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THE SUPPLEMENTARY DIETARY RELATIONSHIPS AMONG OUR NATURAL FOODSTUFFS *

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In order that I may illustrate the supplementary dietary relationship among certain of our naturally occurring foodstuffs, it is essential first that I offer convincing evidence that we are now in a position to devise experimental procedure which is adequate to reveal such relationships. Secondly, it must be shown that we possess sufficiently complete knowledge of the essential factors which operate in making a diet for a growing animal to enable us to interpret correctly the results of feeding experiments. This can be done perhaps best by briefly reviewing the work of the past decade which has been most significant in advancing our knowledge of the chemical complexes which are indispensable to the growing mammal.

Previous to 1909 a number of attempts had been made to nourish animals on diets composed of purified protein, carbohydrates, fats and inorganic salts, usually with a small admixture of cellulose. Such attempts were attended with failure. In every instance the cause of the failure was entirely unknown. The speculations regarding the cause dwelt principally on the dependence of the mammal on a supply of some organically combined forms of phosphorus, as phosphoprotein, lecithin and nucleic acid; its requirement of iron in some special organic form, and with the need of purin bases performed in the diet.[1] The first experimental work which proved fertile in advancing our knowledge regarding the factors which are essential in an adequate diet was that of Stepp.[2] He attempted to estimate the importance of lipoids in nutrition, and found that bread prepared with milk was after extraction with ether and alcohol no longer capable of maintaining life in mice. The total material extracted by the solvents, when put back into the diet, made the food efficient once more. Stepp was unable to obtain this result by the addition of any known lipoid. The latter result is significant in the light of later developments.

In 1911 Osborne and Mendel[3] reported remarkable results 'in experiments involving growth in young rats which were fed a mixture of purified protein, carbohydrate, fat, and 28 per cent, of what they termed "protein free milk," a preparation made by removing the casein of skim milk with acid and the albumin so far as possible by coagulation with heat. The "protein free" whey was evaporated to dryness. "Protein free milk" was found to induce normal growth when supplemented with purified food ingredients, and its discoverers were inclined to attribute its virtues to a nice adjustment of the inorganic constituents of the diet, although they appreciated the possible importance of unknown constituents. Two years previously Hart, Steenbock, Humphrey and I[4] had reported most marked improvement in the capacity of cows fed on a ration restricted to the products of the wheat plant, to produce viable young, by suitable supplementing of the food mixture with certain inorganic salts, and this seemed at the time to be an adequate explanation of the good effects of feeding "protein free milk."

There were observations at this time available in the literature of pathology which were of great value in suggesting profitable lines of procedure to those who were engaged in studying the problems of normal nutrition during growth. In 1897 Eykmann[5] had reported his observations on the production of experimental polyneuritis in fowls, analogous to human beriberi, restricting them to a diet of polished rice. He further showed that undecorticated rice could induce a cure of fowls in this condition.

Eraser and Stanton[6] in 1907 had employed alcoholic extracts of rice polishings for the relief of experimental polyneuritis. In 1911 Funk[7] took up the study of the problem and showed that pressed yeast, hydrolyzed with 20 per cent, sulphuric acid for twenty-four hours, still retained its property of curing polyneuritis when administered to birds. This observation disposed of the view, which had been much discussed, that some organic phosphorus compound was the curative agent. All such compounds are reduced to their simplest cleavage products by such vigorous treatment. Funk and simultaneously Suzuki[8] and his co-workers in Japan showed that the substance which relieves polyneuritis is precipitated by phosphotungstic acid and is therefore an organic base.

It would be obvious to any one who made careful inspection of the literature up to the end of 1911 that further efforts directed toward the nutrition of animals with purified food substances must be attended with failure. As early as 1906, Hopkins[9] had reported

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1 The earlier experiments in this field are summarized by the author in the American Journal of Physiology, 1909, **25**, 120.

2 Stepp W.: Biochem. Ztschr., 1909, **22**, 452; Ztschr. f. Biol., 1912, **57**, 135; ibid., 1912-1913, **59**, 366.

3 Osborne, T. B., and Mendel, L. B.: Publications of the Carnegie Institution of Washington, Bull. 156, Pt. 2, 1911.

4. Hart. E. B.; McCollum, E. V.: Steenbock, H., and Humphrey, G. C.: Research Bull, 17, Wisconsin Expt. Sta., 1911.

5. Eykmann, C,: Arch. f. Hyg., 1906, **58**, 150; Arch. path. Anat., 1897, **148**, 523.

6. Fraser, H.. and Stanton, A. T.: Lancet, London, March 12, 1910, p. 733; The Etiology of Beri Beri, Study 12 from the Institute for Medical Research, Federated Malay States, 1911.

7. Funk, C.; Lancet, London, 1911, **2**, 1266.

8. Suzuki, S.; Shimamura, T., and Odake, S.: Biochem. Ztschr., 1912, **43**, 89.

9. Hopkins, F. C.: Jour. Physiol., 1912. **44**, 425.

his observation that the addition of small amounts of milk to food mixtures consisting otherwise of purified protein, fats, carbohydrate and salt exerted a favorable influence on nutrition which was out of all proportion to the calorific value of the added milk, and he expressed the belief that there existed certain "accessory food substances" indispensable from the diet. These observations convinced me of the importance of further examination of the lipoid moiety of the diet. In 1912 Miss Davis and I observed the remarkable stimulating action on growth of purified butter fat and of the ether extract of egg yolk, when these were added to a mixture of supposedly purified food substances. Lard and olive oil possessed no such properties.[10]

10. McCollum. E. V., and Davis. M.: Jour. Biol. Chem., 1913, **15,** 167; ibid., 1915, **23,** 231,

I am conscious of the question which will be asked concerning the cause of scurvy and of beriberi. Are not these both dietary deficiency diseases? During the past two years Mr. Pitz and I[20] have repeated all the more important work reported by others on the production by diet of experimental scurvy in the guinea-pig. We have confirmed the observations of Jackson and Moore to the effect that with a diet of oats and milk *ad libitum,* scurvy ordinarily results. Rolled oats induce the onset of the symptoms sooner than unhulled oats. Only those diets which produce feces of a character readily eliminated will relieve or prevent the disease. Milk to the extent of 10 per cent, of the solids of the diet supplies all the unidentified dietary factors necessary for growth in the rat or swine and probably for other mammals as well. We are convinced that the guinea-pig suffers from scurvy on a diet of oats and milk because of the constipating character of the diet. Oats produce pasty feces, and the guinea-pig, being unfortunate in the anatomy of its digestive tracts, is quickly debilitated by its inability to empty the large and delicate cecum. This harmonizes with our observation that orange juice, the panacea for scurvy in the human infant, gives protection to the guinea-pig, but is not so efficient as to enable this species to take an oat and milk diet and grow continuously over a long period. We have furthermore been able to effect a complete cure of guinea-pigs on a milk and oat diet after they could no longer walk, and showed badly swollen joints and the hemorrhage of the gums, by liberally dosing them with liquid petrolatum. Cavies so relieved have been as active and healthy as if on a diet of green grass, and have resumed growth and have continued to grow steadily, though at a rate slower than the normal during three months following the attack of scurvy, while confined to the same milk and oat diet which gave them the disease. The petroleum oil treatment was of course persevered in throughout this period. I question whether any one would postulate the existence in petroleiun oil of a "vitamin" specific as a protection against scurvy.

I venture to suggest that the failure of Holst[21] and his co-workers to prevent or relieve scurvy in guinea-pigs by feeding dried cabbage finds its explanation in the failure of the latter to take up water in the intestine and again act as a succulent vegetable.

On the basis of anatomic lesions and for other reasons, Hess[22] has recently suggested that scurvy and beriberi show more points of similarity than have been recognized by clinicians, and was inclined to consider the two as essentially the same pathologic condition. His efforts toward curing scurvy with wheat germ and with yeast were unsuccessful, whereas orange juice was potent as a curative agent, and he was forced to conclude that the two conditions were distinct. I will offer the suggestion that the latter view is correct. Scurvy in the guinea-pig is the result of the retention of feces. I do not know whether or not the same is true of human scurvy. Neither do I know the cause of the hemorrhage of the joints and gums, whether they are the result of the absorption of a toxic substance of bacterial origin, which injures the blood vessels, or whether they are due to the invasion of the tissues by an organism, through an injured cecal wall. The recent observation by Jackson and Moore of a streptococcus in the congested joints is suggestive in this connection.

I am inclined to attribute the protective power of orange juice as an antiscorbutic to its content of certain salts of citric acid, rather than to the presence of an unidentified organic substance of the class of the so-called vitamins. Its efficiency for the guinea-pig appears to be somewhat less than for the human being. This may well find its explanation in the much more delicate and inefficient structure of the digestive tract of the cavy as compared with that of man, so that less efficient protective agents may serve for the latter than for the former. While guinea-pigs are protected against scurvy by orange juice, we have not seen them grow to any appreciable extent on a diet of oats and milk fortified with orange juice. If the results of experiments of three months' duration are to be trusted, orange juice appears no more efficient than petroleum oil in protecting guinea-pigs against scurvy when the animals are kept on a diet of oats and milk.

20. McCollum, E, V., and Pitz, W.: Unpublished data.

21. Holst and Frohlich: Ztschr. f. Hyg. u. Infektionskrankh., 1912, **72**, 1.

22. Hess, A. F., and Fish, Mildred: Infantile Scurvy: the Blood, the Blood Vessels and the Diet, Am. Jour. Dis. of Child., December, 1914. p. 383. Hess, A. F.: Infantile Scurvy: THE JOURNAL. A. M. A , Sept. 18, 1915, p. 1003; Proc. Soc. Exper. Biol. and Med., 1915, **13**, 50; ibid., 1916, p. 145; Am. Jour. Dis. Child., August, 1916, p. 152.