While these patients were only temporary carriers, still, spread of the infection was possible if proper precautions were neglected.

In one case the bile and stool showed no typhoid bacilli, while the urine showed a profuse typhoid growth. This finding persisted on several examinations, proving the existence of a typhoid cystitis. It finally cleared up. It is not the object of the duodenal cultures to replace the examination of the urine. A typhoid infection of the urinary tract may persist for months without any infection of the bile or gastrointestinal tract. A bacteriologic examination of the urine, therefore, is always essential. It is the aim, however, to replace the stool examination by the much simpler and apparently more accurate examination of the bile.

Gaeltgens⁸ has shown that typhoid bacilli decrease in numbers in the intestinal tract as we pass downward from the duodenal opening of the bile duct to the rectum, and that they are to be found most constantly in the gallbladder. Flutterer⁹ in 1888 first called attention to typhoid bacilli in the gallbladder, and now it is definitely known that the infection may be perpetuated in the gallbladder for many years following convalescence.

Kaspar¹⁰ was able to detect typhoid bacilli in the bile removed from the stomach after a test oil breakfast seven years after an attack of typhoid fever.

Thus the idea of cultivating typhoid bacilli from the duodenal contents, rather than from the stool, was considered long ago, on account of difficulties experienced with stool examinations. In a series of cases, Kayser¹¹ found no typhoid bacilli on three repeated examinations of the stool, whereas later tests proved the individuals to be carriers.

In 1912, Dr. Hess¹² passed a duodenal catheter on a baby 22 months old, suffering from typhoid fever, in the beginning of the third week; a small amount of bile-containing fluid was aspirated from the duodenum, and from this fluid typhoid bacilli were cultivated in very large numbers. In that paper Dr. Hess suggested that this simple procedure might be of value in the diagnosis of typhoid carriers.

MacNeal and Chace¹³ recovered typhoid bacteria from the duodenum in a case of relapse from typhoid. Einhorn¹⁴ reported a case in which I recovered typhoid bacteria from the duodenum of a typhoid carrier. Whether or not examination of the duodenal contents can be of aid also in the early diagnosis of acute typhoid fever is an interesting topic for further study.

CONCLUSION

Cultures from duodenal contents (bile) removed by means of the duodenal tube seem to be a more reliable and simpler method for the detection of typhoid bacilli than stool examinations.

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8. Gaeltgens: Berl. klin. Wehnschr., 1912, xlix, 296.

9. Flutterer: München. med. Wehnschr., 1888, p. 315.

10. Kaspar: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxvi, No. 5.

11. Kayser: Arb. a. d. k. Gsndtsamte, 1906, xxiv, 173.

12. Hess: Jour. Infect. Dis., July, 1912, xi, 71.

13. MacNeal and Chace: Tr. Am. Gastro-Enterol. Assn., 1913, p. 26.

14. Einhorn: Tr. Am. Gastro-Enterol. Assn., 1913, p. 52.

A Measure of Greatness.—A great clinician is remembered either by his original contributions to scientific medicine or by the effect of his mind and personality on his time and on the pupils he has formed.—Armand Trousseau: A Master Clinician, Fielding H. Garrison.

THE RELATION OF DIET TO BERIBERI

AND THE PRESENT STATUS OF OUR KNOWLEDGE OF THE VITAMINS

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The title of this paper is very broad, and as a comprehensive discussion of it would carry me far beyond the limits assigned to papers of this character, I shall necessarily confine myself to certain phases of the subject.

At the present day, there is a general consensus of opinion to the effect that beriberi is caused by a dietary deficiency, or that it is a disease resulting from faulty metabolism, and is directly caused by the deficiency of certain accessory food substances that have been called vitamins. In a general way this opinion is based on the following facts:

1. The complete failure of the adherents of the infection and intoxication theories to prove their case.

2. The carefully planned and controlled human feeding experiment of Fraser and Stanton,¹ in which they demonstrated beyond all cavil that beriberi can be experimentally produced in men by too exclusive feeding on overmilled or highly polished rice. This experiment was later repeated by Strong and Crowell² in the Philippines with a similar result.

3. The long series of animal experiments which have been repeated with substantially the same results in all parts of the world and by which it has been equally demonstrated that various animals, but particularly birds, when fed on diets that will produce beriberi in man suffer with a disease which in some instances is identical in symptomatology and pathology with human beriberi, and in other instances is so similar that we must believe that it is essentially the same disease.

4. The instances in which beriberi has been eradicated from various institutions or groups of men by certain simple but radical changes in the dietary. Every sanitarian should be familiar with the practical results of this character reported by Van Leent,³ Vorderman,⁴ Takaki,⁵ Fletcher,⁶ Highet,⁷ Heiser,⁸ Theze,⁹ Chamberlain¹⁰ and others.

Inasmuch as I have written at some length concerning this evidence elsewhere,¹¹ I shall not go into it further here, but will briefly mention some of the work that has led us to our present knowledge of the beriberi vitamins. Eijkman's discovery that fowls develop polyneuritis, a condition resembling if not

1. Fraser and Stanton: Studies from the Institute for Medical Research, Federated Malay States, 1909, No. 10.

2. Strong and Crowell: The Etiology of Beriberi, Philippine Jour. Sc., 1912, vii, 271.

3. Van Leent: Arch. de méd. nav. October, 1867, p. 241; Communication sur le beriberi, Cong. Internat. d. Sc. Med. Amst., 1880, vi, 170, etc.

4. Vorderman: Onderzoek naar het verband tusschen den aard der rijstvoeding in de gevangenis op Java en Madoera en het voorkomen van beriberi onder de geïnterneerden, Batavia, 1897.

5. Takaki: Three Lectures on the Preservation of Health Amongst the Personnel of the Japanese Navy and Army, Lancet, London, 1906, i, 1369, 1451, 1520, etc.

6. Fletcher: Rice and Beriberi, Jour. Trop. Med. and Hyg., 1909, xii, 127; Lancet, London, 1907, i, 1776, etc.

7. Highet: Beriberi in Siam, Philippine Jour. Sc., 1910, v, 73.

8. Heiser, V. G.: Practical Experiences with Beriberi and Unpolished Rice, Philippine Jour. Sc., 1911, vi, 1237; Practical Experiences with Beriberi and Unpolished Rice in the Philippines, THE JOURNAL A. M. A., April 29, 1911, p. 1238.

9. Theze: Note sur le beriberi a poulo-condore, Ann. d'hyg. et de méd. col., 1910, xiii, 16.

10. Chamberlain: The Eradication of Beriberi from the Philippine Scouts by Means of a Simple Change in Their Dietary, Philippine Jour. Sc., 1911, vi, 133.

11. Vedder, E. B.: Beriberi, New York, William Wood & Co., 1913.

identical with beriberi in man, when fed on an exclusive diet of polished rice, formed the entering wedge, and gave us an experimental animal. Eijkman also made numerous other additions to our knowledge, including the fact that the addition of rice polishings to the diet would prevent the disease. The next great step was made when Fraser and Stanton¹² showed that the protective substance was dissolved out of rice polishings by a 0.3 per cent. hydrochloric acid solution, and remained in solution even when sufficient alcohol was added to precipitate out the phytin. Chamberlain and Vedder¹³ then showed that the protective substance was water soluble, alcohol soluble, but insoluble in ether, that it was dialyzable, adsorbed by animal charcoal, and that an extract of rice polishings containing only those substances soluble in both water and alcohol would cure infantile beriberi with marvelous rapidity. With the exception of the demonstration that infantile beriberi was curable by an extract of polishings, the work referred to above was all based on feeding experiments in which various extracts or substances obtained from rice polishings were administered to fowls subsisting on a diet of polished rice, and in which the protective power of the extracts was determined.

At this point in a brilliant series of researches, Funk¹⁴ succeeded in obtaining from rice polishings a crystalline base which would promptly cure fowls that had already developed polyneuritis. Funk believed that he had succeeded in isolating this substance in a state of chemical purity, that it belonged to the pyrimidin group, and he even gave it an empiric formula, and coined the name "vitamin" for it. Vedder and Williams¹⁵ found that, using Funk's method, they were able to obtain a crystalline substance which promptly cured fowls, but they were unable to obtain a sufficient quantity in pure form to subject it to accurate chemical analysis. At about the same time, Edie and his co-workers¹⁶ obtained a similar curative substance but gave it a different formula, and Suzuki, Shimamura and Otake¹⁷ by a different method obtained another vitamin of still different chemical composition. The careful chemist who reads these papers might come to the conclusion that the very existence of such a substance as the so-called vitamin was doubtful. However, the fact that such a substance exists is as well-proved as any natural fact can be. All of the foregoing investigators have succeeded in obtaining from rice polishings a chemical substance which in doses of a few milligrams was capable of curing birds suffering with polyneuritis induced by a diet of over-milled rice. But it is now evident that these investigators, and particularly Funk, were a little premature in announcing the chemical formula of the pure vitamin. Evidently none of them were working with pure vitamin, a fact which was admitted¹⁸ by Drummond and

Funk in a later article, who there state that they cannot isolate the pure vitamin, but that it is apparently decomposed during the fractionation and that all trace of it is lost. It should therefore be plain that while Funk's work gave a tremendous impetus to this investigation, neither he nor any of the foregoing workers succeeded in isolating pure vitamin, and that its chemical formula remains unknown. Williams,¹⁹ however, now began an entirely new line of work. Guided by the information obtained in the previous analytic work on rice polishings outlined above, he succeeded in preparing, synthetically, substances that would cure polyneuritis in fowls. These substances display a remarkable dynamic isomerism which has a most profound influence on their antineuritic properties. The curative form of each compound readily undergoes at ordinary temperature a rearrangement of its atoms resulting in the formation of a physiologically inert substance. By the application of dry heat, the noncurative form can be readily reconverted into the curative one. Although the synthetic substances in which this physiologically important isomerism was first discovered were hydroxypyridins, it now seems possible that the antineuritic properties are not peculiar to them but are inherent in the type of isomerism of which they are capable. Later unpublished work of Williams and Seidell has furnished further evidence that a similar isomerism exists in the vitamin of yeast, and is primarily responsible for the instability of these compounds which has so far prevented their isolation.

The substance isolated from yeast which appears to display this isomerism is the well known purin base adenin. Just how narrowly defined the group of naturally occurring substances of this type may be remains for future investigation. Nothing is yet known as to the exact identity of the vitamin as it occurs in rice polishings or as to the chemical relation existing between vitamins obtained from various sources.

It is quite evident that this work indicating the importance of isomerism affords an idea which is quite as new and startling as the conception of the vitamin was three years ago. The study of dietetics from the point of view of the vitamins has only just begun, but it is evident that there are many of these accessory food substances which play an important rôle in metabolism, and that this fact must be taken into account in planning diets in institutions, and in interpreting the relation of diet to such diseases as pellagra.

The exact rôle which these vitamins play in metabolism has not yet been elucidated, and any opinions which have been expressed must be in the nature of tentative hypotheses. With regard to the antineuritic vitamin, I have proposed the hypothesis that this chemical substance acts as a building stone of the complex structure of the nervous tissue, without which it cannot be repaired.²¹ When a deficiency in this vitamin exists, the nervous tissue becomes first exhausted and then degenerated until finally the symptoms of polyneuritis appear in fowls or dry beriberi in man. This theory is based on experimental observations. Thus Vedder and Clark²⁰ found that the mitochondria in the nerves of fowls showed definite

12. Fraser and Stanton: The Etiology of Beriberi, Studies from the Institute for Medical Research, Federated Malay States, 1911, No. 12.

13. Chamberlain and Vedder: Contributions to the Etiology of Beriberi, Philippine Jour. Sc., 1911, vi, 251, 395; The Cure of Infantile Beriberi by the Administration to the Infant of an Extract of Rice Polishings, Bull. Manila Med. Soc., 1912, iv, 26.

14. Funk: On the Chemical Nature of the Substance Which Cures Polyneuritis in Birds, etc., Jour. Physiol., 1911, xliii, 26; *ibid.*, 1912, xlv, 75, etc.

15. Vedder and Williams: Concerning the Beriberi Preventing Substances or Vitamins Contained in Rice Polishings, Philippine Jour. Sc., 1913, viii, 175.

16. Edie, Evans, Moore, Simpson and Webster: The Anti-Neuritic Bases of Vegetable Origin with a Method of Isolating Torulin, Biochem. Jour., 1911-1912, vi, 235.

17. Suzuki, Shimamura and Otake: Ueber Oryzanin, etc., Biochem. Ztschr., 1912, xliii, 89.

18. Drummond and Funk: The Chemical Investigation of the Phosphotungstate Precipitate from Rice Polishings, Biochem. Jour., 1914, viii, 598.

19. Williams, R. R.: On the Chemical Nature of the Vitamins, read before the Second Pan-American Scientific Congress, January, 1916, and not yet published.

20. Vedder and Clark: Polyneuritis Gallinarum, A Fifth Contribution to the Etiology of Beriberi, Philippine Jour. Sc., 1912, vii, 423.

changes after only seven days on a diet of polished rice, and long before the fowls showed any clinical symptoms of polyneuritis, and these changes were progressive the longer the deficiency lasted until evident degeneration could be demonstrated. Chromatolysis and changes in the tigroid substance of the cells of the cord, similar to that observed in pigeons which have been exhausted by long flights, may also be demonstrated in birds which have developed polyneuritis.

More recently Funk²¹ and Braddon and Cooper²² have published experimental work indicating that the antineuritic vitamin is concerned in some way in carbohydrate metabolism. This conclusion is based chiefly on the fact, which they claim to have demonstrated, that the rapidity of the onset of polyneuritis depends on the amount of carbohydrate eaten. In other words, if a definite but deficient amount of antineuritic vitamin is furnished, the fowls receiving 100 gm. of rice daily will develop the disease sooner than the fowls receiving 50 gm. of rice daily. I believe this observation to be erroneous. I shall not go into this subject in detail here, as I hope to publish the results of my experiments at another time. It is sufficient now to state that fowls will develop polyneuritis on diets containing absolutely no carbohydrate, such as exclusive diets of sterilized egg, or sterilized meat. In the light of this fact it is difficult to understand how the vitamin can be concerned in carbohydrate metabolism. The antineuritic vitamin is the only one of the accessory food substances concerning which there is sufficient evidence to even theorize concerning its action in the body, and it is certain that much more experimental work must be performed before we shall have any adequate conception as to the physiologic action of the vitamins.

The study of beriberi, scurvy and other deficiencies has led us to a working hypothesis that there are a number of different accessory food substances or vitamins and that each deficiency disease is caused by the absence of its particular vitamin. The question may naturally be asked, Why assume the existence of so many vitamins in our present state of ignorance concerning the chemistry of these bodies? May it not be a single substance acting differently under different circumstances and in different animals? I have elsewhere¹¹ stated the reasons which lead me to believe that dry beriberi and wet beriberi in man are caused by the deficiency of two distinct though possibly chemically related vitamins. With regard to scurvy it may be pointed out that men or monkeys fed on rice will develop beriberi, but if fed on bread will develop scurvy. It seems reasonable to suppose that there must be two vitamins concerned, the deficiency of one producing scurvy and deficiency of the other producing beriberi, and that the scurvy preventing vitamin is present in rice. Further, Funk and McCallum²³ and others have shown that diets which produce neither beriberi nor scurvy in rats may still be deficient in accessory food substances so that young rats are unable to grow on them. Indeed, McCollum and Davis²⁴ have shown that this failure to grow is due to the deficiency of two substances, one water soluble and one soluble in butter fat, both of which must be pres-

ent before growth can proceed. From all of these facts and many others, it seems that we must assume that there is a whole group of accessory food substances or vitamins, and that further investigation will be necessary to determine the relation of these various substances to each other.

Much criticism has been expended on the term "vitamin." Most of this criticism is from chemists who point out that the termination "amin" indicates a definite chemical structure and that since the chemical structure of these accessory food substances is not definitely known, the term is probably a misnomer. To me this appears a splitting of hairs. Perhaps the term is not chemically exact, but neither is the use of the word "vaccine" etymologically correct. Most vaccines have nothing to do with a cow. The term "vitamin" is simply a convenient expression to use in place of the elaborate phrase "accessory food substance," and it will probably continue to be used because of its convenience. Vitamins are certainly necessary to life, and to that extent the term is etymologically correct and expresses a fact in one word which is lacking in the phrase "accessory food substance."

Finally, I wish to discuss briefly the application of some of the information obtained with regard to beriberi and scurvy, to other possible deficiency diseases. The deficiency in the dietary that causes beriberi is not by any means limited to rice, for it has been shown repeatedly that too exclusive diets of ordinary white flour, canned goods that have been sterilized, and most carbohydrate foods such as sugars and starches, tapioca, sago, hominy and certain kinds of cornmeal will produce polyneuritis in fowls and beriberi in man. Beriberi has been reported repeatedly in communities, asylums, prison camps, etc., where the diet has consisted largely of such foods. For this reason we may expect to find the disease more often than is generally supposed in the United States. I have already pointed out²⁵ the instances reported by Bondurant, Bradfield, Sams and Parker, and Wood²⁶ has recently reported the presence of beriberi in Carolina. It may be of interest to note that Jürgens²⁷ has recently reported what is probably wet beriberi in the prison camps of Europe, but describes it as the edema disease.

Rice, so far as known, has not been shown to produce scurvy in man or animals, but with this exception practically all of the articles named above have been definitely associated with outbreaks of scurvy. Salted meats are also notorious scurvy producers. Thus a diet of hard bread and bacon has often produced scurvy among soldiers when fresh vegetables and fruits were inaccessible, and similar diets produced scurvy with great regularity among sailors on long voyages before the compulsory use of lime juice.

It is noteworthy that where pellagra is prevalent in the United States, the sufferers from that disease are living very largely on articles that have been demonstrated to produce either beriberi or scurvy or both, namely, flour, cornmeal, canned goods, salt meat, etc. It is quite possible that these people have been protected from scurvy and beriberi because they have eaten a sufficient quantity of other foods that protected

21. Funk: Die Rolle der Vitamine beim Kohlenhydrat-Stoffwechsel, *Ztschr. f. physiol. Chem.*, 1914, lxxxix, 378.

22. Braddon and Cooper: The Influence of Metabolic Factors in Beriberi, *Jour. Hyg.*, 1914, xiv, 331; *Brit. Med. Jour.*, 1914, i, 1348.

23. Funk and McCallum: Studies on Growth, *Jour. Biol. Chem.*, 1915, xxiii, 413, etc.

24. McCollum and Davis: The Nature of the Dietary Deficiencies of Rice, *Jour. Biol. Chem.*, 1915, xxiii, 181.

25. Vedder, E. B.: Some Further Remarks on Beriberi, *Am. Jour. Trop. Dis. and Prev. Med.*, 1914, i, 826.

26. Wood, E. J.: The Question of the Existence of Beriberi in the United States, read before Association of American Physicians, May 9, 1916.

27. Jürgens: Edema Disease Among Prisoners of War, *Berl. klin. Wchnschr.*, Feb. 28, 1916; abstr., *THE JOURNAL A. M. A.*, April 15, 1916, p. 1278.

them against those diseases, such as fruit and beans, but left them susceptible to a third deficiency that produced pellagra. Dietary deficiency as a cause of pellagra has been dismissed summarily many times, simply because the investigator was ignorant of or misinformed with regard to the facts that the study of beriberi has developed.

For instance, it is obviously absurd to assume that pellagra must be an infection or an intoxication because of its peculiar pathology. The degenerations in the nervous system in pellagra resemble certain known intoxications, but so does the degeneration of the nervous system in beriberi. Indeed, because of this fact, beriberi was for many years supposed by some to be an intoxication. It is hard to believe that the profound changes seen in the bones in scurvy can be due to the deficiency of any substance found in fruit juices, yet it has been proved that this is the case.

Again, if pellagra is a deficiency disease, as I believe it is, it has an extremely long depletion period. If Goldberger and his associates produced pellagra in their human feeding experiment, the depletion period on the diets used may be placed at at least five months. This long period that must elapse between the adoption of a deficient diet and the appearance of pellagra may easily mislead us in the interpretation of epidemiologic data, and it makes it very difficult to find a suitable experimental animal in which pellagra may be produced, for the simple reason that many animals, fed on presumably pellagra producing diets, will die of some other deficiency disease. I have myself fed four monkeys on diets similar to those observed among pellagrins, but these monkeys all died of scurvy.

The errors and pitfalls into which an observer may fall in trying to elucidate a deficiency disease are many, but for the future I think it will not be disputed that the investigator of pellagra should be fully informed with regard to the literature on other deficiency diseases.

CONCLUSIONS

As there are many conditions under which it is difficult for certain people and institutions to procure a rich and varied diet, I should like to repeat and emphasize the simple dietary rules which I have elsewhere formulated²⁵ for the prevention of deficiency diseases:

1. In any institution where bread is the staple article of diet, it should be made from whole wheat flour.

2. When rice is used in any quantity, the brown undermilled, or so-called hygienic rice, should be furnished.

3. Beans, peas or other legumes, known to prevent beriberi, should be served at least once a week. Canned beans or peas should not be used.

4. Some fresh vegetable or fruit should be issued at least once a week and preferably at least twice a week.

5. Barley, a known preventive of beriberi, should be used in all soups.

6. If cornmeal is the staple of diet, it should be yellow meal or water-ground meal, that is, made from the whole grain.

7. White potatoes and fresh meat, known preventives of beriberi and scurvy, should be served at least once a week, and preferably once daily.

8. The too exclusive use of canned goods must be carefully avoided.

I am sure that the strict application of these rules will eradicate scurvy and beriberi, and believe that they would be equally efficacious in eradicating pellagra from the United States.

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SYPHILIS WITH NEUROLOGIC SYMPTOMS SIMULATING OTHER CONDITIONS

SOME CASES AND THEIR TREATMENT*

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Since the introduction of the Wassermann reaction as a diagnostic test of syphilis, we have come to recognize more and more the protean manifestations of this disease and to realize that types of disease which before the introduction of the Wassermann reaction were regarded as being due to other causes may be caused by syphilis. At least, we failed to recognize the relationship of various types of disease to syphilis on account of the failure to obtain any very definite history of syphilitic infection or of symptoms in the past suggesting syphilis. The etiologic relationship to syphilis of these cases would pass unnoticed but for the positive Wassermann reaction. Such cases emphasize strongly the importance of carrying out in a routine way Wassermann reactions in practically all cases as is done on the medical service and on the neurologic division of the surgical service of the Peter Bent Brigham Hospital.

With the recognition of the incidence of syphilis and of the probability that syphilis may be the cause of the symptoms in a given case, the inauguration of antisyphilitic treatment is often followed by excellent results. There are, however, cases with neurologic symptoms and with a positive Wassermann reaction in which it cannot be said whether or not syphilis is the cause of the symptoms, inasmuch as these cases do not respond favorably to antisyphilitic treatment. In such cases it may be that there is a chronic cerebrospinal lesion of nonsyphilitic nature and coincident syphilis, or it may be that we are dealing with a case in which syphilis has produced permanent chronic changes from which recovery is impossible following antisyphilitic treatment. The following cases illustrate the association of syphilis as a probable cause of various neurologic symptoms, inasmuch as there was a positive Wassermann reaction, and an amelioration of symptoms occurred following antisyphilitic treatment.

CASE 1 (Peter Bent Brigham Hospital Medical No. 1533).—A woman, aged 29, entered the hospital, Aug. 5, 1914, complaining of trigeminal neuralgia. A diagnosis of trigeminal neuralgia was made. There was no history suggestive of syphilitic infection or of antecedent syphilitic disease. Four years previous she had had a sudden onset at night of pain back of the angle of the left jaw; this was repeated on three successive nights. Following this there developed a typical picture of trigeminal neuralgia. Later there was a paralysis of the left side of the face, and subsequently the right side of the face became involved with attacks of sharp, cutting pain.

Physical examination was negative except for a moderate ptosis of the left eyelid and a greater fulness of the left side of the face and limitation of all voluntary movements of the right side of the face. The blood serum gave a strongly positive Wassermann reaction. The spinal fluid showed a slightly increased globulin, a cell count of 27, and a negative Wassermann reaction. She was treated with fourteen intravenous injections of salvarsan, a total of 4.1 gm. in four months. This was followed by intramuscular mercury for three months. Following the first four treatments with salvarsan there was steady improvement. Gradually the pain and tenderness along the right side of the face disappeared.

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