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NEWER ASPECTS OF SOME NUTRI- TIONAL DISORDERS*

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One of the most novel medical conceptions is that serious diseases or functional disorder may be occasioned by a mere lack of certain constituents in the dietary. Until recently we were wont to associate tissue damage or functional disturbance solely with the introduction of some harmful foreign substance—chemical or bacterial—into the body. It is not only remarkable but also creditable that a concept so revolutionary should have gained wide acceptance in so short a time, not only among the medical and scientific world, but among the public at large. The first to bring forward convincing evidence in favor of this view was Eijkman¹ who noted in the course of his experiments in Java that fowl fed on decorticated rice became paralyzed and developed symptoms resembling beriberi, which disappeared when rice polishings or their alcoholic extract were added. The subject slumbered for some fifteen years when, less than a decade ago, Hopkins² established it on a scientific basis by demonstrating that animals were unable to live on a dietary composed of casein, starch, lard, water and a mixture of inorganic salts, after these ingredients had been carefully purified, but that this diet could be rendered adequate merely by adding a small amount of a natural food—a few cubic centimeters of milk. It will be noted that the new path was blazed as the result of empiric observation as well as carefully planned scientific investigation, and furthermore, that as has happened so frequently in the past, alert empiricism outran and prepared the way for the more carefully planned laboratory experiment. Today the fact that there are deficiency diseases and vitamins is taught to children in the schools, is banded about in the advertising pages of the daily papers, and is the proper concern of the up-to-date mother. This rapid diffusion of scientific knowledge, despite the interruption of the war, furnishes a striking illustration of present-day alertness in connection with topics affecting personal health and vigor.

No doubt the disorders brought about by a deficiency of the vitamins or accessory food factors have occurred for centuries. To a considerable extent, however, they must be regarded as typically modern disorders.

Viewed as a group they are a consequence of our unnatural mode of life and peculiar civilization, of the growth of immense cities housing millions of people, who are dependent on perishable foodstuffs transported from a great distance. To even a greater extent they are the product of countless ingenious methods devised mainly to render food stable—drying, heating, the addition of preservatives—most of which accomplish their objects, but incidentally rob the food of one or more of its essential constituents. In a measure these nutritional disturbances are a consequence of the supreme domination of the bacterial point of view, of the ever present dread of infection and solicitude to protect ourselves against contaminated foodstuffs. This fear has led to the demand for a more or less complete sterilization of foods, and to a preference of foodstuffs whose unsullied whiteness lends them the appearance of purity—as in the case of polished rice, and highly milled flour.

The current view associates deficiencies of the various vitamins with specific disorders, for example, with beriberi or with scurvy. Now, although it is quite true that such diseases demonstrate conclusively the absolute necessity of certain constituents in our dietary, it is likewise true that clear-cut disorders should not be regarded as the most common or important result of food deficiencies. It should be realized that a lack of these essential food factors generally does not bring about typical pathologic states, but obscure alterations of nutrition, ill defined functional disabilities, which cannot be characterized or even recognized as disease. It is such incomplete, larval forms of the deficiency disorders to which physicians will have to address themselves.

Nor should the domain of the deficiency disease be restricted to the narrow confines of disturbances brought about by a lack of vitamins. In a broader sense it includes malnutrition due to an insufficiency of any food constituent which is essential to normal metabolism. The peoples of the Central Empires, for example, as the result of a great lack of meat, milk, cheese and eggs, were compelled to subsist during the war on a dietary which was deficient in phosphoric acid as well as in one or more of the vitamins.

Many observations lead to the conclusion that these disorders are not limited to man, but to a large extent affect the animals which man uses for food. It has been found in Victoria, for example, that cattle raised on certain pastures develop paralysis and other infirmities which can be cured by fertilization of the soil. In the United States in some areas it is impossible to maintain cattle in good condition until the forage is improved by mineral or animal fertilizers, which illustrates that a deficiency in plant tissues leads to nutr-

* Read before the Harvey Society, Jan. 15, 1921.

1. Eijkman, C.: Eine beriberiaehnlliche Krankheit der Huehner, *Virchows Arch. f. path. Anat.* **148**: 523, 1897.
2. Hopkins, F. G.: Feeding Experiments Illustrating the Importance of Accessory Factors in Normal Diets, *J. Physiol.* **44**: 425, 1912.

tional disorder in animals. Recently Hart, Steenbock and Humphrey,³ have confirmed these observations by careful experiments which showed how the mere addition of calcium to the fodder of cows prevented the birth of premature, weak or dead calves. Indeed, the extensive investigations of Forbes showing that cows producing large amounts of milk, and fed common winter rations, undergo constant losses of calcium, magnesium and phosphorus from their skeletons, suggest that large numbers of milch cows are suffering from a deficiency disease. These chemical analyses recall Hanau's report⁴ of almost thirty years ago, to the effect that the bones of pregnant women, who had enjoyed apparent health, frequently were the site of lesions resembling osteomalacia—an interesting observation that might be substantiated during life by means of roentgenologic examinations.

SCURVY

The most clear-cut and sharply defined deficiency disease is scurvy. In fact, it is the only nutritional disorder brought about by inadequacy of diet—whether of vitamin, of a definite chemical substance, or of calories—which is associated with characteristic pathologic alteration. For we must bear in mind that the nerve degenerations of beriberi are not typical or diagnostic as are the bone lesions of scurvy. The latter disorder, therefore, is preeminently qualified to serve as the prototype of this class of diseases. The clinical picture usually called to mind by the word "scurvy" is that of an individual afflicted with a severe, acute disease; either an adult with bleeding, fungous gums, hemorrhagic eruption and painful gait, or a pale, unhappy infant, with gingival hemorrhages, and tenderness or swelling of one or both lower extremities. This is the classic text-book picture, which should not, however, be regarded as the ordinary or prevalent type of scurvy, either in adult or infant. The more common form is far more subtle in its manifestations, as is true of other nutritional disorders. In the adult it is evidenced by a lack of physical or mental vigor, vague pains suggesting rheumatism, an increased susceptibility to infection—conditions often impossible to diagnose when occurring sporadically, but conclusive when scurvy pervades a large group of individuals. Such scurvy was noted during the War of the Rebellion among the Northern troops, being referred to as a "scorbutic taint," and is mentioned in the recent report of the British troops in Mesopotamia. It has been described by me in relation to infants,⁵ and during the war by physicians in Vienna who had charge of child-caring institutions.⁶ They noted, in addition to infants suffering from manifest scurvy, a far larger number of what may be termed "subacute" or "latent" cases with the characteristic muddy complexion, lack of appetite, stationary weight and fretful disposition. That this syndrome is truly scorbutic has been proved repeatedly by the miraculous improvement which follows the addition of an antiscorbutic to the dietary. From our knowledge that about six months of the inadequate diet is required to bring about definite clinical manifestations, it follows that there must be a mild or

latent type of scurvy and that this form must comprise the majority of the cases.

I shall not weary you with a review of the symptomatology of scurvy, but rather consider briefly the tissues and bodily functions which are particularly affected when the antiscorbutic food factor is lacking in the dietary. This vitamin is probably needed for the normal functioning of all the cells of the body—if we may interpret in this sense the general loss of mental and physical vigor—however its lack is evidenced in particular directions; in a failure of the integrity of the epithelium of the blood vessels; in a disintegration of the structure of the bones; in various disturbances of the circulatory system. It may be of interest to discuss briefly these three conditions, as their occurrence must be closely associated with the function of the antiscorbutic vitamin.

The lesion of the lining of the blood vessels is one of the most characteristic signs of scurvy; it is the cause of the hemorrhage of the gums, of the petechiae in the skin, of the subperiosteal hemorrhage, the hematuria, and all the other hemorrhagic manifestations which have frequently led to the inclusion of scurvy among the group of hemorrhagic diseases. The coagulability of the blood is almost normal in this disorder, the escape of the blood from the vessels being due to a weakening of their walls, or to a lesion of the endothelial cells or their cement substance. Applying a tourniquet to the upper arm (the "capillary resistance test"), thus subjecting the vessel walls to additional strain, will generally demonstrate this weakness, causing the appearance of numerous petechiae on the forearm. A similar weakness of the vessel walls does not occur in beriberi, or in any clinical condition attributed to a lack of vitamin.

It is unnecessary to dwell on the fact that the bones are particularly vulnerable to a lack of the antiscorbutic factor. For decades attention was centered to such a degree on the bones that clinicians as well as pathologists gave little heed to manifestations occurring in other organs.

The association of circulatory disturbances with "latent" or "subacute" scurvy is of particular interest as, until recently, these symptoms have been overlooked. They furnish a clinical link between scurvy and beriberi, the deficiency disease attributed to the lack of the so-called water-soluble vitamin. Frequently one of the earliest signs is tachycardia, a heart beat of 140 or 150 in an infant. But a still more noticeable and characteristic sign is the marked instability of the pulse rate, an increase of 20, 30 or 40 beats to the minute on the least exertion or from a slight rise in temperature. This tachycardia is similar to that of exophthalmic goiter, the electrocardiogram showing merely an exaggerated T-wave. Accompanying this tachycardia there is generally a polypnea—respirations mounting to 40, 50 or 60 to the minute. These symptoms may be termed "the cardiorespiratory phenomenon" of scurvy. That it is truly scorbutic may be deduced from the fact that it yields promptly to antiscorbutic treatment. Its occurrence points to an involvement of the nervous system, and at least to a functional relationship between this vitamin and nerve tissue, thus illustrating the inaccuracy of the appellation "antineuritic vitamin" as applied to the beriberi vitamin.

Another scorbutic symptom is enlargement of the heart, especially of the right heart, a lesion which has been considered typical of beriberi. For many years

3. Hart, E. B.; Steenbock, H., and Humphrey, G. C.: Influence of Rations Restricted to the Oat Plant on Reproduction in Cattle, Research Bull. 49, Agric. Exper. Station, Univ. Wisconsin, 1920.

4. Hanau, A.: Ueber Knochenveränderungen in der Schwangerschaft, Fortschr. d. Med. 10: 237, 1892.

5. Hess, A. F.: Subacute and Latent Scurvy: The Cardiorespiratory Syndrome, J. A. M. A. 68: 235 (Jan. 27) 1917.

6. Tobler, W.: Der Skorbut in Kindersalter, Ztschr. f. Kinderh. 18: 63, 1918.

this lesion was overlooked in scurvy, owing to the fact, as stated, that attention was narrowly focused on the bones, an oversight which is strikingly evident in reviewing necropsy protocols. It may be noted that Erdheim⁷ of Vienna recently published a paper with the significant title of "Das Barlowherz," in which he describes thirty-one necropsies of infantile scurvy in which the heart was found enlarged in almost every instance.

In concluding this summary of the relation of scurvy and its vitamin to the circulatory system, passing attention should be called to oliguria, the diminished secretion of urine in the course of scurvy, a symptom at once alleviated on administering an antiscorbutic. This sign is still more common in beriberi.

NATURE OF VITAMINS

As is well known, the exact chemical structure of a vitamin is as yet a mystery. This lack of knowledge has led to skepticism, even to the point of doubting the very existence of the vitamins. This attitude is strange, in view of the fact that for almost a generation we have become quite accustomed to conceding the existence of factors which we are unable to isolate chemically. We know quite as much about the chemical nature of the vitamins as we do of complement, hemolysin or immune bodies—substances which have gained general recognition and are admitted to the select company of scientifically established entities. Not only the nature of the vitamins but also their mode of action is unknown: whether they exert their effect directly on the tissues, or indirectly, as has been suggested, through a hormone action. It seems clear that man cannot manufacture them, or at most can do so to a limited extent—insignificant from the standpoint of his well-being. We are therefore entirely dependent on our food supply for these essential factors. Nor has it been shown that any other of the higher animals possesses this ability. Lower forms of animal life, such as the yeast cell, seem to be able to elaborate vitamin, and plant cells possess this faculty to a high degree. Not only are we unable to manufacture these vitamins, but it is probable that we are unable to store them to any great extent. A series of experiments planned to investigate this question, and described in detail elsewhere,⁸ led to the conclusion that at least guinea-pigs are unable to store the antiscorbutic vitamin. In other words, we are leading a precarious hand-to-mouth existence in regard to food factors which are essential not only to our health but also to our lives.

ANTISCORBUTIC VEGETABLES

It is hardly an exaggeration to state that in the temperate zones the development or nondevelopment of scurvy depends largely on the potato crop. In Ireland, when the potato has failed, scurvy has developed. The same thing has been true in Norway. To a minor degree this happened in 1914 in various localities in the United States, when the potato crop was inadequate. This is attributable in part to the fact that the potato is an excellent antiscorbutic, but to a greater extent because it is consumed during the winter in amounts that exceed the combined total of all other vegetables. The great nutritional value of the potato has not been explained. Its protein is stated to be of

inferior quality, and it is poor in the water-soluble and in the fat-soluble vitamins. Nevertheless, the practical dietetic experience of nations and the prolonged investigations of Hinshelwood prove that it is a food of exceptional value.

One of the recent advances in the study of scurvy has been a more exact appreciation of the antiscorbutic value of foods, an appraisal of vegetable and animal foodstuffs from a quantitative standpoint. This has led to some surprises; for example, that the lime, which has been time honored as the most potent of antiscorbutics, is not comparable in this respect to the lemon or the orange. We have learned also to appreciate the value of the swede and of the tomato. But of still greater importance is the realization that any categorical statement of the relative value of antiscorbutic foods must be accepted with qualifications. *Foods should not be considered as chemical entities.* A lack of understanding of this fact has led to nutritional disease in man, and to confusion in investigations on animals. For example, a vegetable such as the carrot may possess moderate or very little antiscorbutic power, depending on attendant circumstances. If it is old, it is poor in the antiscorbutic vitamin, whereas if it is young and succulent, it is far richer in this factor. We had a surprising experience some years ago when guinea-pigs developed scurvy in spite of a ration which included large amounts of carrots such as are ordinarily fed laboratory animals. Experiment readily showed that 35 gm. a day per capita of these carrots was insufficient to protect a guinea-pig, whereas the same quantity of a young carrot sufficed. Furthermore, it is not immaterial whether the vegetables are freshly plucked or whether they are stale, and it is quite possible that antiscorbutic potency depends to a certain extent on the composition of the soil; in other words, that the vegetable may in turn suffer from a vitamin deficiency disease. Such being the case, the influence attributed to climate in the causation of scurvy—for, as is well known, certain countries have always been associated with scurvy—may be due partly to the effect of the soil on the vegetation. Therefore, in rationing individuals or groups, the quality as well as the quantity of antiscorbutic foodstuffs must be considered.

ANIMAL FOODS

Similar qualifications exist in regard to animal foods. For some years there has been marked divergence of opinion as to the antiscorbutic value of milk. This is an important question, as milk constitutes the basal diet of infants during the first year of life, and constitutes frequently their sole antiscorbutic supply. The conflicting opinions of various investigators have been reconciled recently and the results of those who believed milk to be poor as well as of those who believed it rich in this vitamin have been substantiated. Its potency depends almost entirely upon the fodder of the cow. We should long ago have established this fact, fortified by our knowledge that animals are unable to synthesize the vitamins. Hart, Steenbock and Ellis,⁹ Dutcher and his associates,¹⁰ and Hess, Unger and Supplee¹¹ have all reported similar results. In our

9. Hart, E. B.; Steenbock, H., and Ellis, N. R.: Influence of Diet on the Antiscorbutic Potency of Milk, *J. Biol. Chem.* **42**: 383 (July) 1920.

10. Dutcher, R. A.; Eckles, C. H.; Dohle, C. D.; Mead, S. W., and Schaefer, O. G.: The Influence of Diet of the Cow upon the Nutritive and Antiscorbutic Properties of Cow's Milk, *J. Biol. Chem.* **45**: 119, 1920.

11. Hess, A. F.; Unger, L. J., and Supplee, G. C.: Relation of Fodder to the Antiscorbutic Potency and Salt Content of Milk, *J. Biol. Chem.* **45**: 229, 1920.

7. Erdheim, J.: Ueber das Barlowherz, *Wien. klin. Wchnschr.*, 1918, p. 1293.

8. Hess, A. F.: Scurvy, Past and Present, Philadelphia, J. B. Lippincott Company, 1920.

experiment, cows that had been for a period of three weeks on fodder which was almost completely devoid of antiscorbutic vitamin produced a milk that was almost devoid of this factor, although of normal caloric value and adequate in its fat, protein and carbohydrate content. Such results may well have far reaching dietetic significance; they raise the question whether "winter milk" supplied by stall-fed cows is a well balanced and complete food. It is quite possible that it may become part of dairy inspection to note the adequacy of the fodder as well as the sanitary conditions. Human milk no doubt also varies according to the nature of the woman's food, and in some instances is deficient in antiscorbutic vitamin, owing to eccentricities of diet or to poverty. During the winter months this may at times exert its influence on the nutrition of the child. In closing this brief consideration of the intrinsic variations of vitamin in animal tissues, I should like to suggest that the blood from which the milk is elaborated may also vary in its antiscorbutic content, and that from this standpoint it should not be regarded as a chemical entity.

FACTORS TENDING TO DESTROY THE VITAMIN

To understand the etiology of scorbutic malnutrition it is important to know the antiscorbutic value of natural foodstuffs; but it is equally important to appraise correctly the factors that tend to destroy the vitamin in these foodstuffs. Until recently this problem seemed very simple. The subject was summed up by the statement that foods which have been dried, heated to a high degree, or canned, lose their vitamin content and induce scurvy. The ravages of scurvy in the mercantile marine and in the navy, in the days of the sailing vessel seemed a convincing demonstration of the deleterious effect of preserved food. The matter, however, is not so simple, and recent investigations have proved the fallacy of these generalizations. In regard to the effect of heat, it has been shown that the duration of the heating process is of greater importance than the degree of temperature to which the food is subjected. For example, milk that has been heated to a temperature of 145 F. for thirty minutes has lost more of its antiscorbutic potency than milk that has been raised to 212 F. for a few minutes. This result confirms clinical experience that scurvy occurs more frequently on a diet of pasteurized than on one of boiled milk. It has been shown also that the reaction of the medium is of importance in regard to resistance to heating—that substances which are acid, such as orange juice or tomato, retain their potency in spite of subjection to high temperatures.

Our views on the effect of the dehydration of foods have swung back and forth on insufficient evidence. For centuries it was known empirically that dried vegetables possessed practically no antiscorbutic virtue, as demonstrated in many wars, including our War of the Rebellion. Nevertheless, in the recent World War dried vegetables were again relied on as antiscorbutics. They proved to be the greatest cause of scurvy in the Central Empires. In this country the conception that dried vegetables are the nutritional equivalent of the fresh nearly led to their extended use and general adoption for our army. But although vegetables have not yet been dried by a process which enables them to retain their antiscorbutic vitamin, we must not infer that desiccation per se destroys this factor, as dried orange juice or tomato juice retains almost all of its antiscorbutic value. Nor is this resistance dependent

solely on the acid reaction of these foods, for milk, dried by the Just roller process (by which it is subjected to 230 F. for a few seconds) loses little of its potency. Evidently, drying does not necessarily destroy the sensitive antiscorbutic factor.

We should also maintain an attitude of open-mindedness in regard to the effect of canning, commonly regarded as absolutely destructive of this vitamin. In general, this view is sound; but animal experiments as well as clinical tests have proved that this rule has exceptions—that tomatoes may be canned, and that milk may be both dried and canned, and yet preserve its antiscorbutic quality. Indeed, we found this to be true of dried milk which had been canned and kept for over a year at room temperature; an astonishing result, considering that such treatment involves subjection to almost all the influences commonly associated with the destruction of this vitamin—drying, heating to a temperature above the boiling point in a neutral or slightly alkaline medium, canning, and finally the deteriorating influence of age.¹² In view of these experiences, the statement of the British Medical Research Committee to the effect that foods lose their antiscorbutic vitamin after having been dried or tinned requires qualification. The stability of dried milk cannot be attributed, as we at first supposed, to its low moisture content (less than 3 per cent.), as sweetened condensed milk, containing more than three times as much water, was found also to retain the larger part of its antiscorbutic factor.

EFFECT OF OXIDATION

Such irregular and contradictory results suggested the action of some other destructive agent. We were led to believe that oxidation might be a harmful factor, and undertook experiments to investigate this question.

A Typical Test.—Four cubic centimeters of a normal solution of hydrogen peroxid was added to a liter of raw milk, which was then placed in the incubator over night. Eighty cubic centimeters per capita daily, in addition to oats and straw, was fed to a series of guinea-pigs. The animals promptly developed scurvy. Indeed, they manifested signs of this disorder as quickly as when fed milk that had been autoclaved for one hour at 115 C. Cure was accomplished by adding orange juice to the dietary. Evidently the antiscorbutic vitamin was almost completely destroyed by this small amount of hydrogen peroxid. Another experiment showed that orange juice subjected to oxygen had lost a definite degree of its potency, so that an increased quantity was required to cure scorbutic guinea-pigs.

These investigations indicate that oxidation destroys the antiscorbutic vitamin and must be considered in the etiology of scurvy.¹³

Let us in a few words reconsider the antiscorbutic value of milk from this point of view. Dried milk may retain its antiscorbutic virtue, in spite of drying, canning and aging, owing to the fact that it is well packed and hermetically sealed. It loses its potency after it is exposed to the air. When we refer to the deleterious effect of aging—a vague term—we may well be alluding to oxidation. Sweetened condensed milk, which we found to contain antiscorbutic vitamin,

12. In this respect, however, it should be borne in mind that there is an essential difference between a food which is of an alkaline or neutral reaction in its natural state, and one which has been rendered so artificially; for instance, orange juice rapidly loses its antiscorbutic vitamin after it has been made faintly alkaline, whereas the potato, in spite of its natural alkaline medium, retains this vitamin throughout the winter.

13. These results were referred to in a discussion of the vitamins at the meeting of the British Medical Association (Cambridge, July 1, 1920). At this session Hopkins also reported that the fat-soluble vitamin is destroyed by oxidation.

is zealously protected from access of air in the course of its manufacture, not for fear of oxidation or destruction of any of its food constituents, but to avoid the danger of bacterial contamination. It is probable that oxidation plays a rôle in the partial destruction of this vitamin in the pasteurization of milk; this seems the explanation of an experience referred to in 1915: the decided difference in the production of scurvy between milk which had been pasteurized in the home and that which had been pasteurized commercially. It may also account for the clinical results of Variot and others, who have repeatedly stated that they fed thousands, indeed, tens of thousands of infants on sterilized milk, and never encountered cases of scurvy; their milk was sterilized in hermetically sealed bottles. Bearing the factor of oxidation in mind may make it possible to so alter the process of manufacture or of the preservation of foods as to increase their antiscorbutic content, and render them more nearly the equivalent of the fresh food.

The deleterious influence of apparently unimportant processes in industrial methods warns us to proceed cautiously in the handling of foods, and not to concentrate our attention too narrowly on the bacterial dangers, for even some slight mechanical manipulation may damage and denature.

RICKETS

We are all aware of a renewed interest in another nutritional disorder affecting primarily the health of children, namely, rickets. This awakening closely followed the recent activity in the study of scurvy—always regarded as a closely allied disorder—and has been further stimulated by the remarkable outbreaks of rickets and osteomalacia in the Central Empires. Today we find clinicians and laboratory investigators in England, Germany, Austria and the United States endeavoring to shed light on the etiology of this disorder, which Glisson described so vividly more than 250 years ago. Rickets is the most common nutritional disease occurring among the children of the temperate zone, fully three fourths of the infants in the great cities, such as New York, showing rachitic signs in some degree. Schmorr's pathologic studies present evidence that this percentage is still higher when we include cases of latent rickets which can be diagnosed only by the microscope. Furthermore, rickets has the distinction of being the most frequently overlooked disorder of childhood—an important omission, in view of the fact that we possess an efficient agent for its cure.

Broadly considered, there are two main theories as to the etiology of rickets: the dietetic and the hygienic. It would lead too far afield to discuss the respective merits of these theories. It is my opinion that rickets is primarily a dietetic disorder, but that hygienic factors, such as lack of sunlight, poor ventilation,

crowded quarters, and infection, are important contributory influences, far more important than in the case of scurvy. That climate is not the determining etiologic factor is amply proved by the recent experiences of Europe, where rickets developed during the war in almost epidemic form. For example, Dalyell¹⁴ reported from Vienna that, in one community which included many breast-fed infants, rickets was diagnosed in 50 per cent. of the infants at 5 months, and in 100 per cent. at 9 months of age. Davidsohn¹⁵ has emphasized the great increase of severe cases in Berlin during the year following the armistice. This increment occurred despite the fact, shown by an analysis of some thousands of cases, that at the beginning of the war 40 per cent. of the babies were nursed for more than two months, whereas in 1918 more than 50 per cent. were nursed for a similar period.

I believe that I may safely state that today attention is centered on the rôle of the vitamins in relation to the etiology of rickets, and specifically on the fat-soluble vitamin. As the result of the investigation

of Mellanby on dogs and the acceptance of his results by the Medical Research Committee of Great Britain, many regard it as an established fact that the fat-soluble vitamin is synonymous with the antirachitic vitamin. About a year ago Dr. Under and I expressed the opinion that although this vitamin may be a factor in the etiology of rickets, it is not the dominant factor in its pathogenesis.¹⁶ The conclusion was based on a clinical study carried out in an institution for children. As this theory of etiology is the paramount one at the present time, I shall waive other aspects and discuss it in the light of my experience, which embraces a period of two

and a half years, and a careful observation of about 150 cases. My opportunity for a clinical study has been exceptional, as the children were in a model institution, where the diet was prepared in a central kitchen, and all the conditions were uniform and capable of control. Furthermore, I was sure that the infants received a diet adequate in calories and in other food factors. It is only under similar conditions that studies on chronic nutritional disorders can be carried out.

Time will not allow a detailed review of these observations, which will be reported at another time. It may, however, be of interest to summarize the results of two groups of cases, one which received a "fat-soluble minimal" diet and the other a full quota of

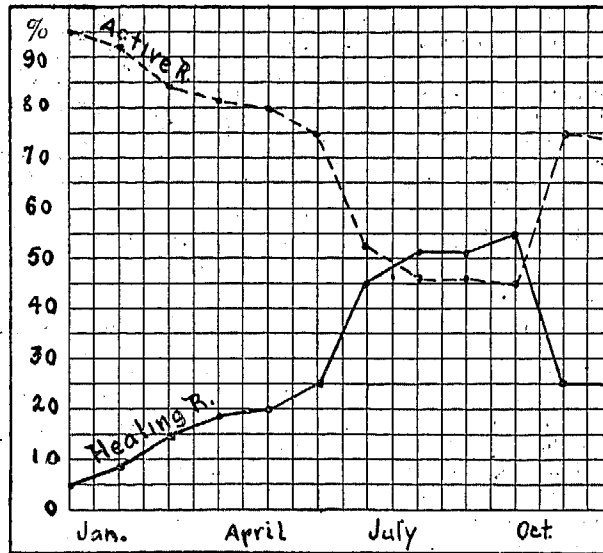


Chart 1.—Result of microscopic study of the bones of 386 consecutive necropsies on infants: marked decrease of active rickets accompanied by marked increase of healing rickets during the summer months.

14. Dalyell, E. J.: The Present Position of the Vitamines in Clinical Medicine, Brit. M. J., July 31, 1920.

15. Davidsohn, H.: Die Wirkung der Aushungerung Deutschlands auf die Berliner Kinder, Ztschr. f. Kinderh. 21: 349, 1919.

16. Hess, A. F., and Unger, L. J.: The Clinical Rôle of the Fat-soluble Vitamin: Its Relation to Rickets, J. A. M. A. 74: 217 (Jan. 24) 1920.

milk.¹⁷ Among six infants who were given a diet which was generous in every respect excepting in fat-soluble vitamin, a diet comprising adequate colorific value, a full amount of the water-soluble and antiscorbic vitamins, and an adequate salt mixture, after a period of more than six months only one showed rachitic signs by physical examination or by the roentgen ray. For, as many no doubt know, the course of this disorder can be studied by means of roentgenograms, and its development or cure thus visualized. Roentgenography, which has been employed extensively abroad, and by Phemister¹⁸ and by Howland and Park¹⁹ in this country, has formed part of our monthly routine examination for the last year.²⁰ This procedure has great value in the investigation of rickets, and no doubt will aid in elucidating some of its perplexities. As stated, one of these six infants receiving a minimal amount of fat-soluble vitamin in the dietary—only so much as was included in the equivalent of 20 ounces of a dried skimmed milk—showed signs of rickets after a long period of observation. In one case, which was observed for eighteen months, rickets existed at the onset and disappeared on this diet.

At the same time the development of rickets was followed in infants who were receiving daily from 24 to 32 ounces of raw or pasteurized milk. Surely this amount should suffice to protect against a disorder, were its occurrence dependent on the fat-soluble vitamin. Among this group, numbering twelve, who were receiving a dietary rendered adequate by the addition of orange juice, autolyzed yeast and cereal (for babies over 6 months of age), six developed rickets. That this disorder was truly rickets was proved by its rapid subsidence on the administration of cod liver oil, as shown by physical and roentgen-ray examination. The inference would seem to be that cod liver oil, which is regarded as the prototype of the fat-soluble vitamin, must differ not merely quantitatively but also qualitatively from milk fat. This view is strengthened by metabolism experiments of Schabad, Orgler²¹ and others, which show that although cod liver oil almost invariably causes calcium retention in cases of rickets, the substitution of large amounts of milk in the dietary leads to a negative calcium balance. Evidently the fat-soluble vitamin, as it exists in milk, is not the antirachitic factor; neither will a large amount of milk protect against rickets, nor a small amount lead to its development.

In passing, it may be of interest to refer to an investigation of the diet of the negro mother carried out a few years ago by Dr. Unger and myself²² in a negro district of New York. As is well known, rickets is far more frequent among negro infants in the large cities of the North than among those of any other race, occurring in marked degree in fully one third that are breast-fed. We came to the conclusion that the main defect and the chief variation in the dietary, compared to what they had been accustomed to at home in the

West Indies, was a lack of fresh vegetables and fruits, and an excess of carbohydrates. Last spring and fall Dr. Gertrude McCann carried out a similar investigation in this district and came to the same conclusion. This deficiency of fresh vegetable food, accompanied by a high incidence of rickets, is worth noting.

THE EFFECT OF "SEASON"

A remarkable phenomenon noted by Kassowitz years ago, and one which has not been sufficiently emphasized, is the marked seasonal incidence of rickets; its increased occurrence and intensity in the spring, and tendency to fall to its lowest level in the late summer or autumn. In the course of two years' observations, this fact stood out both winter and summer in bold relief; in August and September, rickets almost disappeared in the institution. Not only the clinician, but also the pathologist, is well aware of this seasonal augmentation and diminution; Schmorl's²³ study of some 386 cases brings it out admirably. So definite is this occurrence that any theory which attempts to explain rickets must satisfactorily interpret this remarkable seasonal variation in its incidence. Pellagra, tetany, keratomalacia, and to a less extent beriberi, are associated with a similar variation. The marked increment of rickets in the spring was attributed by Kassowitz to prolonged indoor confinement of the infants throughout the winter, and was the basis of his "domestication" theory. It may, however, be due to a change in diet not that the infants are given different food, but that the milk in the late spring and summer, when the cows are on pasture and no longer stall-fed, differs from that of the winter. The nature of this difference is obscure. This interpretation does not exclude the beneficent effect of the improved hygienic conditions which come about in the late spring.

COD LIVER OIL

Happily, we have a drug which, if given in sufficient amount, cures rickets. Cod liver oil has been used therapeutically for almost 100 years, but even today it has not been accorded its proper place in therapy. It is recognized as a drug which benefits nutrition, but the fact that it has unequalled value in the prevention and cure of rickets is hardly realized. Some three years ago a study of the effect of cod liver oil on negro children in a district of New York showed that it was of decided value in 80 per cent. of the cases. This test was carried out during the winter and early spring. Since this time, roentgen-ray examinations month by month in a series of cases have shown objectively the benefit of this therapeutic agent. It is quite remarkable how rapid is the deposition of calcium under this treatment.

It is possible to rid New York, or any locality, of rickets by means of the use of cod liver oil. There are approximately 125,000 children in New York City between the ages of 3 and 15 months, the period of greatest susceptibility to rickets. If we estimate generously that the families of one third to one quarter of these children are unable to purchase cod liver oil, and if we agree that the development of rickets may be prevented by giving a teaspoonful three times a day, then, at the present cost, rickets could be practically abolished in this city by the expenditure of about \$100,000 a year. This is merely one of many instances in which the community does not get the full benefit

17. The "fat-soluble minimal" diet consisted of 60 gm. of dried skimmed milk, 30 gm. of sucrose, 30 c.c. of cottonseed oil, orange juice, autolyzed yeast and wheat cereal. In some cases the oil was discontinued for over six months, and an increased quantity of cereal substituted.

18. Phemister, D. B.: The Effect of Phosphorus on Growing, Normal and Diseased Bones, *J. A. M. A.* 70: 1737 (June 8) 1918.

19. Howland, J., and Park, S. A.: Some Observations on Rickets, *Arch. Pediat.* 37: 411, 1920.

20. Hess, A. F., and Unger, L. J.: Diets of Infants in Relation to the Development of Rickets, *Proc. Soc. Exper. Biol. & Med.* 17: 220, 1920.

21. Orgler, A.: Zur Theorie der Lebertranwirkung, *Jahrb. f. Kinderh.* 37: 459, 1918.

22. Hess, A. F., and Unger, L. J.: The Diet of the Negro Mother in New York City, *J. A. M. A.* 70: 900 (March 30) 1918.

23. Schmorl, G.: Die pathologische Anatomie der rachitischen Knochenerkrankung, *Ergebn. d. inn. Med. u. Kinderh.* 13: 403, 1914.

of our medical knowledge. A similar example exists in connection with the prevention of beriberi. As is well known, this disease is the main factor in the exceedingly high infant mortality in the Philippines, leading to a death rate in the city of Manila of 430 out of every thousand infants under 1 year of age. The preventive of beriberi is the water-soluble vitamin, which is furnished in high concentration in brewers' yeast, a by-product of the brewing industry. Yet this high mortality is allowed to continue unabated in spite of the fact that the country is under a stable, civilized government.

MALNUTRITION NOT TYPICAL DISEASE

The harmful effects of food deficiencies should not be associated in our minds essentially or chiefly with specific diseases such as scurvy or rickets, but rather as disorders of nutrition producing slight and manifold disturbances of function. This is probably quite as true of rachitic as of scorbutic malnutrition. It is probable that every organ or system in the body may be affected by faulty nutrition, so that the deficiency diseases must engage the attention of every physician, whatever his particular interest or specialty. For example, involvement of the eyes may lead to impaired vision or night-blindness; or, on the other hand, neuritis, cardiac enlargement, disturbances of the circulatory system, atrophic disorders of the skin, nails or hair, caries of the teeth, or unaccountable lack of appetite and constipation, may each in turn be the earliest symptom. A more careful inquiry into the dietary of patients will result in bringing to light many cases in which vague and ill defined symptoms can be remedied simply by rendering the diet adequate.

The fat-soluble vitamin has been termed the "growth-vitamin." The designation is unfortunate, not only because this vitamin cannot be credited with this specific faculty, but also because no single food constituent deserves such distinction, or is endowed with this all-important function. It is probably true that if the fat-soluble vitamin is deficient, growth will not progress normally. This is certainly the case with rats, which are particularly sensitive to a lack of this vitamin, but which require a very small amount to render their diet adequate. Similar observations have not, however, been made on infants, so that we do not know, even approximately, how much fat-soluble vitamin food is needed for normal growth. The stunting effect of a lack of antiscorbutic vitamin on infants has been definitely shown, so that with equal justice this might be termed the growth vitamin. The sounder physiologic view, however, would be to regard no food constituent as entitled to be styled the growth vitamin or factor. If an essential amino-acid, vitamin or inorganic salt is lacking in the dietary, this inadequate factor—whatever its chemical nature—must be

regarded as and will prove to be the growth factor. In other words, for adequate growth the diet must be complete; and when it is incomplete—whatever the nature of the inadequacy, or however minimal its amount—growth will suffer.

INTERRELATIONSHIP OF NUTRITION AND INFECTION

Studies of the deficiency diseases have served to illustrate in a most convincing manner the intimate relationship of nutrition to infection, and have led to our attributing increased significance to the former. Indeed, the chief clinical importance of disorders of nutrition seems to be associated with the fact that they bring about an abnormal condition of the tissues which renders them more susceptible to the invasion of bacteria or their products. This relationship was exemplified in 1913, when, as the result of a dietary of pasteurized milk, latent scurvy developed among a group of infants under our care. This "scorbutic taint" was followed by a widespread grip infection, with hemorrhagic skin manifestations, which disappeared on the administration of orange juice. For

some years I was uncertain how to interpret this peculiar clinical picture, whether to regard the epidemic as due to scurvy or to infection. As the result of subsequent experience I realized that it was due to both causes, the result of a primary nutritional disturbance and a secondary bacterial invasion. Another illustration of the interrelationship of disordered nutrition and infection is furnished by the frequent coincidence of nasal diphtheria and latent or subacute scurvy. This concurrence is so suggestive that when a large number of cases of nasal diphtheria develop, suspicion should be

aroused that the infection was implanted on tissues rendered susceptible by scorbutic or other nutritional disorder. This view holds true for animals as well as for man. Veterinarians and farmers are well aware that faulty nutrition leads to fatal infections. The so-called "snuffles" of hogs is recognized as a disorder of this twofold nature. It is probable that plants which have been poorly nourished, owing to an inadequacy of the soil, also react by diminished resistance, and that this is a factor in the infectious diseases of plant life. This "nutritional-infectious" aspect has been convincingly illustrated on a large scale among the peoples of the Central Empires, who during the many years of the war suffered from various forms of malnutrition. The general impairment of health was most strikingly manifested both in adults and in children by the great spread of tuberculosis and its increased mortality. Davidsohn¹⁵ has reported that in Berlin there was a marked increase in infection with tubercle bacilli in children under the age of 5 years, and that they had been infected earlier in life than formerly; whereas in 1913, 30 per cent. gave a positive

Case	Without C. L. Oil	With C. L. Oil	Case	Low Milk Fat	High Milk Fat
	1	+0.060		+0.175 +0.141	6
2	-0.014	+0.143 +0.519	7	+0.038	-0.034
3	+0.073	+0.303	8	+0.043	-0.120
4	-0.038	-0.285 +0.141 +0.108	9	+0.037	-0.267
5	+0.067	+0.465			

Chart 2.—An aspect of the calcium metabolism in rickets. The favorable effect of cod liver oil on the calcium balance and the unfavorable effect of an abundance of milk-fat.

reaction at 4½ years, in 1919 this percentage was reached at 2½ years. The mortality of children from tuberculosis showed a similar difference in the year previous to the war compared to that of the year succeeding the armistice, the figures being thirty-two as compared to about forty-eight deaths among children under 6 years of age, on the basis of 10,000 living individuals.

Clinical investigations in the domain of the deficiency diseases have, as a rule, differed essentially from laboratory experiments. The latter, if accurately planned and correctly executed, study but one deficiency at a time; whereas the clinician investigating the dietary inadequacies of an individual or of a group, is necessarily confronted by a lack of more than one food factor. For example, an analysis of the cases of xerophthalmia or keratomalacia—a disorder ascribed to a lack of the fat-soluble vitamin—reported by Block of Copenhagen shows that many of the infants were receiving an insufficient quota not only of this vitamin but also of the antiscorbutic vitamin and of caloric food equivalents. Furthermore, in many localities where there was prolonged subnutrition during the recent war, there was a lack of vitamin, of adequate salts, of other essential substances and of calories. This confusion renders it impossible to unravel the clinical phenomena or to assign the various food factors their respective rôles. This criticism applies to the study of war or hunger edema which in 1917 spread through Poland and other countries, and which probably was the result of partial starvation combined with an unbalanced diet.²⁴ For this reason it is questionable whether we shall derive much increased knowledge from subsequent detailed reports concerning this vast experience of human suffering. On the other hand, a great deal will be learned in the future from clinical studies of nutrition when the diets are carefully controlled so that the results are capable of exact interpretation. We may expect such investigations to be undertaken more frequently and more intensively than heretofore.

On the other hand, for the laboratory worker there is the temptation to draw sweeping deductions from animal experiments, and to apply them *en masse* to the deficiency diseases of man. It should be remembered that the results of animal experiments are provisional and require the confirmation of clinical experience. Only too often has it been found that laboratory conclusions which at the time seemed open to but one interpretation were later explained by unsuspected and entirely different factors. The pitfalls in dietary experiments on animals are especially numerous on account of the varying reactions of the different species, and because the artificial diet—in spite of the greatest care—may be incomplete in more than one particular. In vitamin experiments there is especial danger of attributing failure of growth and nutrition solely to a deficiency of this factor, on which the attention of the investigator is focused, taking it for granted that the dietary is adequate beyond question in salts, protein and all other constituents. It is quite possible that this inconsistency will be found to invalidate some experiments that have seemed conclusive.

The disorders of nutrition have always presented a preeminent opportunity for collaboration between the

24. The experiences in the Central Empires during the war render it improbable that pellagra is due merely to a lack of adequate protein. Adequate protein was lacking to a marked degree—milk, cheese, eggs, meat were all unavailable. Nevertheless there was no prevalence of pellagra throughout these years.

laboratory and the clinic. It will be remembered that at one time the conception of rickets embraced a motley crew—congenital syphilis, scurvy, true rickets, achondroplasia and osteopsathyrosis, and that one by one these diseases were differentiated by the combined investigation of laboratory worker and clinician. The same opportunity exists today. The group of deficiency diseases furnishes urgent problems for the chemist, for the experimental biologist, the pathologic anatomist, the roentgenographer, and last, but not above all, for the trained clinician. The subject is so complex that advance will be along various paths, each worker furthering and checking the work of the other, so that progress may not leap beyond the bounds of well-founded experimental or clinical evidence.

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ARTERIOSCLEROSIS AND CARDIOVASCULAR DISEASE

THEIR RELATION TO INFECTIOUS DISEASES*

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The two conditions mentioned in the title of this résumé, one characterized by certain anatomic lesions and the other a clinical syndrome, are closely related to each other, but by no means identical. It is well known that we may find severe chronic lesions in the arteries without the usual symptoms of cardiovascular disease, and that there are cases of cardiovascular disease practically free from all demonstrable arterial lesions. In the majority of instances both occur simultaneously in varying combination, the exact relation of one to the other not being clearly understood.

It is surmised that the ultimate cause of both conditions is to be found in certain chronic intoxications, the nature of which is still doubtful, although it has been suggested that in the development of these intoxications infectious diseases may play some rôle. In order to determine the latter point, considerable experimental work has been done with bacteria and bacterial toxins on animals; but although suggestive, none of it is thoroughly convincing.

Again, it has been pointed out that certain infectious diseases are likely to involve the arteries acutely, and from this the conclusion has been drawn that they might also be concerned in the production of chronic disease in them. Rheumatic infections and typhoid fever have been most prominently mentioned in this connection, and occasional infections of the arteries have been credited to pneumococci, gonococci and other bacteria. At the same time the lesions produced in the arteries by diphtheria toxin have been carefully studied in man and animals. Tuberculosis and syphilis have also received considerable attention as possible causes of arterial disease.

No altogether acceptable proof, however, has been furnished of this suspected interrelation between certain infectious diseases and the later development of arteriosclerosis or of the syndrome of cardiovascular disease.

It seemed possible to throw light on this subject by a careful study of a series of cases which had been investigated as thoroughly as possible from a clinical

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