PROCEEDINGS SERIES

NUCLEAR ACTIVATION TECHNIQUES IN THE LIFE SCIENCES 1972

PROCEEDINGS OF A SYMPOSIUM ON
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HELD BY THE
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VIENNA, 1972

FOREWORD

Nuclear activation techniques have contributed significantly in recent years to measurements of elemental concentrations in biological and environmental materials, particularly for many of the so-called trace elements that occur at extremely low concentrations, and their range of applications has continued to expand due both to technical improvements in methodology and to an increased awareness on the part of the scientific community at large of the vital importance of trace elements in the biosphere. No fewer than thirteen trace elements have now been identified as essential for man and the higher animals and many others are known or suspected to play an important role in health and disease. Concern over the still largely unknown changes in the exposure of man to trace elements as a result of industrial pollution and newer methods of food processing has given added impetus to much of the research work that is now being carried out.

The first Symposium on Nuclear Activation Techniques in the Life Sciences was convened by the International Atomic Energy Agency in Amsterdam, the Netherlands, in May 1967. Five years later, in March 1972, the second symposium of the same title was held in Bled, Yugoslavia, to provide a forum for reviewing recent advances in our knowledge of the normal biological roles and toxicological hazards of trace elements, and for reporting and discussing some of the newer technical developments in activation analysis techniques and their application in the life sciences.

Ninety-nine participants from 23 countries and three international organizations attended the meeting, and 49 papers were presented on general analytical methods, toxicology and public health, animal and plant studies, and medicine, in-vitro and in-vivo studies.

The Agency gratefully acknowledges the generous invitation of the Government of Yugoslavia to hold the meeting in Bled.

EDITORIAL NOTE

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CONTENTS

GENERAL ANALYTICAL METHODS
(Sessions I and II)

TOXICOLOGY AND PUBLIC HEALTH (Sessions III and IV)

ANIMAL AND PLANT STUDIES (Session V)

MEDICINE, IN-VITRO STUDIES (Sessions VI, VII and VIII)

MEDICINE, In-VIVO STUDIES (Session IX)

GENERAL ANALYTICAL METHODS

Session I

Chairman

L. KOSTA (Yugoslavia)

Opening Review Paper:

ELEMENTS NEWLY IDENTIFIED AS ESSENTIAL FOR ANIMALS*

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Abstract

ELEMENTS NEWLY IDENTIFIED AS ESSENTIAL FOR ANIMALS.

In contrast to the 11 elements of low atomic weight which constitute the bulk of living matter, essential trace elements are effective in very small amounts. They are always linked to organic compounds by co-ordination or covalent bonds. Through special physicochemical conditions they are able to fulfil highly specific functions, playing a decisive role in life. The principal parameters and dimensions which characterize the role of trace elements in health and disease processes are illustrated, using as examples some elements recently discovered to be indispensable. Until 1957 only seven elements were proved essential in animals and man: iron, iodine, copper, manganese, zinc, cobalt, and molybdenum. In 1957 selenium was added. Chromium (III) was established to be essential for glucose utilization in 1959. Subsequently, highly purified, chemically defined amino acid diets and trace-element "sterile" isolator techniques were developed. By this approach tin was recognized in 1970, and vanadium in 1971, to be necessary for growth in the rat, followed by the demonstration that fluorine is essential for growth and development, aside from its effects on teeth and bone. Two other elements, silicon and nickel, may be required but proof for their essentiality is not yet rigid. We are thus confronted with a number of elements newly demonstrated to be indispensable. Selenium serves to illustrate that vastly different deficiency diseases in different species are caused by lack of a specific trace element, and that various compounds of an element can have very different potencies. Chromium shows that deficiency of an essential trace element may produce only minor but clinically important changes, and that different valence states show different biological activity. Hexavalent chromium is inactive, and only trivalent, and possibly bivalent chromium are biologically useful. Thus, determination of an element in diets, tissues, or blood does not constitute an estimate of biological activity. To determine availability, nutritional balance studies and biological assays are unfortunately needed. Tin serves as example of an element for which no biological function was known before it was recognized to be essential for mammalian growth, while vanadium, on the other hand, was suspected for years to have biological and clinical importance, but the crucial experiment with animals could not be done until recently.

Trace elements, aside from their toxicological effects, play a major role in disease mechanisms if there is too little, too much (imbalance), or if there are disturbances in their utilization and metabolism. Highly specific mechanisms are frequently used in absorption and handling of trace-element supplies, and of essential elements in blood plasma. Often there are storage mechanisms, such as ferritin for iron, thyroglobulin for iodine, and fluoroapatite for fluorine. Other elements, such as vanadium and possibly tin, are stored in fat tissue. While some older trace elements are connected with well-known clinical disease entities, such as iron-deficient anaemia and goitre due to lack of iodine, others are not yet connected with specific diseases. It may be expected that some of the newly essential elements may eventually be of clinical importance. Areas where trace-element function may be implicated etiologically are atherosclerosis, cerebral arterial disease, cancer, cardiomyopathy, muscular dystrophy, and some degenerative diseases of the central nervous system, and possibly even some diseases as common as degenerative osteoarthritis. For many of the problems in bioinorganic chemistry and clinical trace-element research, activation analysis appears to be the optimal approach.

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1. INTRODUCTION

Trace elements are elements which occur only in small amounts within a given matrix, whereby the question of what constitutes a trace amount is clearly a matter of convention and usage. However, in biological systems there is a deeper meaning to the term since trace elements within living matrices are often not coincidental contaminants but fulfil important functions. The organism displays some very efficient devices such as membranes to keep out undesirable elements[1]. There is hardly an element, on the other hand, that cannot be detected in animals if highly sensitive methods of analysis are applied. The question, therefore, whether any element found in living tissue is there by coincidence or whether it belongs to that special group of elements which we call essential must be resolved in each case by appropriate experimentation.

The essential elements fulfil functions of paramount importance to life. They are indispensable for normal function, well being, and survival. Some of them are effective in exceedingly small amounts. They are almost always linked to specific organic compounds via coordination or covalent bonds. Through these particular physiochemical conditions they are able to fulfil their highly specialized catalytic functions. Functions, incidentally, which may go back to prebiotic biochemistry.

In the following, I shall attempt to delineate a few parameters and principles which characterize the role of trace elements in health and disease, not by recapitulating the known facts about extensively studied elements such as iron, iodine, copper, zinc, etc., but by describing some elements discovered more recently to be indispensable.

As with almost all good things in life, trace elements are related to disease if there is too little or too much. In addition, diseases are frequently related to trace elements if normal mechanisms of their utilization are disturbed. These mechanisms involve absorption and membrane transport, transport in blood, lymph, cerebrospinal fluid and other liquid vectors, specific systems for storage, and highly specialized protein structures in which trace elements are used as catalytic sites.

I will deal first and foremost with the problem of too little. The problem of too much, i.e., of toxic amounts of trace elements, will be treated by others in this symposium. Problems of metabolic disturbances of trace-element utilization are dealt with briefly within the context of this paper.

2. ESSENTIAL ELEMENTS AND THEIR DISTRIBUTION IN THE PERIODIC SYSTEM

Truly new basic knowledge about trace elements essential to animals and man has been derived mainly from modern nutrition research which has taken an entirely new turn over the past two decades. Almost 100 years were needed to clarify the main organic nutrients, the amino acids and vitamins, which are indispensable for growth and survival of the organism.

[1] This does, of course, not exclude the possibility that traces of certain elements can slip through. The very large amounts of calcium, for example, which are used in the form of calcium phosphate by vertebrate animals, especially the mammals, for structural support, usually contain traces of strontium or barium.

TABLE I. DISCOVERY OF TRACE-ELEMENT REQUIREMENTS

Iron . . . . 17th century	
Iodine 1850	Chatin, A. [1].
Copper 1928	Hart, E.B., H. Steenbock, J. Waddell, C.A. Elverhjem [2].
Manganese 1931	Kemmerer, A.R., W.R. Todd [3].
Zinc 1934	Todd, W.R., C.A. Elverhjem, E.B. Hart [4].
Cobalt 1935	Underwood, E.J., J.F. Filmer [5]. Marston, H.R. [6]. Lines, E.W. [7].
Molybdenum 1953	de Renzo, E.C., E. Kaleita, P. Heytler, J.J. Oleson, B.L. Hutchings, J.H. Williams [8]. Richert, D.A., W.W. Westerfeld [9].
Selenium 1957	Schwarz, K., C.M. Foltz [10].
Chromium 1959	Schwarz, K., W. Mertz [11].
Tin 1970	Schwarz, K., D.B. Milne, E. Vinyard [12].
Vanadium 1971	Schwarz, K., D.B. Milne [13]. Hopkins, L.L., Jr., H.E. Mohr [14].
Fluorine 1971	Schwarz, K., D.B. Milne [15].
Silicon 1972	Schwarz, K., D.B. Milne [16]. Carlisle, E.M. [17].

They have been identified and are now available in crystalline form. This enables us to clarify the need for as yet unresolved inorganic trace elements (Table I). Until 1957 only seven such elements were recognized as essential for animals: iron, iodine, copper, manganese, zinc, cobalt, and molybdenum [1-9]. To them we have added six new essential elements over the past 15 years [10-17]. These are selenium, chromium, tin, vanadium, fluorine, and silicon.

It is interesting to note that of the 92 elements listed in the classic periodic system only 11 account for the bulk of the living matter (Fig. 1). All of them are of low atomic weight. They belong to the smallest 20 elements in the periodic system. All seven essential trace elements known before 1957, and also selenium, chromium, tin, and vandium, are of slightly higher atomic weight but they also have relatively low atomic numbers. With the recent discovery of the essentiality of fluorine and silicon, this clear-cut separation has been obliterated. Now the essential trace elements overlap with the main atomic constituents of the body. However, none of the 39 elements exceeding the atomic number of 53 (iodine) has yet been shown to be of any biological significance for animals, except for toxic manifestations.

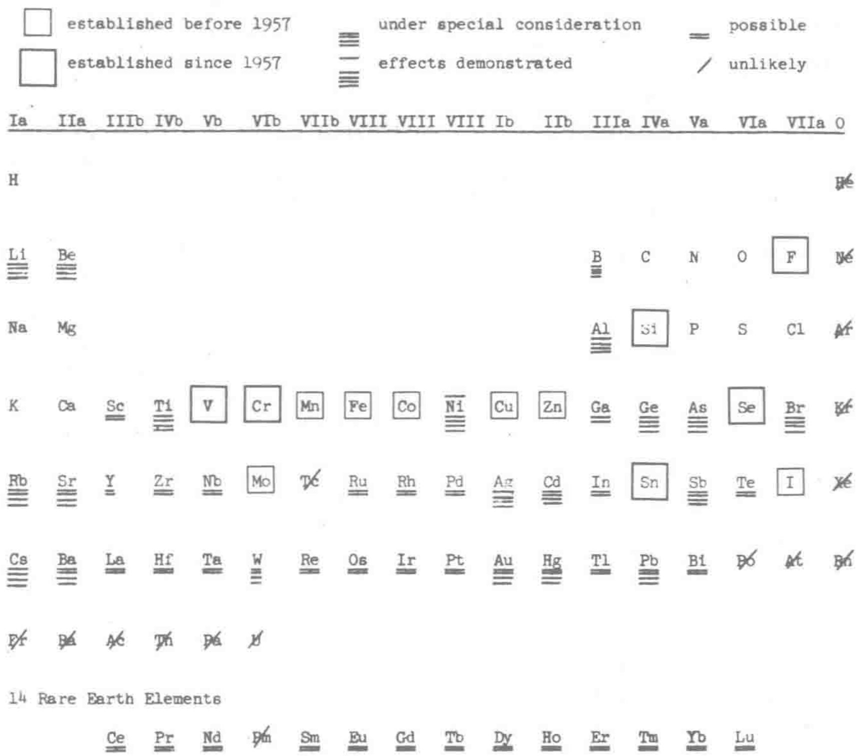

FIG.1. Distribution of trace elements of known and potential importance for the mammalian organism. Status as of 1972.

3. SELENIUM: DIVERSITY OF DEFICIENCY SYMPTOMS, STRUCTURE/ACTIVITY RELATIONSHIPS, AND INTERDEPENDENCE WITH OTHER NUTRIENTS

The physiological importance of selenium and chromium was established in our laboratory in 1957 and 1959. Until 1957, selenium, one of the rarer elements of our planet's surface, was known only for its toxic effects and was never thought to be of benefit to animals or man [18]. We identified this element as the integral, active principle of the so-called Factor 3, an agent found in yeast, liver, kidney, and many other source materials, which prevents fatal dietary liver necrosis in the rat [19]. The discovery of selenium concluded seven years of attempts to fractionate and isolate Factor 3 which we thought to be a new vitamin. In natural source materials selenium is organically bound.

The principle that an inadequate supply of a specific trace element can cause vastly different deficiency symptoms in various animals is well illustrated by selenium responsive deficiency diseases which occur in many species (Table II) [20]. Almost all of them are fatal. In many species