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SYMPOSIUM ON DISEASES DUE TO DEFICIENCIES IN NUTRITION*

THE "VITAMIN" HYPOTHESIS AND THE DISEASES REFERABLE TO FAULTY DIET†

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The studies of the past decade have revealed the fact that the adequate diet of the higher animals must contain protein of the type known as "complete," by which we mean a protein yielding all the amino-acids that are required in the nutrition of an animal. It must contain, in the form of suitable salts, at least nine of the inorganic elements, namely, calcium, magnesium, sodium, potassium, iron, chlorine, iodine, phosphorus and sulphur. "The sulphur must be in organic combination in the form of the amino-acid cystine. The diet must supply a suitable quota of energy in the form of protein, carbohydrates and fats, and must, in addition, contain certain substances of unknown chemical nature, to which Funk gave the name "vitamins." There are still differences of opinion concerning the probable number of these substances.

There are two ways of attacking the solution of this problem. We may attempt to show that the several syndromes that are referable to faulty diet can be relieved by the administration of such preparations as make it certain that the relief is not brought about by any known and well recognized constituent of the diet. For each of the syndromes now usually spoken of as "deficiency" diseases, which can be conclusively demonstrated to be relieved by such a method, the existence of a substance of the class frequently designated as "vitamins" is demonstrated. Successful attempts in this direction have been limited to two syndromes. Beriberi, which is recognized as being due to the lack in the diet of a sufficient amount of a substance, which is an organic compound, and of which an animal requires only a very small amount, and more recently, a type of xerophthalmia which results from specific starvation for a substance that is especially abundant in the fats of milk and of egg yolk, but is found in all foods which contain cellular struc-

tures, whether these are of animal or vegetable origin. McCollum and Simmonds¹ first pointed out that this syndrome is analogous to polyneuritis in that there is an organic substance which is found widely distributed in natural foodstuffs which, when administered, causes a prompt relief of all the symptoms in animals that are moribund as the result of specific starvation for this substance. Efforts to demonstrate the existence of a specific substance which can relieve scurvy, a disease which is certainly brought about by faulty diet, have up to the present time proved unsuccessful. Although pellagra has been suspected by some as being one of the "deficiency" diseases in the same sense as beriberi, no evidence of a convincing nature has been brought forward in support of this view.

A second method of approaching the problem of determining the number of chemically unidentified substances which are present in the normal diet and are essential for the preservation of a state of physiologic well-being is through a study of diets simplified - as far as possible, and containing only known chemical compounds. The early work in this field by Henriques and Hansen² was not sufficiently thorough to contribute much, and that of Hopkins³ did nothing more than demonstrate the necessity of having in the food of an animal some substance or substances other than the long recognized dietary essentials, protein, carbohydrate, fats and mineral salts. The announcement of the necessity of certain "accessory" food substances, by Hopkins, marked the beginning of a new era in nutrition studies.

Osborne and Mendel⁴ conducted an extensive experimental inquiry into the possibility of adequately nourishing an animal during growth on mixtures of carefully purified foodstuffs for the purpose of studying the relative biologic values of the numerous purified proteins that Osborne had isolated from vegetable sources. All their efforts were unsuccessful, and they ultimately adopted a basal food mixture containing a liberal amount of "protein free milk," a product containing all the constituents of milk other than the casein, lactalbumin and fat. To this was added carbohydrate, fat, the indigestible substance agar-agar, and the protein which it was desired to study. Diets of this character cannot be considered as containing only purified foodstuffs, and are not comparable with them.

McCollum and Davis⁵ made a systematic effort to find why animals do not thrive on diets consisting of proteins, carbohydrates, fats and inorganic salts. The

* This symposium includes the papers by E. V. McCollum; Alfred F. Hess; Joseph Goldberger, G. A. Wheeler and Edgar Sydenstricker; John R. Murlin, and Paul Roth—the first five papers in this issue.

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‡ Read before the joint meeting of the Section on Pharmacology and Therapeutics and the Section on Pathology and Physiology at the Sixty-Ninth Annual Session of the American Medical Association, Chicago, June, 1918.

1. McCollum, E. V., and Simmonds, N.: Jour. Biol. Chem., 1917, 32, 181.

2. Henriques, V., and Hansen, J.: Ztschr. f. physiol. Chem., 1905, 43, 417.

3. Hopkins, F. G.: Jour. Physiol., 1906, 44, 425.

4. Osborne, T. B., and Mendel, L. B.: Bull. 156, Publications of the Carnegie Institution of Washington, Parts 1 and 2, 1911.

5. McCollum, E. V., and Davis, M.: Jour. Biol. Chem., 1915, 23, 231.

details of these studies cannot be described here,⁶ but the results led them to the belief that in addition to the above named substances the diet, to maintain health, must contain two chemically unidentified substances. These have been designated by McCollum and his co-workers as fat-soluble A and water-soluble B. The first of these is found abundantly in certain fats, as those of the egg yolk and milk; the second is never associated with any fats of either animal or vegetable origin. When the diet lacks the substance of fat-soluble A, animals develop a peculiar eye affection in which the tissues surrounding the orbit swell until the eyes cannot be opened. There is inflammation of the cornea, and blindness results within three or four weeks. The eyes resume the normal appearance after a period of feeding such foodstuffs as contain the dietary essential in question. What we term water-soluble B is the "curative" substance for polyneuritis, or beriberi.

According to the view of my co-workers and myself, these two syndromes constitute the only "deficiency" diseases in the sense in which Funk used this term. Scurvy and pellagra, while due to faulty diet, are apt to be explained in other ways than by a lack of specific complex in the diet.

SCURVY

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Whatever I may say regarding the nature of the cause of scurvy need apply only to the disease as it is produced experimentally in the guinea-pig, for I have had no extensive opportunity to observe it in the human subject. There are certain well established facts regarding the causation of the disease in the guinea-pig that must be given careful consideration before one forms an opinion concerning the etiology of the syndrome. These will be briefly considered, but first a few words should be said about the character of the most simplified diets with which success has been attained in the nutrition of other species of animals. The animal with which most of the experimental work has been done with such diets is the rat.

It is possible with a diet consisting of carefully purified protein, starch, a suitably constituted inorganic salt mixture, a small amount of indigestible substance, such as agar-agar, together with a fat that contains the dietary essential fat-soluble A (for example, butter fat) and an extract, either by water or alcohol, of some natural foodstuff (such as wheat germ or yeast) to nourish young rats so as to induce practically a normal growth curve to about the full adult size. The extract must, therefore, contain the one or more unidentified dietary essentials not furnished by the butter fat. Either the butter fat or the extract alone in the diet is not sufficient. If the former is omitted, xerophthalmia will appear, and if the butter fat is included and the extract is omitted, polyneuritis will result. A problem of great interest is to determine whether this extract contains one or more than one indispensable substance. Since rats do not develop scurvy on such a diet, one of two assumptions must be accepted. Either the rat does not require a certain chemical complex, a hypothetical antiscorbutic substance which is necessary for the normal nutrition of certain other species, as man and the guinea-pig, both of which are susceptible to the disease, or the antiscorbutic substance, if there be one, is furnished by the extract in question. To say that all the experimental evidence,

which is now extensive, points to the conclusion that the chemical requirements of one species of the higher animals is the same as another is scarcely sufficient to dispose of this view.

My associates and I⁷ have thrown light on the problem as to whether such extracts contain but one or more than one indispensable dietary complex by our studies of the dietary properties of extracts of natural foods prepared in a somewhat elaborate manner. It was shown that navy beans can be thoroughly extracted with ether, then with benzene, and that neither the ether-soluble nor benzene-soluble material has the power to relieve polyneuritis in the rat, when the animals were caused to develop the disease by restricting them to a diet of purified foodstuffs plus fat-soluble A (butter fat). That the antineuritic substance (water-soluble B) was not destroyed by this treatment of the beans was shown by the fact that the extracted beans or an alcoholic extract of the same still caused prompt recovery of the animals, and resumption of growth when added to the diet. It was further observed that when the material which can be extracted by hot alcohol from beans previously extracted with both ether and benzene was spread over a large surface, by evaporating the alcohol on some finely divided substance, such as dextrin, and the latter then extracted with hot benzene, the benzene-soluble material was capable of inducing prompt recovery of animals suffering from polyneuritis, and of causing them to grow during several weeks. It cannot be argued that the "cure" was temporary in these experiments, for the animals were in a perfectly normal condition when the experiments were discontinued. It follows that, if in addition to the antineuritic substance the benzene extract of the alcohol-soluble material from beans likewise contained an antiscorbutic substance, these, as they exist in the bean, must have both been practically completely insoluble in ether and in benzene, for the extractions were conducted in a continuous extract or for a period of eighteen hours, and that both must have been soluble in hot alcohol, which solvent was likewise continuously applied for a like period. After being removed from the beans by means of hot alcohol, both must have been soluble in hot benzene. The probability that there should be two substances with such unlike physiologic properties, which should agree so completely in their solubility relations, is exceedingly small.

My associates and I⁶ have described feeding experiments with rats, in which a purified food mixture consisting of casein, starch (dextrinized), a salt mixture, and butter fat formed 75 per cent, of the food supply, and 25 per cent, of navy beans the remainder. The beans were soaked and heated in an autoclave :it 15 pounds pressure for an hour and a quarter, dried and ground. The beans furnished the only source of chemically unidentified food substances other than fat-soluble A, which was supplied in the butter fat, and which, as has been stated, bears no relation to scurvy. On this diet young rats grow well and reach the full adult size. According to the commonly accepted views concerning the properties of the supposed antiscorbutic substance, it should be destroyed by such drastic treatment.

A very significant fact in connection with the production of scurvy in the guinea-pig is that the disease

6. McColhanr, E. V.: The Supplementary Dietary Relationships Among our Natural Foodstuffs, THE JOURNAL A. M. A., May 12, 1917. pp. 1379-1386.

7. McCollum, E. V., and Simmonds, N.: Jour. Biol. Chem., 1918, 33, 55.

develops when the animals are confined to a diet of rolled oats and milk. This diet is highly satisfactory for the maintenance of health and the support of growth in those species of animals which we have observed (rat and swine) with the exception of the guinea-pig. There can be nothing lacking from a diet of oats and milk which is essential for the maintenance of growth and health in the swine and rat, yet the guinea-pig suffers malnutrition promptly when confined to this food supply. In fact, it has been shown by McCollum and Pitz⁸ that a number of diets which suffice for the nutrition of the rat are very unsatisfactory for the guinea-pig. The latter ordinarily thrive only on diets which contain a succulent vegetable, since its cecum becomes packed with feces on diets which are unsuited to its digestive tract. The cecum in this species is very large and delicate, and such a constipating diet as oats and milk causes malnutrition because of the physical properties of the feces which are formed from it, rather than because of a lack of any antiscorbutic substance.

McCollum and Pitz⁸ were able to cause the recovery of guinea-pigs which were near death, by the lubrication of their alimentary tracts by the administration of liquid petrolatum, and by the administration of suitable doses of phenolphthalein, which induced sufficient secretion of liquid into the tract to keep the contents of the cecum soft and capable of elimination. Relief and protection in this species were also afforded in several instances by the addition to the diet of an artificial orange juice, made up of such a salt mixture, sucrose and citric acid, as furnished these in about the proportions contained in the edible portion of the orange.

That the condition characterized by swollen joints, hemorrhages in the knees and elbows and gums was actually scurvy rests on the microscopic examinations of their animals by Jackson and Moore,⁹ who first described development of the disease by restricting guinea-pigs to an oat and milk diet, and on the diagnosis of the disease by Holst,¹⁰ in animals restricted to an oat diet.

Very important information relating to the etiology of scurvy is furnished by the observations of Hess¹¹ on human infants. I regard his discussion of the relation of heated milk to the causation of scurvy in infants as the best correlation of the clinical observations that has yet been made, since it harmonizes the conflicting views of various observers, and his conclusions are in harmony with the results of studies on animals fed on simplified diets. Briefly summarized, the data seem best explained as follows:

One of the factors in the pathogenesis of infantile scurvy is faulty diet. Pasteurized milk is a contributing cause when it is stale, and therefore, not in good bacteriologic condition. Aging of milk, with its development of an abnormal flora, is a more important factor in the production of scurvy than is heating, whether the heat treatment involves only pasteurization or heating to the boiling point. Boiled milk or milk pasteurized at from 140 to 145 F. is less liable to induce scurvy than is milk heated at 165. Boiling tends to destroy all the bacteria in milk. Heating to from 140 to 145 for thirty minutes fails to destroy all

the lactic acid forming organisms, and milk so heated will sour. The souring is a protective process, in that the development of acid holds in check the growth of putrefactive forms, which constitute the dangerous factor in stale heated milks. Milk that has been pasteurized at 165 will no longer sour unless reseeded with lactic acid bacteria after the pasteurization process. In clean, well regulated pasteurization plants this does not happen, but may occur in slovenly managed plants.

Holst¹⁰ believed that scurvy in the guinea-pig develops as the result of a lack of an antiscorbutic substance in the diet, and believed that this is so unstable that the ordinary drying of cabbage causes its destruction. He held that the oat kernel lacks this antiscorbutic substance. McCollum, Simmonds and Pitz¹² have shown that rolled oats can be supplemented with pure protein (gelatin), an inorganic salt mixture, and butter fat, so as to render it capable of satisfactorily nourishing young rats from weaning time to full adult size, growth taking place at the normal rate. Jackson and Moore⁹ have emphasized that butter fat has no tendency to protect the guinea-pig against scurvy, and this I have fully confirmed. It must follow that the oat kernel contains a satisfactory amount of antiscorbutic substance, provided the rat requires such a complex. The fact that the guinea-pig, when fed this diet of oats and purified food additions, rapidly fails necessitates the assumption that the guinea-pig requires a chemical complex not necessary for the normal nutrition of the rat, or the abandonment of the view that an antiscorbutic substance exists.

Hess¹¹ has also pointed out that one of the common symptoms of scurvy is oliguria, and that the mild therapeutic effect of citric acid may be ascribed to its diuretic properties. He likewise noted in infants the diuretic effects of orange juice. This is an important observation which should aid one in appreciating the fact that the organism may react with the development of profound pathologic states, such as constitute the most prominent features of scurvy, from causes other than a specific starvation for a hypothetical antiscorbutic substance. Injury to the mucosa of the digestive tract may be brought about through diets of faulty physical character, in such an animal as the guinea-pig, because of the peculiar disability of this species due to the unfortunate anatomy of its digestive apparatus. Stagnation of the contents of the cecum are followed by abnormal decompositions, and contact of the mucosa with these may be reasonably held to cause injury. It is not necessary to assume the invasion of the body by organisms as a factor in the causation of scurvy, although this may take place, as the studies of Jackson and Moore⁹ indicate. The absorption of abnormal decomposition products of proteins under these conditions may be chiefly responsible for the changes observed. The observation of Lewis¹³ that there is no increase in the excretion of phenol in guinea-pigs fed an oat diet can have but little bearing on the extent to which protein is undergoing fermentative decomposition in the digestive tract of the animal, since phenol production is limited by the yield of aromatic amino-acids by the proteins which are being putrefied. Longcope¹⁴ points out that the characteristic result of acute anaphylactic shock in guinea-pigs is the

8. McCollum, E. V., and Pitz, W.: *Jour. Biol. Chem.*, 1917, **31**, 229.
9. Jackson, Leila, and Moore, J. J.: *Jour. Infect. Dis.*, 1916, **19**, 478.
10. Holst, A., and Fröhlich, T.: *Ztschr. f. Hyg. u. Infektionskrankh.*, 1912, **72**, 1.

11. Hess, A. F.: *Infantile Scurvy*, *Am. Jour. Dis. Child.*, November, 1917, pp. 337-353.

12. McCollum, E. V.; Simmonds, N., and Pitz, W.: *Jour. Biol. Chem.*, 1917, **29**, 341.

13. Lewis, H. B., and Karr, W. G.: *Jour. Biol. Chem.*, 1917, **28**, 17.

14. Longcope, W. T.: *Harvey Lecture Series*, 1915-1916, p. 296.

appearance of hemorrhages. He further states that "undoubtedly infection is the most important factor in the cause of nephritis in man," a view that has gained wide acceptance within recent years.

Recovery from scurvy following a change of diet, or an improvement of the bacteriologic condition of the food, or following the administration of substances having diuretic properties, may be more satisfactorily explained in other ways than by the assumption that such changes in the dietary regimen produce their effects because of the introduction of a hypothetic antiscorbutic substance. It is necessary, henceforth, that those who discuss the etiology of scurvy should take into consideration the results of recent researches in nutrition with simplified diets. Whoever would seek to establish the validity of the theory of the existence of a specific antiscorbutic substance should first furnish new explanations for the experimental results that are not in harmony with the antiscorbutic theory, rather than present new experiments that harmonize with this most attractive hypothesis.