . . triphosphopyridine nucleotide (NADP)
TRH . . . . TSH-releasing hormone
Try. . . . . tryptophan
TSH . . . thyroid-stimulating hormone
Tyr. tyrosine

UDP . . . . uridine diphosphate
USP . . . . *United States Pharmacopeia*
UV . . . . .ultraviolet
v . . . . volt
Val. .valine
Vaso. . . . . vasopressin
Vit. .vitamin

Contents

Part 1

The following 15 mineral elements consist of 5 macro or bulk essential elements (Ca, Mg, Na, K, P) and 10 micro or trace elements (Fe, Cu, Mn, Zn, I, Se, Mo, Cr, Co, F). Not all of the latter have been proved essential for life in man, but they have been proved essential for some living system or for normal health and longevity in humans. On the basis of present ongoing research, it is most likely that the elements in question (Se, Mo, Mn, Cr, F) will be shown to be essential for the human system in the near future. Need for the bulk essential elements has already been demonstrated. Several other elements (e.g., Sn, Si, V, As, and Ni) may also be found to be essential in extremely small amounts, but much research remains to be done before such determinations can be made.

It should be noted that under physiological conditions (i.e., in aqueous solution) 10 of the 15 elements (Ca, Mg, Na, K, Fe, Cu, Mn, Zn, Cr, Co) are positively charged (cations). Five elements (P, I, Se, Mo, F) are negatively charged (anions), three of them occur as oxide complexes (PO_4, SeO_4, MoO_4). Four elements (Na^+, K^+, F^-, I^-) are univalent in physiological solutions; ten elements (Ca^{2+}, Mg^{2+}, Fe^{2+}, Cu^{2+}, Co^{2+}, Mn^{2+}, Zn^{2+}, $SeO_4{}^{2-}$, $MoO_4{}^{2-}$, $HPO_4{}^{2-}$) are divalent; one is trivalent (Cr^{3+}).

These elements can and do interact with one another as shown in the solubility table where the physiological forms of the minerals and other physiological ions present in the gastrointestinal tract are charted (as negative ions against positive ions). It will be noted that the divalent negative ions tend to form more insoluble products when in the presence of oppositely charged

Solubility Table

	I^-	Cl^-	SeO_4^{2-}	SO_4^{2-}	CO_3^{2-}	F^-	PO_4^{3-}	OH^-	MoO_4^{2-}
H^+	S	S	S	S	S	S	S	S	sa
NH_4^+	S	S	S	S	S	S	S	S	S
Na^+	S	S	S	S	S	S	S	S	S
K^+	S	S	S	S	S	S	S	S	S
Mg^{2+}	S	S	S	S	sa	sa	sa	Ia	sa
Ca^{2+}	S	S	sa	sa	sa	sa	sa	S	Ia
Co^{2+}	S	S	S	S	Ia	S	Ia	Ia	—
Fe^{2+}	S	S	—	S	sa	sa	Ia	Ia	—
Cu^{2+}	—	S	S	S	Isa	sa	Ia	Ia	—
Mn^{2+}	S	S	S	S	sa	Ia	Ia	Ia	—
Zn^{2+}	S	S	S	S	sa	Ia	Ia	Ia	—
Cr^{3+}	S	I	—	I	S	Ia	I	Ia	—

S = soluble in water; sa = sparingly soluble in water, soluble in acids; Ia = insoluble in water soluble in acids; Isa = insoluble in water, sparingly soluble in acids; I = insoluble in water and acids.

divalent positive ions than with univalent ions. Note that most ions are soluble at the acid pH of the stomach, (H^+ row), but when the pH turns alkaline in the intestine, most of the divalent positive metal ions become insoluble (OH^- column) especially trace elements. This property has significance for the human uptake of metallic ions, making it harder for them to be absorbed and necessitating special mechanisms for absorption (e.g., active transport, vitamin D, bile salts, etc.). Although it makes absorption of a toxic excess of metal ions more difficult, it hinders absorption of essential minerals as well. This may explain why practically all essential minerals have a mineralovitamin form that is preferentially absorbed (e.g., vitamin B_{12} and Co, GTF and Cr).

The effective concentrations of some trace elements are very low (parts per million, or micrograms per gram). However, the toxic limits of some are uncomfortably close to the required dosages. This means that a very delicate balance exists for many trace elements between toxicity, vitality, and deficiency. This balance could easily be upset by the presence of excessive trace amounts of precipitating ions, as might occur with incorrect mineral pill supplementation. These precipitates could form in sensitive tissues such as kidney, heart, and brain, with possibly fatal consequences. Moreover, imbalance of ions could disturb intracellular enzyme reactions, and pH, or affect the irritability of muscle or nerve (with resulting tetany or convulsions).

For these and similar physiological considerations, it is definitely not advisable to attempt self-medication with mineral pill supplements without medical supervision. It will be noted that most if not all of the 15 essential trace elements are already present in the average normal American diet in sufficient concentrations, with supplementation indicated only for special conditions such as pregnancy, senescence, and so on. If a deficiency is indeed medically or professionally indicated, it would be far safer to use dietary measures to correct this deficiency, than using pill supplements, using the tables furnished in this book which indicate foods enriched in the particular mineral question. The dangers of exceeding a toxic dose would be minimized, while at the same time one would obtain synergistic vitamins and minerals from the enriched foods.

The picture of the role of essential minerals is by no means clear or complete. With the advent of new, more sensitive analytical methods, discoveries of new functions can be expected in the near future. In addition to the fundamental chemical roles outlined in the succeeding pages there is every likelihood of more basic functions being discovered for several minerals, especially for Cr, Se, Zn, Mo, Mn, and V, such as roles in the fine control of DNA synthesis, mechanisms of development, the onset of senescence, and arteriosclerosis.