

New Perspectives on the Essential Trace Elements

Earl Frieden

Florida State University, Tallahassee, FL 32306

The remarkable development of molecular biology has had its counterpart in an impressive growth of a segment of biology that might be described as atomic biology (1). The past several decades have witnessed an explosive increase in our knowledge of the many elements that are essential for life and maintenance of plants and animals. This research also encompasses the subject area which is frequently identified as bio-inorganic chemistry and trace element research. Summarized in Table 1 are the 30 essential elements classified into the six bulk or structural elements, five macrominerals, and 19 trace elements. The dominance of the eleven common structural elements, which in humans account for over 99% of the atoms, is shown in Figure 1 (2). Beginning with fluorine and iron, the trace elements appear in much lower concentrations. The 19 essential trace elements include the three prominent biologically active metals—iron, zinc, and copper. All the remaining essential elements are considered ultratrace since they involve less than 10 mg in the adult human (except in the special circumstances of fluorine and boron). Their positions in the periodic table are shown in Figure 2.

The story of the discovery of the essential trace elements has been outlined by Schrauzer (2). Knowledge of the biological function of the trace elements has lagged far behind our understanding of their chemistry. The treatment of anemia with iron and the association of iodine deficiency with goiter marked these as the only two trace elements recognized as essential for animals well into the twentieth century. Early experiments by plant physiologists established the absolute requirement of zinc in mold growth, but this work was overlooked.

In the twentieth century there were two major periods of activity in biological trace element research (2). In an early classical period, 1925–56, serendipity contributed to the discovery of the essentiality of copper, zinc, cobalt, manganese, and molybdenum in animals. A more active “modern” period, 1957–1980, dominated by the late Klaus Schwarz, (3) was based on the experimental induction of trace element deficiencies. These efforts have resulted in evidence supporting the essentiality of selenium, chromium, tin, vanadium, fluorine, silicon, nickel, lead, cadmium, arsenic, and, most recently, lithium (4).

The addition of these recently identified essential ultratrace elements brings to a total of 30 the essential elements, with perhaps more yet to be discovered (Fig. 2). We believe that this research presents new perspectives about the trace

Table 1. Classification of the Essential Elements

1. Bulk Structural Elements: H, C, N, O, P, S.
2. Macrominerals: Na, K, Mg, Ca, Cl, PO₄, SO₄.
3. Trace Elements: Fe, Zn, Cu.
Ultratrace Elements:
Nonmetals: F, I, Se, Si, As, B.
Metals: Mn, Mo, Co, Cr, V, Ni, Cd, Sn, Pb, [Li]

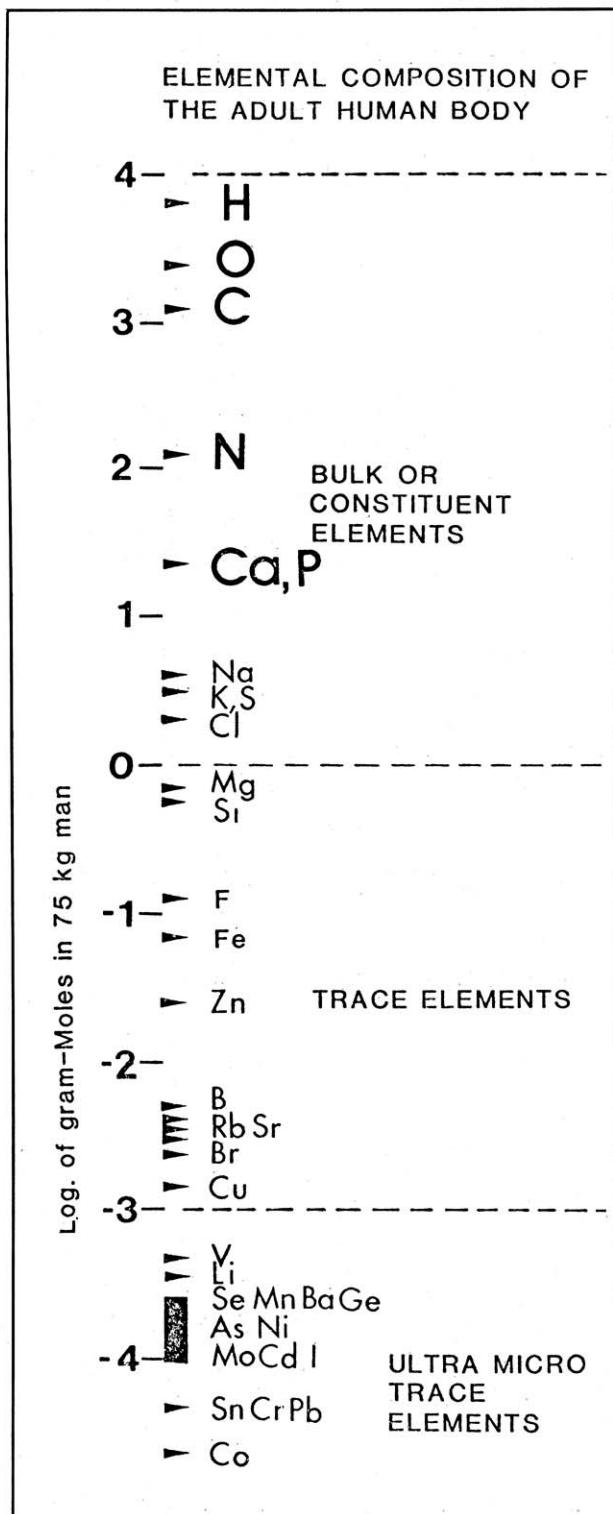


Figure 1. Elemental composition of the human adult expressed on a logarithmic scale (from G. N. Schrauzer (2)).

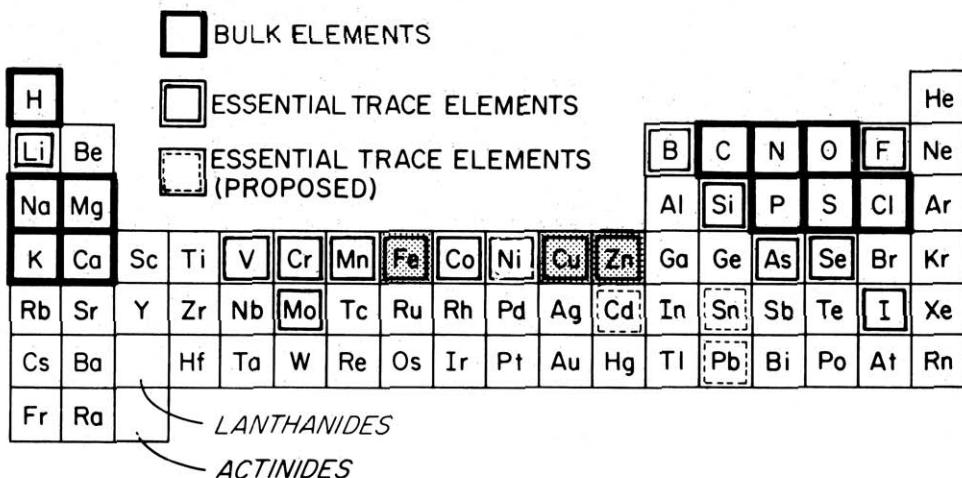


Figure 2. Present status of the essentiality of the elements and the periodic table. The 11 bulk or structural elements, 3 essential trace elements (Fe, Zn, and Cu), 16 essential ultratrace elements, are identified. (Adapted from Valkovic (26)).

elements and how they can function as essential ultratrace atoms.

The Concept of Essentiality

The contemporary era of biological trace element research arose from success in devising experimental methods to induce specific trace element deficiencies in laboratory animals. This required maintaining animals on special formulated synthetic diets in controlled environmental chambers (3). This set the stage for a rigorous challenge to the problem of essentiality (Table 2).

The simplest definition of an essential element is that it is an element required for the maintenance of life; its absence results in death or a severe malfunction of the organism. Experimentally, this rigorous criterion cannot always be satisfied and this has led to a broader definition of essentiality. An element is considered essential when a deficient intake produces an impairment of function and when restoration of physiological levels of that element relieves the impaired function or prevents impairment. The organism can neither grow nor complete its life cycle without the element in question. The element should have a direct influence on the organism and be involved in its metabolism. The effect of the essential element cannot be wholly replaced by any other element.

Some years ago, the late G.C. Cotzias (5) defined several additional biochemical criteria for an essential element. (1) The element is present in tissues of different animals at comparable concentrations; (2) its withdrawal produces similar physiological or structural abnormalities regardless of species; (3) its presence reverses or prevents these abnormalities; and (4) these abnormalities are accompanied by specific biochemical changes that can be remedied or prevented when the deficiency is checked.

The essential trace elements provide a classic example of required nutrients as described by Bertrand (6) as early as

1912. An organism passes through several stages as the concentration of an essential nutrient progresses from deficiency to excess (Fig. 3). In absolute deficiency, death may result. With limited intake, the organism survives but may show marginal insufficiency. With increasing nutrient a plateau representing optimal function is reached. As the nutrient is given in excess, first marginal toxicity, then mortal toxicity are attained. While this curve may vary quantitatively for each essential nutrient, the basic pattern holds for virtually all the essential trace elements. This is illustrated in Figure 3 for selenium and fluoride (1). For these two elements there is barely a tenfold range between intake per day for survival and that for the appearance of toxic effects. Obviously high toxicity has not prevented the recognition of these two elements as essential ultratrace elements although their high toxicity complicates experimental design. Several additional proposed essential elements—Pb, As, Cd—also show significant toxicity.

The Evolution of the Trace Elements

A survey of possible future essential trace elements has been published (1). In this review the close relationship between elemental abundance and the requirement for specific elements was emphasized. The elements abundant in living systems reflect their relative concentrations in the oceans (see Table 3) and, to a lesser extent, in the earth's

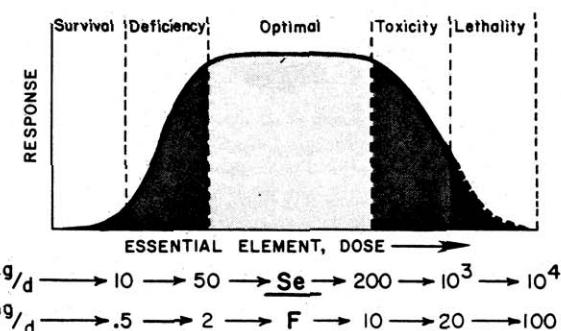


Figure 3. Dose response range of an essential element. Estimates of specific requirements in terms of micrograms per day for selenium or milligrams per day for fluorine are included.

Table 2. Criteria for Essential Elements

- 1) A physiological deficiency appears when the element is removed from a purified diet.
- 2) The deficiency can be relieved by the addition of one specific element.
- 3) A specific biochemical function is associated with a particular element.

Table 3. The Abundance of the Elements in the Oceans

> 10 ⁶ nM	H, O, Na, Cl, Mg, S, K, Ca, C, N
10 ⁶ –10 ² nM	Br, B, Si, Sr, F, Li, P, Rb, I, Ba
10 ² –1 nM	Mo, Zn, Al, V, Fe, Ni, Ti, U, Cu, Cr, Mn, Cs, Se, Sb, Cd, Co, W

Adapted from Egami (8).

crust (7). Since it is probable that life originated in water or nearby shore, the elements required for life were primarily derived from their concentrations in the primitive oceans (8).

However, this close correlation was mitigated by several factors. The first relates to the enriched content of carbon, nitrogen, phosphorous, and sulfur in living organisms. This is accounted for by the probability that life originated at the edge of the sea or in sediments where the concentrations of phosphates and other minerals were much higher than in primitive oceans. Perhaps these sediments also contained higher concentrations of the other three possible essential elements (As, Pb, Sn), which were too dilute in the oceans to be included in Table 3.

Another factor to be considered is that the distribution of the elements in our oceans today does not reflect that of an earlier era when the earth's atmosphere was not strongly oxidizing. Then iron would have been present in the more soluble Fe(II) oxidation state. This would explain why iron is so prevalent in later biochemical systems despite its high dilution in water.

A third factor is the natural selection process, which led to the choices of a few elements that had superior reactivity. For example, divalent manganese, nickel, cobalt may have had a function similar to zinc, as illustrated by the observation that these metals can replace zinc ions in certain metalloenzymes. The reconstituted enzyme is usually less efficient whenever a metal other than zinc is bound at the active site, indicating that zinc possesses the optimal properties for that metalloenzyme.

However, it is clear that elemental abundance is not the only determining factor. As noted above, the solubility of these elements will be another crucial factor. R. J. P. Wil-

Pre-transition metals																	
Transition metals			Post-transition metals														
Li	Be																
Na	Mg	Al															
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga					
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb			
Cs	Ba		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po		
Fr	Ra		I04	I05	I06	I07		I09									
Lanthanides		La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu	
Actinides			Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lw

Figure 5. The classification of the different metals based on their relationship to the transition metals.

liams (9) has enumerated a number of general chemical parameters which influence the selection of metal ions by living cells. These include charge-type, ionic radius, liganding atom(s), preferential coordination geometry, spin-pairing stabilization, kinetic controls, and the chemical reactivities of metal ions in solution. These factors have been discussed at length by DaSilva (10) and permit some brief speculations about possible future essential trace elements.

Possible Future Essential Trace Elements

All of the nonmetals, (Fig. 4) excluding the inert gases, with an atomic weight less than bromine are now considered to be essential. Bromine is probably the most likely remaining nonmetal to qualify as an essential element for a limited number of biological species.

Most of the remaining lighter elements are metals and most of the recognized trace elements can be regarded as transition metals or as a subdivision of the group as shown in Figure 5. The pre-transition metals include the alkali metals (Group IA), the alkaline earth metals (Group IIA), and the Group III elements. Many of these metals are essential—Na, K, Mg, Li. Rubidium, strontium, and barium are the strongest remaining candidates that may eventually be found useful biologically.

The most prominent groups of trace elements are observed in the transition and the post-transition metals. The transition metals have *d* orbitals that are increasingly filled with electrons, leading to a gradual transition in metallic properties. They are also especially effective in forming stable complexes with sulfur, nitrogen, and oxygen, all of which are side-chain constituents of proteins. Iron occupies a dominant position among the transition metals in the vertebrates as the metal of choice for hemoglobin and other heme proteins.

Except for titanium, all the first-level transition metals (V, Cr, Mn, Fe, Co) are considered to be essential. Several of the neighboring post-transitional metals (Zn, Cu, Ni) are also important trace elements. The abundance of several of these elements particularly iron, zinc, and molybdenum, in the early oceans has stimulated speculation about the origins and the evolution of the dependence of organisms on the transition metals.

The remaining transition elements do not suggest any strong additional possibilities. Titanium inhibits numerous hydrolytic enzymes, and as titanate, can be stimulatory to

H	NON-METALS							He
Li	Be	B	C	N	O	F	Ne	
Na	Mg	Al	Si	P	S	Cl	Ar	
K	Ca	Ga	Ga	As	Se	Br	Kr	
Rb	Sr	In	Sn	Sb	Te	I	Xe	
Cs	Ba	Tl	Pb	Bi	Po	At	Rn	
Fr	Ra	METALS						

Figure 4. A part of the periodic table of the elements showing the division between metals and nonmetals.

growth, but there is no evidence that it is required. Zirconium is relatively nontoxic and inactive; 5 ppm in the drinking water of mice did not affect their health and longevity (11). Of the heavier transition elements, only molybdenum has been proven essential. The remaining transition metals are poorly absorbed by cells and are relatively nontoxic. Tungsten deserves further comment because it is frequently antagonistic to molybdenum; it decreases the activity of several oxidative enzymes that require molybdenum (xanthine oxidase, nitrogenase). Tungsten has been reported to be biologically active as a component of the enzyme formate dehydrogenase in several bacteria (12).

The post-transition metals have filled *d* subshells when they give up electrons. This gives these metals strong reactivities and the ability to form coordination complexes. The most prominent essential trace elements in this group are zinc and copper which serve as coenzymes or prosthetic groups for a large number of enzymes. Probable additional essential ultratrace elements in this group are Ni, Cd, Sn, and Pb. Several other post-transitional metals (Au, Ag, Pt, Hg) have played a significant role in the history of our civilization, but they have not been shown to be essential.

Lanthanides and Actinides

Lanthanides and actinides are two groups of heavy elements that are so radioactive and/or toxic as to be precluded from serving a useful part in any biochemical system. Moreover, the actinides are found only in extremely small quantities. The lanthanides are more common and more metallic than usually realized. Normally, neither the lanthanides nor actinides occur in animal or plant tissues. Only traces of lanthanides (<0.5 ppm) are detected in the bones of animals exposed to them. It is not anticipated that further studies will provide evidence for any essential role by either of these series of elements. However, there is interest in that lanthanide ions possess unique chemical properties that make them valuable probes for the interaction of calcium ion with biological systems (13).

How Do the Essential Trace Elements Work?

The essential ultratrace elements are universally required for growth and survival of cells and organisms. They normally occur and function in cells at extremely low concentrations, usually far less than 1 μM and as low as 10^{-8} to $10^{-9} M$ (50 $\mu g/day$ for selenium).

How can the ultratrace elements serve as essential atoms or molecules in cells? There is an impressive number of trace elements, especially among the transition metal ions, that have been shown to serve as required growth factors at extremely low concentrations (Table 4). Perhaps there is a universal transition metal binding site that can respond individually to a variety of different metal ions as long as they are not blocked by another metal ion. Thus when the diet and the environment are rigidly controlled, the general transition metal binding site becomes accessible to new metal

ions which were removed previously by the diet preparation process.

Most of the facts available about the function of the trace elements focus on their role as metalloenzymes. The dominant theme has been that the trace elements are essential because they serve as required prosthetic groups in active sites and/or as coenzymes for indispensable metalloenzymes or metal-ion activated enzymes. In the metalloenzymes, a fixed number of specific metal atoms (usually Fe, Zn, Cu, Mn, Mo, Co, Ni, etc.) are firmly associated with a specific protein. This combination produces a unique catalytic function. It has been estimated that one-fourth to one-third of all known enzymes require a metal ion as a functional participant.

The Metalloenzymes

The prime example of metalloenzymes are the proteins that contain iron, zinc, or copper ions in their active sites. Zinc enzymes have been identified for all six major classes of enzymes: oxido-reductases, transferases, hydrolases, lyases, isomerases, and ligases. The zinc ion serves as a super acid active center in proteins which are capable of promoting hydrolysis of a variety of susceptible chemical bonds. The protein portion of the metalloenzyme also selects and limits the substrates that provide the bond to be hydrolyzed. Metal ions can also play a major role in the geometry of the protein, the positioning of the substrate, and the formation of the active site.

Metals such as iron and copper have another dimension, that of readily changing their oxidation states so that they can also serve as catalytic electron carriers. They produce oxidized substrates which then can fit into a variety of metabolic cycles. The importance of coordinated oxidases cannot be overstated. One widely held view proposed by Fridovich and coworkers (14) is that a team of enzymes is necessary for the survival of eukaryotes in aerobic life conditions. The utilization of oxygen inevitably involves the production of

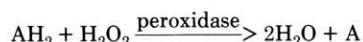
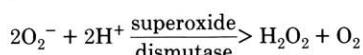
Table 5. Properties of the Essential Ultratrace Metals

Ultratrace Metal	Deficiency Signs	Specific Function
Manganese	Growth depression; bone deformities; membrane abnormalities connective tissue defects.	Carbohydrate metabolism Superoxide dismutase pyruvate carboxylase, etc.
Molybdenum	Growth depression	Oxidases: aldehyde, sulfite, xanthine. Molybdopterin.
Cobalt	Anemia; growth retardation	Constituent of vitamin B ₁₂
Chromium	Insulin resistance	Potentiation of insulin action on carbohydrates and lipids; active as a bioorganic chromium complex
Vanadium	Growth depression	Control of sodium pump; inhibition of ATPase, p-transferringases
Nickel	Growth depression Reduced N utilization Reduced Fe metabolism	Constituent of urease; Reduced hemopoiesis
Cadmium	Growth depression; Reduced reproduction	Stimulates elongation factors in ribosomes
Tin	Growth depression	(Interactions with riboflavin)
Lead	Growth depression; anemia	(Many enzyme effects)
Lithium	Growth depression Reduced reproduction	Control of sodium pump

Table 4. Recommended Safe and Adequate Dietary Intakes for Adults

Element	Intake (mg/day)
Iron (males)	10
Iron (females)	18
Zinc	15
Manganese	2.5 to 5.0
Fluorine	1.5 to 4.0
Copper	2.0 to 3.0
Molybdenum	0.15 to 0.5
Chromium	0.05 to 0.2
Selenium	0.05 to 0.2
Iodine	0.15

reactive toxic oxygen byproducts, particularly O_2^- and H_2O_2 . Thus, to survive, all aerobic cells must have a complement of intracellular enzymes whose major activity is to convert O_2^- and H_2O_2 into nontoxic forms of oxygen, O_2 , or H_2O , as depicted below:



Catalase and many peroxidases are typical heme enzymes which require iron. The metalloenzyme, superoxide dismutase, isolated from eukaryotic cytoplasm contains two atoms of copper and two atoms of zinc per molecule. No active replacement of copper has been found, but almost any transition metal will substitute for zinc at the zinc site (15). Vallee (16) has described how cobalt and various other metal ions can substitute for native zinc atoms in several zinc enzymes (carboxypeptidase, alkaline phosphatase) with retention of appreciable enzymic activity.

For the ten or so postulated essential ultratrace metals listed in Table 5, only four (Mn, Mo, Co, Ni) have been clearly identified as forming metalloenzymes. Manganese metalloenzymes are present for several important enzymes: superoxide dismutase (mitochondrial), arginase, pyruvate carboxylase, and glycosyl transferase. Manganese also appears to be rather directly involved in the enzymic machin-

ery of carbohydrate metabolism with a possible links to lipid metabolism. In all but one (nitrogenase), molybdo-metalloenzymes, the metal exists as a Mo cofactor, a complex of the metal with a novel organic molecule, called molybdopterin (17) (Fig. 6). Molybdenum may be additionally coordinated to two oxo ligands or with one oxo and one terminal sulfide ligand. In nitrogenase, the metal is present in a unique cluster containing Fe, Mo, and S^{2-} . In plants and microorganisms, nickel is known to function in several metalloenzymes—urease, several hydrogenases, and carbon monoxide dehydrogenase.

The role of cobalt, despite its complexity, is the best understood of any of the essential ultratrace metals. Both vitamin B_{12} and coenzyme B_{12} , have a cobalt ion complexed in their equatorial positions by four nitrogens of a macrocyclic ligand called corrin (Fig. 7). The corrin is covalently bonded through an amide-phosphate-ribose side chain to a 5,6-dimethylbenzimidazole group with coordinates with the cobalt ion. These compounds serve as cofactor in various enzyme reactions in which a hydrogen atom is interchanged with a substituent on an adjacent carbon atom. The best-known example of a cobalt mammalian enzyme is methylmalonyl-Co A mutase which is a mutase that catalyzes rearrangement to succinyl Co A (18).

Thus far the metalloenzymes have provided the best model for determining how the trace metal ions operate. However, data supporting this model for the six remaining ultratrace metals, Cr, V, Cd, Sn, Pb, and Li, are lacking. Chromium functions in vivo as an organic (peptide?) chromium complex. Its biological role is to potentiate insulin activity. In addition to chromium, this organic complex may contain nicotinic acid and glutathione or its constituents. Vanadium compounds inhibit numerous enzymes, particularly ATPases and phosphotransferases. This has suggested a role for the vanadate ion in the control of the sodium pump. Vanadium also serves as a biocatalyst for oxidation of substrates involved in cholesterol metabolism. Except for metallothionein induction, most biological effects of cadmium have been inhibitory. Alleviators of lead deficiency resulted in the correction or prevention of changes in iron metabolism and hematology. Data on the possible actions of tin and lithium are lacking. Thus we have no definitive explanation for the action of these last six ultratrace elements and there is no guarantee that specific peptide or protein reactants will be found. The challenge to bioinorganic chemists to solve these problems is clear.

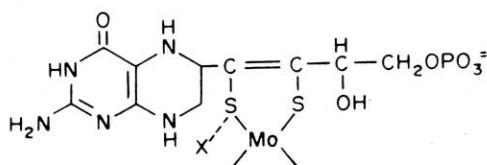


Figure 6. The proposed structure of the molybdenum cofactor, molybdopterin (17).

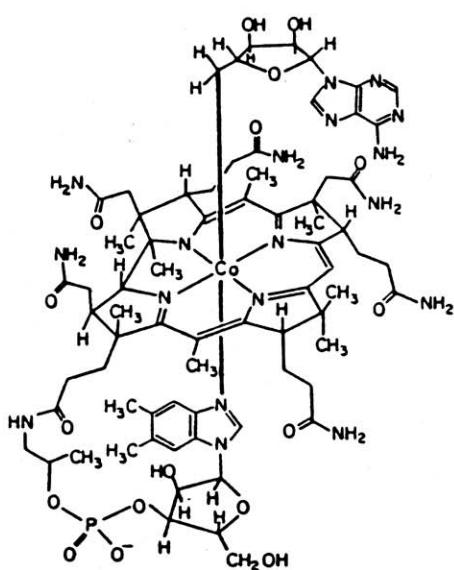


Figure 7. The chemical structure of coenzyme B_{12} showing Co(II) complexed to the macrocyclic ligand corrin.

Table 6. Properties of the Essential Ultratrace Nonmetals

Ultratrace Nonmetal	Deficiency Signs	Specific Functions
Fluorine	Growth depression; Dental caries	Structure of teeth and bones; replaces OH, inhibits enolase, pyrophosphatase
Iodine	Goiter; reduced thyroid function	Constituent of thyroid hormones— T_3 , T_4
Selenium	Muscle and pancreas degeneration; hemolysis	Constituent of glutathione peroxidase and other enzymes. Protection against oxidation of erythrocytes
Silicon	Growth depression; bone and matrix deformities	Structural role in connective tissue and osteogenic cells
Arsenic	Impairment of growth, reproduction, heart function	Increased arginine → urea + ornithine.
Boron	Growth of angiosperms; Impaired nitrogen-fixation	Metabolism of methyl compounds. Control of membrane function; nucleic acid biosynthesis; lignin biosynthesis

The Nonmetals

As shown in Table 6, the essential nonmetals comprise a much more heterogeneous group than do the transition metals, whose properties are all closely related. The two essential halogens, F and I, are highly specific and very different. Fluoride has a remarkable anti-dental caries effect. This may be related to its ability to replace OH , thereby stabilizing the structural matrix of bones and teeth. Fluoride also can inhibit strongly certain key enzymes: enolase, pyrophosphatase. Yet we cannot point to any specific enzyme or other systems that can account for the biological actions of fluoride.

One of the major surprises among the nonmetals is provided by selenium. Despite its high toxicity (0.2 mg/d), selenium has been shown to be a component of several enzymes involved in essential oxidation-reduction reactions. One enzyme, glutathione peroxidase (GSH) appears to play a major role in the protection of red blood cells against the effects of hydrogen peroxide which is readily generated inside the cell as shown below. This is a prime example of an enzyme that relies on an ultratrace nonmetal ion for its biological activity (19).



What little is known about the three remaining nonmetals, Si, As, B, emphasizes the probability of their mechanisms, as well as the previous metals, being independent for all six nonmetals. Silicon has a structural role in connective tissue and in osteogenic cells. No specific biological function for arsenic is claimed. Recent findings suggest that arsenic affects arginine, membrane phospholipid, and zinc metabolism (20). It is less toxic than selenium, an ultratrace element with an established role. The primary focus on boron has been on its essential role in plants, possibly involving membrane function and nucleic acid biosynthesis. Its role in these plant systems could be easily extrapolated to similar systems in animals.

Iodine and The Thyroid Hormones

To conclude our perspective on the nonmetals let us consider the unique relation between iodine and the thyroid hormones. Perhaps no other idea is more deeply entrenched as legend in medical history. Iodine was firmly established as an indispensable constituent of the thyroid gland by Baumann in 1896. Since then the presence of iodine has dominated consideration of thyroid hormone structure and function, with special emphasis on the properties of iodine as an electron sink. It was assumed that the 3, 5, and 3' positions on thyronine had to be filled by halogens, particularly iodine or bromine, in order to satisfy the minimum electronic and structural requirements for thyroid hormone activity. Then Jorgensen, Block, and their coworkers (21) synthesized several halogen-free derivatives which had significant thyromimetic activity, especially 3,5-dimethyl-3'-isopropylthyronine (Fig. 8) which had 20–25% of the activity of thyroxine. Thus there is no absolute requirement for iodine or any halogen for thyroid hormone activity in amphibians or mammals. The primary role of iodine is to provide appropriate spatial constraints on the 3, 5, 3'-substituents on a semirigid three-dimensional matrix (thyronine) and to facilitate the biosynthesis of tri- and tetra-iodothyronines (T_3 , T_4) in the thyroid gland (22).

What then is the unique relationship of iodine to the thyroid hormones? It is to be found in the biosynthesis and metabolism of T_4 and T_3 (22). Since early animals originated in the sea, they had ready access to iodine, for which early trapping mechanisms were developed. The presence of iodine along with H_2O_2 -peroxidase systems afforded a convenient mechanism for introducing iodine ortho to the phenolic group of tyrosine in or out of proteins to form mono- and

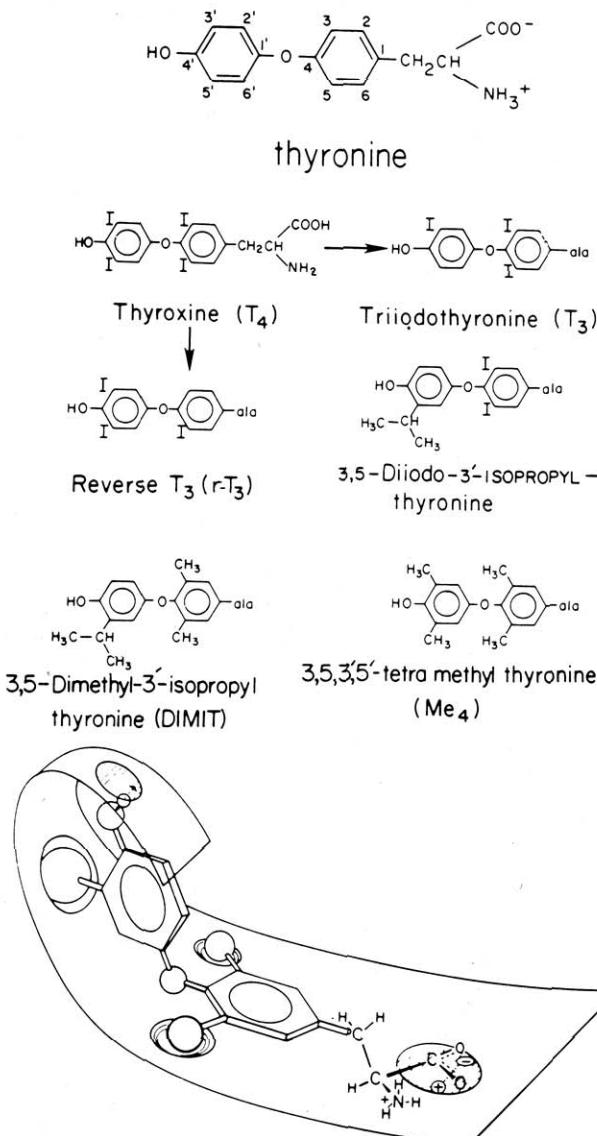


Figure 8. The structure of thyroxine, triiodothyronine, and several substituted thyronines.

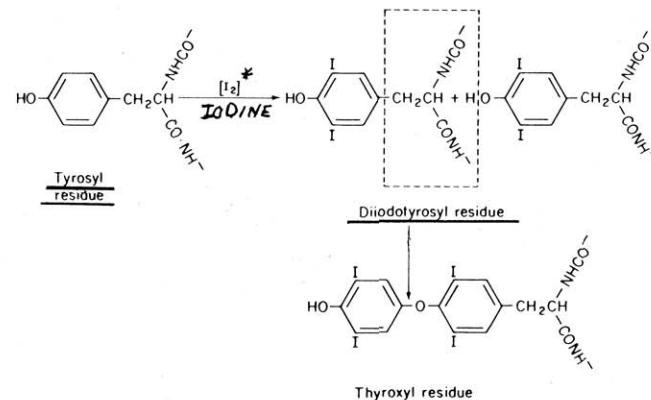


Figure 9. The formation of a thyroxyl residue from the iodination and condensation of the two tyrosyl residues.

METAL ANTAGONISMS

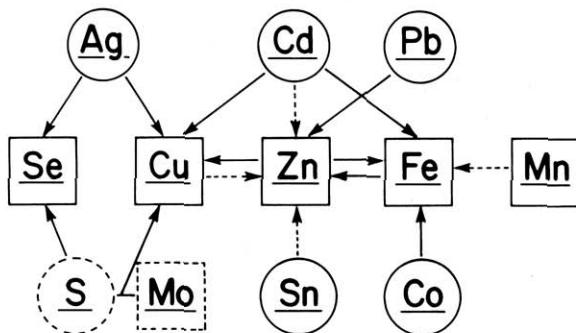


Figure 10. Antagonisms in the bio-availability of metals and nonmetals. Each solid arrow indicates a strong antagonism between the two elements. The dashed arrows suggest weaker blocks. From Ref. (23).

diiodotyrosine. The introduction of groups of similar size, e.g., methyl or isopropyl, ortho to a phenolic hydroxyl group is extremely rare in vertebrate metabolism. Under oxidative conditions, these single-ring iodo compounds were favored to undergo coupling reactions to form the iodothyronines, especially T₄ (Fig. 9). Ample proteases were available for the hydrolytic release of iodothyronines from their peptide linkages into the serum. Specific serum binding proteins, T₄-binding globulin and prealbumin, evolved to provide protective transport of the iodo amino acids.

The ability to preferentially trap iodine permitted reutilization of the iodine after metabolic deiodination, further contributing to the economy of thyroid hormone synthesis. All these circumstances combined to favor the biosynthesis of T₃ and T₄ with their unique function in the vertebrates (22).

Antagonism among the Essential Trace Elements

Our research objectives on the trace elements will not be completely achieved even after all the elements have been carefully studied for their required presence. It will then be necessary to investigate the impact of a particular essential trace element on other essential trace elements. Eventually we will want to explore the interaction of nonessential trace elements and essential trace elements. Numerous antagonistic and synergistic effects have already been observed. For example, zinc absorption is impaired by Fe(II). High zinc intake induces a relative copper deficiency, probably by interfering with copper absorption. Molybdenum and sulfur also antagonize copper by a ternary interaction involving the formation of copper thiomolybdate, which also causes a re-

duced copper uptake. Tungsten is antagonistic to molybdenum in several oxidative enzymes which require molybdenum (e.g., xanthine oxidase). Several examples of element antagonisms are presented in Fig. 10 (23). We also might expect competition among the four halides in their uptake by the thyroid gland of the vertebrates (24).

Trace element interactions are not limited to competition and antagonism. An example of a positive interaction is the role of copper (in the form of the plasma copper protein, ceruloplasmin) in promoting iron mobilization and hemoglobin biosynthesis (25).

Summary

Of the 109 known elements, 30 elements are believed to be essential to the survival of living organisms. Nineteen of the 30 are trace elements, of which 12 are transition metals. There may be several more essential elements yet to be identified. We can account for the biological activity of about one-half of the essential trace elements which function in metalloenzymes, including Fe, Zn, Cu, Mn, Mo, Co, Ni, and Se. However, we cannot explain with certainty the action of numerous essential metal and nonmetal ultratrace elements, including V, Cr, Cd, Pb, Sn, Li, F, Si, As, and B. This latter group provides a new challenge in atomic biology to the bioinorganic chemist, the biochemist, and the nutritionist.

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