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VITAMINS IN OTOLARNGOLOGY*†

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IN the past decade there has been a rapid growth of interest in vitamins. This interest has not been confined to the laboratory but has rapidly spread to the medical and lay public. A great deal of specially prepared vitamins are now consumed not only under the direction of a physician but more often on the advice of the corner druggist or as the result of direct advertising. This interest in vitamins is shared by the otolaryngologist and is perhaps a natural development of laboratory research in this field. Constant search for a better understanding of many of the obscure diseases that the otolaryngologist is called upon to treat, together with a desire to follow any suggestive lead in therapy, and the constant pressure of the patient for help in relieving his illness often spurred on by unwarranted claims of advertisements and inaccurate information, has resulted in a widespread interest and use of vitamins in the practice of otolaryngology as in many other fields of medical practice.

It appears indicated to review the subject at this time in an attempt to evaluate present scientific information about the vitamins as it may relate to otolaryngology. In looking for this relationship between vitamin physiology and clinical otolaryngology, the most sound approach is to review the clinical picture of known deficiency states in man and not in the experimental animal. These vitamin deficiency diseases have occurred in outbreaks in various parts of the world, are endemic in some places, and have been reproduced in man under controlled laboratory conditions. It is safe to assume that if otolaryngological manifestations

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are not found in the full blown deficiency state, they are not likely to be found in any so-called subclinical deficiency state. On the other hand, if we have otolaryngological signs in the classical deficiency states, we may be permitted the view that the presence of these signs help to define the deficiency state and when correlated with other objective evidence of the specific deficiency, these signs can be of definite importance in clinical otolaryngology. While many vitamin fractions have been identified by controlled animal experiments only a few of the vitamins have been connected with known clinical states in man. These may now be reviewed briefly.

Vitamin A deficiency produces zerophthalmia and night blindness in man. This deficiency state is endemic in some portions of the Orient. A particularly large incidence has been found in some parts of India and in the Malay peninsula. Sexually mature persons with zerophthalmia may have cutaneous lesions of a papular nature due to hyperkeratosis of the hair follicles. As many as 5 per cent. of all hospital admissions in some parts of Java are patients with zerophthalmia.[1] Many cases among children are seen in Latin American hospitals. Furthermore an epidemic of zerophthalmia broke out in Denmark shortly after the last World War.[2] Occasional post-mortem examinations have been made on infants and children dying with this deficiency state. In reviewing the clinical picture from reports of these cases and the post-mortem findings there is very little evidence of ear, nose or throat pathology. An occasional report of metaplasia of the bronchial and sinus mucous membrane appears in the autopsy findings.[3]

Vitamin B_1 or thiamine deficiency produces a disease called beriberi. This is endemic in certain portions of the Orient as the result of eating a diet largely confined to polished rice. The clinical picture is that of a multiple neuritis, not as isolated neuritis, and this neuritis regularly affects the nerves of the legs first—leading soon to muscular and skin atrophy. This is called the " dry type ". A " wet type " is characterized by œdema and cardiac changes that may cause death. Again in the clinical and pathological reports of these cases otolaryngological signs are singularly scarce.

Nicotinic acid deficiency is endemic in some of the southern areas of the United States in the form of pellagra. Ulcerations in the mouth and glossitis are the principal otolaryngological signs. A dry œsophagitis with ulcers was also present in a number of the pellagra patients according to Dr. Fisher's report at the October 1943 meeting of the American Academy of Ophthalmology and Otolaryngology. Dermatitis, dementia and diarrhœa are the chief late signs of this disease. Often associated with this deficiency is riboflavin deficiency, another vitamin B fraction. Inflammation of the lips and rhagades about the corner of the mouth and nose appear to be its principal clinical signs. Before these symptoms

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appear burning of the mouth, tongue and eyes have been noted in carefully studied groups of patients.[4] During the Spanish Civil War many cases of glossitis were seen. These appeared to respond to vitamin B complex in the form of yeast, better than to nicotinic acid.[5] The ulcers of the tongue and oral cavity seen in nicotinic acid deficiency tend to become infected with Vincent's organisms and respond to nicotinic acid therapy.[6] Similar chronic ulcers encountered in the clinic, even when no other signs of deficiency exist, have occasionally responded to nicotinic acid therapy.[7] Other fractions of vitamin B have been identified only on experimental animals and have no clinical counterpart.

Vitamin C or ascorbic acid deficiency is seen among large numbers of the South African natives beginning work in the mines[8] and has been described years ago in epidemics among sailors long deprived of fresh fruits and vegetables. It has been reproduced in man under controlled conditions.[9] This later study revealed that an ascorbic acid level of zero in the plasma appeared after 41 days and in the white cell platelet layer after 87 days of complete depletion. No symptoms other than loss of weight appeared for 4 months. This is corroborated by observations in this clinic that some individuals may have no ascorbic acid in their plasma and yet show no effects of this. After about 132 days of complete depletion there appeared a papular skin eruption and only after about 161 days did the first classical sign of perifollicular hæmorrhage develop. An experimental wound now showed delayed healing due to failure to form intercellular substance, while after 3 months of complete depletion wound healing was normal. Capillary fragility tests were normal. No other signs appeared in this controlled depletion experiment. Low ascorbic acid has been found in a few cases or gingivitis at the dental clinic, one or two with irritations from dentures. These have responded to ascorbic acid therapy.

Vitamin D deficiency produces symptoms during the growth period and these are related to imperfect and delayed bone formation manifested in the clinical picture of rickets. Again no otolaryngological signs are common to this deficiency state. No other known clinical vitamin deficiency states are known although the tocopherols of vitamin E appear to be concerned with the reproductive and nervous function in animals and vitamin K is important in the formation of prothrombin. The latter information has been used clinically in controlling surgical bleeding of patients with obstructive jaundice and is useful in hæmorrhagic states of the newborn before the bacterial flora of the intestinal tract becomes established. With the aid of bile salts, bacteria in the intestine can apparently mobilize this vitamin.

Criteria for defining known deficiency states in man are still in the process of formulation.[10] They include quantitative chemical determinations. Until these criteria are established the subclinical vitamin

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deficiency state cannot be seriously considered. In the otolaryngologic literature a number of articles have appeared in which the author has attempted a correlation between vitamins and the diseased states[11, 12, 13, 14]. While a great deal of work was done in attempting to evaluate the general status of the patients studied, the evidence for a vitamin deficiency state was not convincing and the multiplicity of therapeutic procedures with numerous vitamins and endocrines often made it impossible to analyse the results. Furthermore the results reported were not conclusive, but rather could be considered to be within the limits of experimental error as for repeated audiograms or could be explained on the basis chosen for therapy—cases in which variations in symptoms could reasonably be expected—such as patients with tinnitus, allergy or Ménière's disease. Generally there appears to be very little basic information in the clinical vitamin studies reported thus far by otolaryngologists. This is no reflection on the clinician's work except that the evidence presented in this work did not warrant their conclusion of a definite relationship existing in their human material between various clinical pathologic states and the vitamins.

In contrast to many necessarily poorly controlled clinical studies the controlled animal experiment and biochemical studies continue to bring new light on the physiology of the vitamins and suggests possible ultimate application to otolaryngology. However, extreme caution should be exercised in transposing the results of vitamin experiments on animals to the clinic. The following personal observations exemplify this:

From the otologist's standpoint perhaps one of the most suggestive experiments is that of Mellanby on Vitamin A depletion of dogs.[15] I studied this problem in the rabbit and confirmed his observations that you can produce marked hyperplasia of the bone at the internal meatus.[16] His preparations showed also extensive degeneration of the spiral ganglion and end organ. That these changes were secondary to pressure effects of the bone narrowing the internal acoustic meatus and not a primary neural effect of the vitamin A depletion is shown by the absence of these findings in the depleted rabbits. In our animals with one exception the amount of new bone formation was not sufficient to destroy the VIIIth nerve directly or by interference with the blood supply. Furthermore this was verified by testing the cochlear function before and after depletion using the acoustic middle-ear muscle reflex as an index of cochlear function. The experiments were carefully controlled and the vitamin A level of the plasma was determined by the antimony trichloride reaction with the aid of a photo-electric colorimeter. The striking pathology of the temporal bones of these vitamin A depleted rabbits as well as those of Mellanby's dogs would at first glance suggest a really important translation value to clinical otology. However, a careful analysis of all the factors concerned does not bear this out. First of all this experimentally

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produced temporal bone pathology practically has no counterpart in human temporal bone pathology. Of the thousands of human temporal bones that have been studied, there exist but one or two descriptions that resemble this experimental lesion.[17] Furthermore the bony hyperplasia in the experimentally depleted animal is not confined to the internal auditory meatus but rather generally involves the posterior fossa surface as well as the spinal canal. While Mellanby previously thought that the multiple peripheral spinal nerve degeneration he found in his depleted animals was a primary effect, he has now found the explanation in the bony hyperplasia about the spinal nerve foramina.[18] Similar experiments carried out on adult animals are entirely negative probably because the reserve of vitamin A stored in the liver is practically impossible of exhaustion. Only growing young animals will show changes. Further, these animals even on complete depletion have to be carried for a long period relative to their life span before signs of depletion develop. By this time they are markedly retarded in growth, have zerophthalmia and are generally in such a poor state of health that death may soon intervene. Another point is brought out in considering the results of our experiments. Other workers reporting on changes in vitamin A depleted rats noted a high incidence of middle-ear infections[19, 20]. Our animals did not show this. This again illustrates the danger of transposing results from one experimental animal to another and particularly from the experimental animal to man. Referring again to clinical or pathological studies of vitamin A depletion in man we find no mention of this temporal bone or cranial base pathology or evidence of deafness. Lastly we are confronted with the fact that vitamin A deficiency as manifested by its classical signs in man is practically unknown in this country. The adequate vitamin A intake of most of our population plus the fact that liver stores seem adequate through very long periods of depletion explain this. The biophotometer tests for dark adaptation are not considered reliable enough to be proof by themselves of a definite vitamin A deficiency state or at best suggest the extremely mild deficiency state. Reviewing our experimental material in this light, we see that otologic problems in the clinic are not likely to be explained on the basis of vitamin A deficiency. Many of the experimental observations of vitamin depletion in animals have been reviewed from an otolaryngological angle[21] but they should be examined critically along the lines indicated by the analysis of the results of this vitamin A depletion study when considering their clinical application.

The physiology of overdoses of vitamins is still very obscure and as yet offers little prospect of special value to the otolaryngologist. Usually the amount of vitamin in excess of the body need is eliminated. The use of vitamins for a transitory pharmacologic effect—as for example producing vasodilation with nicotinic acid, may be mentioned only to point

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out another doubtful method of use. One cannot expect to relieve a long standing pathological process by inducing a pharmacologic effect lasting only a few hours. Only changes in transient symptoms may be expected by such treatments.

While a critical analysis of our present knowledge of the vitamins gives us little of proven value as regards the clinical problems encountered by the otolaryngologist, one cannot underestimate the contribution of the laboratory worker, biochemist and clinician in increasing our knowledge of basic biologic phenomena of cellular physiology as related to nutrition. Continued growth of our knowledge in this field, together with carefully controlled studies in man give promise that answers to some of the unsolved problems in otolaryngology may be forthcoming.

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