

diction from the curve based on body weight alone is of equal value with that from the formula, taking into consideration not only weight but also stature and age. This is probably in large part explained by the fact that with boys the changes in age, weight, and stature are closely correlated.

<sup>1</sup> Harris and Benedict, *Carnegie Inst., Washington, Pub.*, No. 279, 1919; see also these PROCEEDINGS, 4, 1918 (370-373).

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THE NATURE AND FUNCTION OF THE ANTINEURITIC  
VITAMINE<sup>1</sup>  $\phi$

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Communicated by W. A. Noyes, November 17, 1919

*Introductory.*—Prior to and immediately following the year 1897 various theories were advanced by different investigators relative to the etiology of the oriental disease known as beri-beri. The merits and demerits of the various theories extant at that period are discussed in a very comprehensive way by W. L. Braddon in his book, "The Cause and Prevention of Beri-Beri." It will suffice to say that the prevailing theories held at that time explained the etiology of the disease in terms of bacteria, bacterial poisons, or poisons contained within the food.

During the years 1889 to 1897 Eijkman and his colleagues had advanced the study of the disease to the point where they were able to demonstrate that beri-beri could be produced at will on a diet consisting solely of polished rice, but that a cure could be effected and a recurrence of the disease prevented by the use of hand-milled rice. Eijkman<sup>2</sup> also showed that a disease similar to human beri-beri could be produced in fowls by diets composed of polished rice and that the paralytic symptoms disappeared upon the administration of rice polishings or alcoholic extracts of rice polishings. Schaumann,<sup>3</sup> in 1910, introduced a phosphorus-deficiency theory, basing his convictions upon the fact that all curative foodstuffs possessed a high percentage of phosphorus, while in the case of the non-curative foods the reverse seemed to be true. Schaumann believed the organic phosphorus-containing compounds to be essential in the treatment of beri-beri. This theory was propounded at a time when a great deal of importance was being attached to the lipid content of the dietary. Other writers<sup>4,5</sup> have shown that a parallelism exists between the phosphorus content of cereals and their vitamine activity, but this parallelism is considered to be fortuitous rather than an actual chemical relationship.

*Views Concerning Its Chemical Characteristics.*—In 1911 Funk<sup>6</sup> announced

that he had been successful in isolating an organic base,  $C_{17}H_{18}O_4N(HNO_3)$ , from rice polishings which possessed a curative action. On account of the fact that this nitrogenous substance was apparently indispensable to life, Funk gave it the title "vitamine." This was the origin of the vitamine hypothesis.

Since 1911-12 a number of investigators have studied many phases of the vitamine problem with the result that much has been learned concerning the vitamine content of various food materials and the effect of these diets on the growth and development of animals. However, very little advancement has been made in ascertaining with greater certainty the chemical nature of the anti-beri-beri vitamine. Following the publication of Funk's article, Edie<sup>7</sup> and his co-workers announced the isolation of a basic substance from yeast to which was ascribed the formula  $N(CH_3)_3C_4H_7O_2(NHO_3)$ . They named the substance "Torulin." Suzuki, Shimamura and Odake<sup>8</sup> also publishing the same year obtained a pure chemical substance from rice polishings which possessed a curative action. This substance they identified as nicotinic acid. During the same year Schaumann<sup>9</sup> prepared a phosphorus-free nitrogenous base which had curative properties. He advanced the hypothesis that this base acts as an "activator," stimulating the synthesis of phosphatids which are essential in the regeneration of degenerated nervous tissue.

Funk<sup>10</sup> believed that the curative substance was chemically related to the pyrimidines or purines. To test this hypothesis he fed allantoin, hydantoin, thymus nucleic acid and cytidine, obtaining varying degrees of improvement in polyneuritic birds.

Williams<sup>11</sup> found that the hydroxyl pyridines possessed curative properties which were lost on standing; this, he explains, is probably due to tautomerism and he suggests that the instability of vitamins may be explained on a similar basis. In a later publication<sup>12</sup> this writer concludes that the curative form of  $\alpha$ -hydroxyl pyridine is structurally a pseudo-betaine. He postulates that nicotinic acid and possibly vitamins are of a similar nature. Harden and Zilva<sup>13</sup> confirmed the chemical facts regarding the  $\alpha$ -hydroxyl pyridines and adenine, as put forth by Williams, but failed to obtain relief in avian polyneuritis when these preparations were fed. Voegtlin and White<sup>14</sup> also failed to obtain results as reported by Williams and Seidell.<sup>15</sup>

*Views Concerning Its Metabolic Functions.*—Funk<sup>16</sup> made the observation that when no food was metabolized beri-beri symptoms did not appear, while an increase in food intake, especially carbohydrate food, hastened the paralytic symptoms. This has been substantiated by other investigators, including the writer, except that we are inclined to believe that overloading the oxidative mechanism with any energy-producing food will usually hasten the onset of symptoms. Funk and Schönborn<sup>17</sup> associate this type of vitamine with carbohydrate metabolism and es-

pecially starch metabolism. On vitamine-free diets these authors obtained hyperglycemia with diminished amounts of hepatic glycogen. Vitamine-free and carbohydrate-free diets, in the opinion of these writers, prevents in some manner, the synthesis of glycogen from protein and fat. Vitamine diminished the hyperglycemia and increased the liver glycogen.

The first work recorded, so far as the writer is aware, concerning the relation of vitamine to pathology, is that of Funk and Douglas<sup>18</sup> and Douglas.<sup>19</sup> Pathological examination of the pituitary, thyroid, suprarenals, ovary, testes, kidney, liver, pancreas and spleen showed that on a vitamine-free diet all glands diminished in size and underwent degenerative changes. The thymus gland was caused to disappear and then return by the administration of vitamine.

Drummond<sup>20</sup> has published data indicating that creatinuria follows the feeding of diets deficient in the anti-neuritic vitamine. In this work rats were used as the experimental animals.

Studies made in this laboratory have led us to believe that the vitamine functions indirectly as a metabolic stimulant. We have observed<sup>21</sup> that the body temperature falls during the development of avian polyneuritis and increases after vitamine administration. Measurement of the catalase content of the tissues in polynuritic birds revealed a drop in catalase activity to a point 56% below normal, indicating that oxidative processes are depressed when the organism is not receiving the normal amount of vitamine. It is not improbable that the depression of body oxidations is accompanied by the formation of toxic metabolic products which affect the nervous system, bringing about the typical paralysis and other symptoms.

The mechanism of the stimulation and cure, when vitamine is fed, is not clear. Certainly the process is not a simple one. It would appear that there is some relationship between vitamine intake and endocrine activity. Mr. S. D. Wilkins, working in this laboratory, has recently caponized Single Comb White Leghorn cockerels whose sole diet, for from three to five weeks, was polished rice. The testicles were found to be atrophied to a surprising degree, often being not more than 20% of normal in size and weight. He has been able to show the effect of diet in this connection by removing but one testicle in each rice-fed bird and immediately afterward adding green alfalfa to the rice diet. The birds on the rice-alfalfa diet grow and increase in weight. Upon caponizing these birds the remaining testicle has increased in size and weight, approaching that of the normal birds. Jackson and Stewart<sup>22</sup> point out that underfeeding brings about atrophy of practically all vital organs, including the testes, accompanied by a loss in body weight. Refeeding does not produce normal growth and none of the animals attain the size and weight of the control animals. This, these writers point out, differs from the results

of Osborne and Mendel<sup>23</sup> who concluded that the capacity to grow is not lost on inadequate diets.

The remarkable growth of the animals refed by Osborne and Mendel may have been due to the fact that the diets were adequate in quantity and quality with respect to vitamins and other ingredients with the exception of protein. The organs and ductless glands probably received sufficient nourishment and stimulation to prevent appreciable atrophy. In the case of the underfed rats of Jackson and Stewart the diet was quantitatively inadequate with the result that pathological changes (atrophy) went too far for the normal processes to be restored.

We have been able to obtain decided atrophy of the testes in cockerels without a loss in body weight, which eliminates any possibility of explaining the condition on a starvation or inanition basis. McCarrison<sup>24</sup> has obtained similar results with pigeons, finding atrophy of many of the ductless glands and vital organs. While inanition plays a part, this author believes the unusual pathological condition to be due to the absence of vitamins, which he calls "nucleopasts," due to the fact that he believes them to be essential for nuclear metabolism.

From the standpoint of the feeder and the live-stock producer, as well as from the sociological standpoint, this work suggests two important things which merit emphasis: first, the question of diet in relation to sexual vitality, sterility, etc., and second, the importance of green, fresh feed for all growing animals, especially poultry. Proprietary poultry feeds are often largely carbohydrate in composition, poor in protein and low in vitamins and mineral matter. Many diseases are undoubtedly brought about by poor diets, lowering the resistance of the animal to invading organisms. The rôle that the vitamins plays in this connection is unknown.

We have cured limberneck in fowls by administering a vitamin extract prepared from wheat germ. In each case recovery was preceded by copious bowel evacuations. The action in this case is probably not a typical vitamin action, but there is little doubt but that the vitamin plays its part in the rapid recovery of the birds. Neither do we wish to leave the impression that limberneck is a deficiency disease; in fact, we have been unable to produce it by any method of feeding or treatment. Uhlmann<sup>25</sup> states that water-soluble vitamins acts in a manner very similar to pilocarpine, stimulating gland secretion. It is very possible that the laxative action of many fruits, vegetables, whole grains and brans, is due, in a measure, to increased gland secretion brought about by vitamin stimulation.

With Uhlmann's work in mind and also the work of Kendall,<sup>26</sup> who isolated thyroxin, the hormone of the thyroid gland, we<sup>27</sup> have fed polyneuritic pigeons the stimulants thyroxin, desiccated thyroid, pilocarpine hydrochloride and tethelin. The thyroxin and thyroid were fed because

of Kendall's findings that energy production was dependent upon thyroid activity. Pilocarpine hydrochloride was used because of Uhlmann's work mentioned above. Tethelin, the growth-controlling principle of the anterior lobe of the pituitary body,<sup>28</sup> was fed for similar reasons. All of these substances produced definite relief and cessation of polyneuritic symptoms. The response was slower in all cases than when vitamins are fed.

The hormones from the ductless glands undoubtedly influence to a marked degree the activity, health, growth and well-being of animals. May it not be possible that the hormone supply is dependent upon the vitamin content of the food? As a result of our observations, we wish to suggest tentatively that the activity of the organs of internal secretion are dependent upon the stimulatory action of the vitamins. Whether this is in the nature of a nerve stimulant, nuclear nutrient or the chemical nucleus of a hormone is, of course, a matter of speculation.

<sup>1</sup> Published with the approval of the Director, as Paper No. 185, Journal Series, Minnesota Agricultural Experiment Station.

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<sup>13</sup> Harden, A., and Zilva, S. S., *Biochem. J.*, **11**, 1917 (172-179).

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<sup>27</sup> Dutcher, R. A., *J. Biol. Chem.*, **39**, 1919 (63-68).

<sup>28</sup> Robertson, T. B., *Ibid.*, **24**, 1916 (397-408, 409-421).