Nutritional Disorders of the Nervous System

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Preface

THIS monograph is written as the result of personal experience during the recent war. From what we know of cerebral metabolism and the physiology of the neurone it should not surprise us that defective nutrition may sometimes result in neurological disturbances. Clinical and experimental studies have shown that such disturbances may not only affect the peripheral nervous system—as in dry beriberi—but may also impair the function of certain parts of the brain and spinal cord and the senses of vision and hearing.

I have attempted to bring together the relevant information on this complicated subject without overburdening the text. No doubt there are omissions and some of the views expressed may have to be modified in the light of further knowledge. But in the main, the book is a record of clinical and experimental observation which may serve as a basis for extended study. The origins of many disorders of the human nervous system are quite obscure and theories already advanced—aplasia, inborn errors of metabolism, injury, infection, toxæmia, allergy and the like—have helped little. Now, however, it may be said that the clear association between defective diet and certain neurological syndromes described in the following pages should draw attention to the rôle of nutritional disturbances, antenatal and postnatal, in the production of maladies of the nervous system.

I have been aided in my task by many friends and colleagues. For much information on pellagra and for access to his extensive records and illustrations, I am greatly indebted to Professor Ali Hassan, Farouk 1st University, Alexandria, Egypt. I wish to thank Dr. J. G. Greenfield and Mr. C. S. Hallpike for reports and microphotographs of pathological specimens (Figs. 35–41). My acknowledgments are also tendered to the following for their generosity in allowing me to reproduce illustrations: Dr. R. D. Adams and Dr. C. S. Kubik, and the Editor of *The New England Journal of Medicine* for Figs. 25 and 26; Dr. Leo Alexander and the Editor of the *American Journal of Pathology* for Fig. 16; Dr. H. E. de Wardener and Dr. B. Lennox and the Editor of the *Lancet* for Figs. 19a and 19b; Dr. Jethro Gough for Figs. 23 and 27; Professor B. S. Platt for Fig. 14; Dr. A. Meyer for Figs. 9–12, 20, 21 and 24; Dr. A. Dean Smith for Fig. 29.

The follow-up of repatriated British prisoners of war in this country was made possible through the kindness of Major-General Sir A. G. Biggam, and it was carried out while the writer held the Walter Dixon Memorial Scholarship of the British Medical Association. I am

indebted to Dr. F. M. R. Walshe and Dr. E. A. Carmichael for their helpful suggestions and advice. For his continued interest and encouragement since I approached this subject, I wish to record my thanks to Dr. George Riddoch.

To Mr. Charles Macmillan, of Messrs E. & S. Livingstone Ltd., I am very grateful; it has been a pleasure to work with him on the publication of this monograph.

JOHN D. SPILLANE

February, 1947

Foreword

NUTRITION and malnutrition have been recognised, during and since the late war as never before, by those in authority politically and economically as subjects of first importance. The beneficial results of the careful rationing of food for the civilian population and the armed forces in this country show what scientific planning well carried out can do to raise the standard of health in a community, and to help to resist disease. The distribution of good food to all classes, and the proper use of it, was one of the major forces of resistance in the war; and repeated surveys throughout the country failed to reveal the presence of any serious malnutrition. This does not necessarily mean that evidence of faulty nourishment did not exist for the minor symptoms of it are hardly recognised by the medical profession as a whole, and even the experts who have been actively exploring the field have still far to go to cover the ground.

Nutritional disorders which could not be missed were, unfortunately, all too common elsewhere—in the prison camps in Germany and the Far East and among the slave peoples of Europe. They were due to a number of causes which operated in varying degree in different circumstances of external environment and internal bodily state; for example, grossly reduced quantity, kind and quality of food, as well as vitamin content, climate, age, mental strain and physical exertion, the simultaneous presence of other diseases such as malaria, dysentery or hepatitis, which either, like hard physical work, used up, at spendthrift rate, the meagre store of nutrition or impaired absorption from the gut or prevented proper assimilation. Again, it was observed in a number of camps that disorders of malnutrition developed more easily in some individuals than in others of the same race and in people of different races, although conditions of life were approximately the same for all; as if constitution also entered into the problem.

These "experiments" in nutrition were on a large scale, and it is most fortunate that on the whole the results have been carefully observed and recorded. In P.O.W. camps this was done by medical officers, themselves captive and living with their fellow prisoners in Germany, Burma, Thailand, Malaya, Batavia and Hong-Kong. Some excellent accounts of their observations have already appeared in the medical press, and doubtless more are to come. Lt.-Col. Spillane's book represents, so far as I know, the first attempt to deal systematically with nutritional disorders of the nervous system, which were relatively common, especially amongst prisoners in the Far East, and present

problems of ætiology and therapeutics which are still largely unsolved. Whilst serving in the army as Adviser in Neurology, Middle East Command, he recognised and investigated amongst German and Italian prisoners of war and Polish refugees a number of those syndromes which later were found to have affected a considerable number of captives of various nationalities in Japanese prisons. He discovered that they are not new diseases, but had been described before amongst malnourished natives in West Africa and in Johore prisons.

His book, however, is not confined to this group of disorders, but deals in a practical way with all the known nutritional nervous and mental diseases. No attempt is made to force specific causation and the difficulties of ætiological assessment in terms of vitamins, quantitative and qualitative food deficiencies and accumulation of toxic metabolites are frankly discussed. Treatment which at present is inevitably of the "blunderbuss" kind is clearly described and based on practical knowledge.

It is, in fact, an interesting, balanced and critical account of a fascinating subject.

GEORGE RIDDOCH

February, 1947

Introduction

THE remarkable development of the science of nutrition since the turn of the century is probably due to the impetus given by the discovery of the vitamins. The fact that minute amounts of substances, normally present in foods, could seriously influence the metabolic processes of the body was a new physiological concept. When Funk, in 1911, proposed the term "vitamines" for these substances and suggested that such maladies as scurvy, rickets, pellagra and beriberi were due to their lack in human diets, an era of experimental study was opened up in which his views were amply justified. The isolation and synthesis of ascorbic acid, calciferol, thiamin, nicotinic acid and riboflavin in recent years, and the demonstration of the biosynthesis of vitamins in the human gut, mark the close of a period of intensive investigation.

The discovery of the vitamins came at a time when great social changes were taking place throughout the civilised world. Their significance was just being appreciated in the years before the first World War, and the work of isolation and synthesis has gone on in a generation when shortage of food supplies has existed more or less continuously in different parts of the world. Then, too, vitamins became known when the preparation, storage, processing and canning of foodstuffs were introducing revolutionary changes in modern dietaries. It is not surprising, therefore, that the idea of vitamins captured public attention and that charlatans seized on them and exploited them. There are few therapeutic agents which have been so misused and about which has sprung up such a mass of uncritical literature.

Lack of a vitamin is, in itself, frequently insufficient to give rise to a deficiency disease. Some other factor is also necessary. Starvation—an avitaminotic state—is not attended with such conditions as scurvy, pellagra and beriberi, even if sufficiently prolonged to allow of their development. Deficiency diseases tend only to develop at certain nutritional levels; a certain amount of food is essential. Vitamin B_1 deficiency states are more likely to develop on a high carbohydrate diet than on a low one. This deficiency may then result in an abnormal type of carbohydrate metabolism and certain changes in the nervous system. Viewed in this light these diseases may be regarded as intoxications; the toxins arising in the body during abnormal metabolic processes resulting from the deficiency. The widely dissimilar consequences of these shortages indicate that although vitamins may have

some common biological function they actually interfere with metabolism at different stages and in many ways. They are not all chemically related but constitute a heterogeneous collection of organic substances widely distributed in animal and vegetable life. Not all foods contain similar amounts of these essential substances and many contain them in combination rather than singly. Dietary deficiency in man is, therefore, a complex disturbance. Nature does not provide a diet wanting in only one vitamin; such experiments require the ingenuity of man.

Not only do vitamin requirements vary in different individuals and under different external environments, but they may be considerably influenced by altered states within the body. Growth, pregnancy and illness may call for increased supplies, and in default may lead to manifestations of disease. Lesions of the intestine and liver may interfere with the absorption of vitamins and alteration of the intestinal flora may affect biosynthesis. It is not unlikely that certain foods inactivate vitamins or interfere with their synthesis or absorption. And the results of deficiency of one vitamin may be enhanced by the lack, or indeed by the excess, of another. The final disturbance would then be in the nature of vitamin imbalance rather than simple deficiency.

The results of an inadequate diet may vary in different members of the same community. A diet lacking in the whole B complex may produce pellagra in one individual and beriberi in another; such was the case in certain prisoner of war camps during the recent war. Beriberi may express itself by œdema, cardiac failure or acute paralysis, all of which may yield to treatment with thiamin. Within the nervous system itself it is probable that as a result of vitamin B deficiency there may result more or less selective degeneration of the optic or auditory nerves with or without lesions of the brain, spinal cord or peripheral nerves. It is a remarkable fact that a person may lose his sight or hearing as a result of nutritional disturbance while retaining the outward appearance of health. If we could learn what is involved in this peculiar process of selection we should be in a better position to understand the rôle of vitamins in diseases of the nervous system.

Periodically, it is found that certain sections of a population exist on a diet deficient, by laboratory calculations, in certain vitamins. It is then that the clinician may be tempted to attribute the prevalence of certain disabilities, usually of a vague and minor character, to dietary inadequacy. Corroboration is claimed for such a view when it is pointed out that similar symptoms also occur in the early stages of the classical deficiency syndromes. But the diagnosis of "subclinical" deficiency, in ordinary circumstances, is notoriously difficult. It is largely a matter of conjecture. It by no means follows that the premonitory clinical features of the major deficiency syndromes are

identical with those arising in chronic mild deficiency. In this country, at the present time, the neurologist rarely finds that he can indict vitamin deficiency as the cause of illness, and this, despite the efforts of pharmaceutical firms to persuade him to the contrary. Of course the rarity of pellagra in the British Isles does not necessarily indicate a satisfactory general supply of vitamin B, but it would surely be commoner if deficiency of that vitamin were serious and widespread.

Of the known vitamins—A, B, C, D, E, K and P—we can say that only one, vitamin B, is known to be of importance for the nervous system. This vitamin is in reality a complex of several substances of which some at least are essential for nervous activity. There are no indications that vitamins C, D, K and P are so required and the exact functions of vitamins A and E in this respect have yet to be determined. Experiment has shown that deficiency of vitamin A or E may result in neurological disorders in growing animals. There have also been claims, which have not been substantiated, that certain nervous diseases in man respond to treatment with vitamin E. It might be well, therefore, briefly to summarise the present position of these two vitamins in clinical neurology before we embark on a consideration of the vitamin B complex and its place in neurology which will occupy us in the following chapters.

This does not imply that only deficiency of vitamin B can lead to changes in the nervous system in malnutrition. The importance of the essential amino acids is being increasingly recognised and the rôle of protein deficiencies in malnutrition may prove to be as fertile a field of study as that of the vitamins. Amino acid studies have so far been mainly experimental and what part deficiency of them may play in nutritional disorders of the nervous system is not known. The vitamin B complex, on the other hand, has been studied extensively, and while much of the evidence is controversial there is little doubt that some of its components are essential for normal nervous activity and that serious phenomena may develop in their absence.

Vitamin A.—This vitamin consists of two known factors which are referred to as vitamin A1 and A2. There is little difference between their chemical constitution, distribution and biological action and for general purposes we may refer to them collectively as vitamin A. It is derived mainly from fish and other animal liver oils, and from certain plant pigments known as carotenes which animals can convert into vitamin A. Their value to plants is not known but their association with chlorophyll suggests that they are in some way concerned with photosynthesis. In the human being vitamin A is essential for satisfactory growth in childhood, for the development and maintenance of bodily resistance to infections and for the normal nutrition of epithelial surfaces. In man, deficiency of the vitamin may produce delayed dark

adaptation (nyctalopia), night-blindness (hemeralopia) and keratinisation of the cornea (xerophthalmia) and possibly of the skin (follicular keratosis). In growing animals deficiency of the substance produces degeneration in the brain, the spinal cord and in certain cranial and peripheral nerves. These phenomena are not primarily due to a disturbance of the metabolism of nervous tissue, but are the result of mechanical compression and deformation of these structures by inadequate development of the skull and vertebral column. Blindness, deafness and paralysis arise in this way. The skeletal and nervous systems do not develop in harmony so that the cranial and spinal cavities are undersized and overcrowded.

It is well known that the retina is one of the most delicately adjusted mechanisms of the nervous system. Both rods and cones are very susceptible to lack of oxygen. While the cones are directly stimulated by light rays the rods react only through the medium of the visual purple. This substance is a complex one which is found near the rods and of which vitamin A is an essential component. A shortage of vitamin A is reflected in a shortage of visual purple and this in turn leads to delay in dark adaptation, especially after exposure to bright light. The latter bleaches the visual purple so that, in individuals consuming a diet deficient in vitamin A, the condition of night-blindness may develop. Whether deficiency of this vitamin can ultimately lead to retinal atrophy is not known.

Lathyrism is a disease which some have associated with vitamin A deficiency. Intoxication by different species of vetch or chick-peas is also commonly blamed. The disease is found in times of famine in India, Iran, Algeria, Syria and sometimes in Asia and Europe, but many published accounts of the disease merely tell us that there is an acute development of spastic paraplegia. Information concerning the pathology, course and outcome of the disease is scanty. Reference will be made in the text to the similarity between the clinical features of this condition as I saw it, in a limited way, in Syria, and of spastic paraplegia in prisoners of war from the Far East.

Vitamin E.—This is a complex substance found in the germs of seeds and in green leaves. Its existence was demonstrated in 1922 and since 1936 its structure has been analysed and, partly at least, the vitamin has been synthesised. It contains three related factors called tocopherols (*τόκος*, childbirth, and *φέρω*, to bear); they are designated α, β, γ-tocopherols. Vitamin E is sometimes called the anti-sterility vitamin, as deficiency of the factor in certain animals leads to sterility in the male and abortion, although not failure of conception, in the female.

In 1928 it was shown that the vitamin was concerned with the normal development of the nervous system of certain animals. Young

rats when suckled by mothers deficient in the vitamin became paralysed. The main pathological changes were located in the spinal cord and affected muscles underwent considerable atrophy. Microscopically, they showed the changes seen in human muscles in waxy, hyaline or so-called Zenker's degeneration. Wheat-germ oil, though it will protect the developing animal from these changes, will not cure the established condition. It is not known whether this protective factor is identical with or different from the anti-sterility factor. Its application in clinical neurology arose from the observation that the changes in the spinal cord in experimental vitamin E deficiency resemble those seen in amyotrophic lateral sclerosis and tabes dorsalis. In 1940 the first claims were made for the value of wheat-germ oil in the treatment of neuromuscular disorders. Improvement was recorded in motor neurone disease and in muscular dystrophy, but the consensus of opinion at the present time is that the claims, which were not confirmed, were unjustified. It has been suggested that the nerve lesions in experimental vitamin E deficiency are secondary to degeneration of skeletal muscles and it has been reported that the latter are prevented by section of the muscle tendons or their nerves.

Experimental observations on newly-hatched chicks have also shown that degenerative lesions of the nervous system may arise as a result of vitamin E deficiency. The cerebellum is most severely affected but the cerebral hemispheres, the medulla and mid-brain may suffer milder injury. The lesions are thought to be secondary to vascular disturbance.

Contents

CHAPTER I

The Vitamin B Complex

THE better-known components of the vitamin B complex may be classified as follows:—

Vitamin B1.—The heat-labile substance. Known as *Aneurin*—(from *a*nti-*neur*itic vitam*in*) and as *Thiamin*—(contains thiazole grouping).

Vitamin B2.—The heat-stable substances.

1. *Adsorbed Factors:*	Riboflavin.
	Nicotinamide.
	Pyridoxin.
2. *Filtrate Factors:*	Pantothenic acid.
	P-aminobenzoic acid.
	Inositol.
	Choline, etc.
3. *Unclassified Factors:*	Biotin.
	Folic acid, etc.

The structural formulæ of about nine of these substances are known, and enzyme action of some of them has been demonstrated. The resolution of the vitamin B complex, which is still being actively studied, has been carried out during the past forty years and represents an enormous amount of research work by different teams in many parts of the world. It has been an outstanding scientific achievement. The steps by which it has been accomplished are outlined on page 2.

In its early stages this work was closely related to the study of beriberi, a disease which was known, so it is said, in China as early in the twentieth century B.C. (Macgowan, 1870, quoted by Vedder, 1913). Beriberi was not made known to physicians of the western hemisphere until the seventeenth century A.D.. (Bontius, 1645), and then only as its dry form. The wet form was described in 1808 by Rogers, but not until 1835 (Malcolmson) was it shown that the two conditions were manifestations of the same disease—one sometimes following the other The infantile form of the disease was first described in 1897 (Hirota).

The modern studies which have resulted in the analysis of the B complex may be said to have originated with the work of Admiral Takaki (1882) who, as Director-General of the Medical Department of the Japanese Navy, succeeded in practically eradicating beriberi among naval ratings by the addition of fresh foods to the normal rice rations. He added fish, meat, vegetables and barley. The governing

THE VITAMIN B COMPLEX