DEFICIENCY DISEASE

By RICHARD H. FO

THOMAS

DEFICIENCY DISEASE

Functional and Structural Changes in Mammalia Which Result from Exogenous or Endogenous Lack of One or More Essential Nutrients

By

RICHARD H. FOLLIS, JR., M.D.

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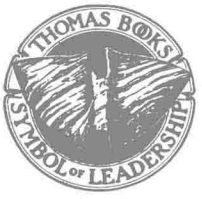

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DEFICIENCY DISEASE

To

Richard H. Follis, Sr., M.D.
Arnold R. Rich, M.D.
Edwards A. Park, M.D.

PREFACE

This volume is the outgrowth of a monograph, *The Pathology of Nutritional Disease,* which was published early in 1948. The cordial reception which it received has prompted a desire to bring the material up to date, since that manuscript went to the press over ten years ago. But of even more consequence was a growing feeling of dissatisfaction in the way I had presented the subject of nutritional disease. That volume mirrored my own introduction to the field of nutrition during the exciting days of the late 1930's and early 1940's when I was privileged to collaborate with Drs. E. V. McCollum, H. G. Day, E. Orent-Keiles, and M. M. Wintrobe. Studies of deficient states produced by a lack of single essential nutrients were then being emphasized; investigations of multiple deficiency states were not popular. As a result, I restricted the discussion to physiological, biochemical and anatomical changes in the deficient mammalian host which could be ascribed to a lack of a *single* nutrient. Abnormal states which could be attributed to lack of *multiple* essentials were excluded. Thus, *The Pathology of Nutritional Disease* dealt almost entirely with experimentally produced nutritional syndromes; this meant it was concerned in large part with nutritional disturbances in laboratory animals.

In the present volume I have attempted to remedy this situation by broadening the scope of the material which is to be presented. In the first place, disturbances will be looked upon from two standpoints: (1) those resulting from deficiencies of *single* nutrients, usually dietary in origin and experimentally produced, and (2) those resulting from lack of *multiple* nutrients, which is the way most deficiency diseases occur naturally. Secondly, we cannot consider only disturbances caused by the reduction in the dietary intake of a single nutrient or group of essentials. Our approach must be broadened so as to include disturbances ascribed to all of the conditioning factors which might produce general or local reductions or deficiencies of essential nutrients. Hence, I have chosen the title, *Deficiency Disease,* which I feel is more appropriate than *Nutritional Disease,* since the latter usually has a much wider meaning to include diseases produced by too much food and by metabolic disorders of varied natures. The scope of this monograph is therefore limited to those functional and anatomical changes in cells, tissues, or organs which may result from a lack of one

or more nutrients which such cells need. These alterations may be effected by impaired ingestion, assimilation, excretion, circulation, or metabolism. The distinction is not as fine as one might like, yet it allows one to restrict the material and perhaps lets him not be overly criticized when something is omitted. I have tried to include all of the recognized naturally occurring human syndromes. Some are doubtless given more space than others, which treatment mirrors my own experience.

Most of the functional and anatomical changes which are described herein are associated with a lack of exogenous essential nutrients, that is, those which must be supplied to the organism preformed in varying degrees of complexity. During recent years we have become more and more aware of situations in which certain cells and tissues of the organism may suffer from a lack of some endogenous nutrient, that is, one which is ordinarily made from the exogenous essentials. A good example of this situation is the hypoglycemic state, which may arise as a result of liver disease, hormonal imbalance, et cetera. Moreover, in this general sense any genetic disease may be viewed as a fundamental expression of protein deficiency. At the present time sufficient data are not available with which to develop this phase of *Deficiency Disease* as completely as we should like. However, the concept of "the biochemical lesion" which was developed by Peters over twenty years ago and his more recent hypothesis of "lethal synthesis" both point to an approach which will doubtless be worthy of further exposition at some future date.

The bibliography is a condensation of the publications which have been consulted. All could not be included. My apologies go to those who feel their material should have been cited. It is hoped that the references which are provided will aid in exploring a given subject further.

In preparing this monograph I have restudied much of the experimental material which has been reported previously. Many histological preparations have been rephotographed. Most of the microphotographs have not been published before. For these I wish to thank Mr. Robert W. Nye of the Photomicrography Section, Armed Forces Institute of Pathology.

Numerous investigators have allowed me to reproduce illustrations, published and unpublished from their work. My sincere appreciation goes to Drs. Maurice Sullivan, Paul Boyle, D. T. Smith, D. W. Woolley, G. Goldsmith, G. H. Cartwright, J. H. Baxter, T. D. Spies, S. Ansbacher, J. Warkany, J. R. M. Innes, R. W. Vilter, W. H. Horwitt, A. Schaefer, C. Tejada, and H. A. P. C. Domen. Drs. E. Lowenhaupt, K. E. Mason, E. H. Oppenheimer, R. J. Lukes, J. H. Yardley, J. N. P. Davies and A. R. Rich have allowed me to study and reproduce some of their material.

For the preparation of the manuscript I am indebted to Martha G.

Edson whose patience and diligence have contributed much to this entire undertaking.

My relations with Mr. Charles C Thomas and Mr. Payne E. L. Thomas have been most cordial. It is a pleasure to express my appreciation for their help and continuing interest.

My scientific career has been sired by three, my late father, Richard H. Follis, Sr., and two who have been more than step-fathers, Arnold R. Rich and Edwards A. Park. The dedication of this monograph allows me to pay tribute to each of them. My father, a surgeon, early stimulated in me an interest in medicine and provided me with an opportunity to follow this career. First as a student, then as a collaborator with Arnold R. Rich, I have gained more than words can ever express. His stimulation, constructive criticism, counsel and example have immeasurably influenced my own development. Dr. Park introduced me to deficiency disease when we began our studies of disturbances in bone in 1937. In my friendship and collaboration with him I have been blessed in a way that only those who truly know him can appreciate.

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Part I

DEFICIENCY DISEASE IN GENERAL

INTRODUCTION

In order to maintain the structural and functional integrity of its cells, the mammalian organism needs only a few of the 102 elements which are found in the periodic table. Of these essentials, the three atoms: carbon, hydrogen and oxygen make up water, simple lipids and carbohydrates. If to these are added nitrogen and sulfur, the proteins and other nitrogenous compounds may be formed. The atoms of calcium and phosphorus give stability to the skeleton. Potassium, sodium, and chlorine maintain, in part, the electrolyte composition of tissue cells and circulating fluids. Certain atoms are concerned with the activity of many enzyme systems or are integral parts of enzymes themselves. Such include: copper, iron, magnesium, manganese, zinc and molybdenum. Cobalt is a structural part of vitamin B_{12} or cobalmin, while atoms of iodine are incorporated into the active principle of the thyroid gland.

This monograph is concerned with physiological and morphological alterations which occur in cells and tissues when they become deficient in one or more essential nutrients. Deficiency disease syndromes may be produced at will in the experimental animal by causing a single nutrient to be lacking in the diet. Such conditions are encountered infrequently, however, in naturally occurring nutritional diseases of animals and man. Here multiple deficiencies exist, so that the problem becomes much more complex. Unfortunately, save for certain studies carried out during the early days of nutritional research, few experimental investigations on multiple deficiency states have been conducted. Studies of this group are of great importance to elucidate those multiple deficiency disease syndromes which occur naturally in animals and man.

Before considering certain broad aspects of deficiency disease, it might be useful to review briefly the chemical composition of the organism, since in the pages which follow we shall be dealing with its various constituents, at least many of which it cannot manufacture.

As is well known, the intact organism consists in large part of water. Values approximating 70 per cent have been reported in the new-born infant; [1] the thirty-five year old "normal" male, who was analyzed by Mitchell *et al.*,[2] contained 67.8 per cent water. The fat content of both the whole organism and its constituent parts is much more variable. For total lipid content the following values are representative: infant, 16 per cent; adult, 12.5 per cent. Values for various tissues will be found in Deuel's monograph.[3]

The total nitrogen content does not appear to vary much above or below 2 per cent.[1]

Excluding carbon, hydrogen, oxygen, nitrogen and sulfur, certain of the elements are present in appreciable amounts. On a total weight basis such include potassium (.35 per cent), sodium (.15 per cent), magnesium (.05 per cent), chlorine (.15 per cent), calcium (2.0 per cent) and phosphorus (1.1 per cent).[4] Approximate values for potassium and sodium are shown in Table I.[5] Other elements are found in much smaller, or even trace amounts; among these are iron, copper, cobalt, zinc, manganese, iodine, fluorine, molybdenum, strontium, rubidium, lead, silicon, aluminum, bromine, and others which will be further considered on page 20.

It must be made clear now that there are several classes of materials which are found in the body. These may conveniently be grouped as follows. *I.* Those which are indispensable and which the organism cannot

TABLE I

POTASSIUM AND SODIUM CONTENT (mEq) OF TISSUES OF MAN[5]

	Weight in Kg.	*Potassium*	*Sodium*
Skeletal muscle	30.0	2730	810
Skin	18.0	360	1600
Red blood cells	2.4	252	36
Plasma	2.6	12	363
Bone	12.0	218	1600
Brain	1.9	150	133
Liver	1.8	135	74
Heart	0.3	24	11
Kidneys	0.3	18	22
Whole body	70.0	3900	4600

manufacture *de novo*. Such include the essential elements, certain amino acids, the vitamins and essential fatty acids. *II.* Those which are indispensable but which the organism can form from those comprising Group *I*. Examples are the non-essential amino acids, enzymes, hemoglobin, collagen, various carbohydrates, saturated and unsaturated fatty acids, et cetera. *III.* Those which are dispensable and which appear to be adventitious as far as the organism is concerned. Such gain entrance via the food, water, external atmosphere, by contact, and so on. They include a number of elements, as well as many more complex compounds.

Now that the term "indispensable" has been used, upon what do we base the qualities, dispensable and indispensable? Since the early studies of F. G. Hopkins, growth has been the criterion which was most commonly used to determine the indispensability or dispensability of a given nutrient. Such would indicate that young, i.e., growing, animals have been employed most often, which is only natural since normal growth imposes the greatest