

## EDEMA DUE TO VITAMIN "B" DEFICIENCY

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"B" avitaminosis is a deficiency disease of unusual interest and infrequent occurrence in this country. Following is the report of such a case in a patient, who suddenly developed generalized edema, following a prolonged reducing diet, deficient in vitamin "B."

The patient, a lawyer, aged 27, was seen first in the Cleveland Clinic, on February 6, 1932. Medical advice was sought because of sudden increase in weight, accompanied by swelling of the face and legs. The illness had begun one week before admission when the patient first had noticed a swelling of his abdomen and legs which had appeared rather suddenly. The patient found that he had gained eleven pounds in weight over a period of three days; at the end of a week he had gained sixteen pounds. The swelling increased in proportion to the increasing weight, and always was worse in the mornings, tending to decrease towards mid-day. On several occasions the patient had awakened in the morning with his eyes swollen completely shut. His only other complaints were of a feeling of discomfort in the lower chest and upper abdominal region, of some weakness and of loss of "pep". There were no genito-urinary symptoms until about two days before his admission when he had noted some frequency and since then had been voiding an unusually large quantity of urine.

On questioning the patient it was found that he had been on a very restricted, poorly balanced diet for the last year and a half. In January, 1930, numerous furuncles, scattered over his entire body had developed. These had proved very resistant to treatment and his physician finally had advised a diet in which starches, sugars and fruits were prescribed. The patient had existed on a grapefruit and a small portion of meat (beef) each day with a little lettuce once or twice a week. After dieting in this manner for about six weeks, the boils had disappeared and the patient had lost about 25 pounds in weight. He felt so much better with his weight reduced, that he decided to continue on this diet, which he carried out with very little variance for a total period of a year and a half. After dieting for a few months, he soon lost his appetite and had no desire for food. During the entire period his weight had been reduced from 165 pounds to 105 pounds. His weight was maintained for three to four months at 105 to 110 pounds, when edema supervened.

The patient weighed 127 pounds and his height was 5 feet, 3 inches. The skin and mucous membranes appeared healthy. The eye examination revealed nothing abnormal; the tonsils had been removed and there was no evidence of oral sepsis. The thyroid was not enlarged and there were no palpable glands in the neck. There was a general puffy appearance of the face, most marked in the tissues around the eyes. The chest was symmetrical, the lungs clear, and no pleural effusion could be demonstrated. The heart seemed normal in size and no murmurs nor arrhythmia could be demonstrated. The skin over the pectoral region was very loose and edematous; palpation showed the existence of pockets of fluid between the chest wall and the underlying subcutaneous tissues. There was diffuse edema of the abdominal wall similar to that found in the chest. There was no evidence of ascites. The external genitalia were entirely normal, without any evidence of edema. The legs, ankles and feet showed a moderate amount of edema which pitted deeply on pressure. All superficial and deep reflexes were normal. There was no evidence of arteriosclerosis. No muscular atrophy or weakness could be demonstrated; there were no sensory disturbances, and the Jongkok test was negative.

The pulse rate was 60 and the blood pressure was 100 systolic, 64 diastolic. The blood count showed 4,400,000 erythrocytes, 7,250 leucocytes, and the hemoglobin, 84 per cent. The blood sugar was 77 milligrams per hundred cubic centimeters one hour after a meal. The level of the urea in the blood was 24 milligrams per cent. The results of the urinalysis were negative except for a low specific gravity, 1.010. The Wassermann and Kahn tests were negative.

The information obtained from the physical examination and from the routine laboratory tests was sufficient to rule out the presence of any of the diseases commonly producing edema.

The history of a low caloric intake over a long period of time, which had resulted in marked loss of weight, anorexia and weakness followed by the rather sudden onset of edema, immediately raised the question as to whether or not this might be a case of so-called inanition edema.

It was felt that the condition might easily be a Vitamin B deficiency disease, that is, a wet form of beriberi in which the neuritic symptoms were absent or masked by the edema.

The rather unusual features of the case prompted further studies. The plasma protein, carbon-dioxide-combining power of the plasma, and the inorganic constituents of the blood were checked with the following results:

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Serum Proteins.....	6.74 per cent
Serum Albumin.....	3.97 per cent
Serum Globulin.....	2.77 per cent
Euglobulin.....	0.99 per cent
Pseudo globulin I.....	0.42 per cent
Pseudo globulin II.....	0.36 per cent
Cholesterol.....	150 mg.
Sodium Chloride.....	577 mg.
Phosphorus.....	3.5 mg.
Calcium.....	9.7 mg.
Urea.....	24.0 mg.
Uric Acid.....	1.7 mg.
Non-Protein Nitrogen.....	22.4
Carbon Dioxide Combining Power.....	57.6
Basal Metabolic Rate:	
Dubois.....	—23 per cent
Sanborn.....	—26 per cent
(Based on 116½ pounds)	
Phenolsulphonephthalein:	
First hour.....	30 per cent
Second hour.....	35 per cent
Urea Clearance.....	67 per cent function

The plasma proteins in which we were most interested, were entirely within normal limits as were the carbon-dioxide-combining power of plasma and the inorganic constituents of the blood. The basal metabolic rate was rather low but this is to be expected in patients with edema. Roentgenographic studies of the gastrointestinal tract revealed pylorospasm and a very large, atonic colon.

The edema in this case could not be explained on the basis of low osmotic pressure of serum proteins, as is found in inanition edema; and hence it was felt that it must be closely related, if not identical, to the edemas which occur in the wet types of beriberi. Although there were no neuritic symptoms in this case, it has been repeatedly shown that ship beriberi, a wet form of the disease, is a deficiency disease in which nervous phenomena are rarely present and that edema of various degrees is the predominating, oftentimes the only, physical finding.

The patient, thoroughly alarmed about his condition, was quite willing to cooperate, and to dispense with his past dietary regimen. He was given a diet with a high vitamin, and low carbohydrate content, with a supplementary supply of vitamin B in the concentrated form of Vitamin B Extract, Parke, Davis & Co., in doses of two drachms three times daily.

The patient's response to this form of treatment was most satisfactory. The edema disappeared rapidly. In a week he had lost 10 pounds, his appetite had returned to normal, and he felt a "hundred per cent better." The edema had entirely disappeared from his

face, but was still evident in the pectoral region and in the lower extremities. He was advised to continue the treatment and to return at weekly intervals for observation. Edema continued to decrease and there was a gradual loss in weight, so that at the end of three weeks, there was no evidence of any gross edema. He had lost 16 pounds, undoubtedly due to the loss of fluid, in fact the amount of fluid lost was probably even greater than would appear from the figures, as most likely he had gained actually on the more substantial diet. The patient then began to gain, hoping to reach and maintain his weight at a level between 125 and 130 pounds, the proper amount for a man of his stature. Simultaneously with the disappearance of the edema there was a very marked increase in the urinary output. In June, 1932, after having been free from symptoms for four months, the patient returned because of a reappearance of the edema. He had gained 10 pounds rather suddenly and had had a very scanty output of urine. These symptoms occurred while the patient was on a three weeks' business trip, during which time he had stopped taking the Vitamin B Extract. The edema appeared almost two weeks after the extract was discontinued. An analysis of the serum proteins was done at this time and was found to be entirely normal. (Serum proteins, 8.32; albumin, 4.74; globulin, 3.58.) Curiously enough, ten days after treatment with vitamin B was reinstated, the edema had entirely disappeared and the urinary output had returned to normal. The patient has remained well to the present time; however, he still is taking a liberal supply of vitamin B daily along with the proper diet. Subsequent examinations failed to show any evidence of peripheral neuritis. Repeated urine analyses during the period of observation showed no evidence of renal damage.

With the marked amelioration of symptoms and entire disappearance of edema on a high vitamin B diet, without the aid of other therapeutic measures, it was felt that this case was indeed one presenting the clinical picture and course of wet beriberi.

#### DISCUSSION

In studying this case, inanition edema had to be considered. This symptom complex has been described under various names, among which are: war edema, famine edema, prison dropsy, and nutritional edema. The edema in these cases is of the generalized nephritic type and usually develops in an individual who has become emaciated from a protracted, semi-starvation diet. The condition has been reported as occurring frequently in famines, in prisons, and in asylums. At times it has been so prevalent that the term, epidemic dropsy, has been used to designate the disease. It was com-

mon in certain European countries toward the end of the World War, and studies were made in an attempt to determine its etiology.

Various workers have ascribed the dropsy in inanition edema to a lack of calcium fat and phosphorus in the blood. The importance of fresh vegetables, protein and vitamins has been emphasized.

After studying a large series of cases in 1920, Maver<sup>5</sup> concluded that it is a deficiency disease and is the result of protracted subsistence on a diet deficient in calories, and especially deficient in protein content; undoubtedly a high fluid intake and possibly a high salt intake are important accessory features. In the cases in his series, the edema was the most prominent feature and was most common in the feet and legs, at times extending to the thighs and trunk and in about one-half the cases including the face. Marked muscular weakness and alimentary disturbances were common. The urine was pale, of low specific gravity, but was free from albumin. Characteristic findings in Maver's group of patients were sub-normal temperature, slow pulse rate, low blood pressure, and low basal metabolic rate. They usually recovered after resuming a normal diet and receiving proper hospital care.

Inanition edema occurring in private medical practice has been variously described. Wolferth<sup>12</sup> reported two interesting cases following profound alimentary disturbances due to postoperative fecal fistula, diarrhea and vomiting. His findings were similar to those found in the cases of war edema, but he also found the serum protein content of the blood to be low. Landis and Leopold<sup>4</sup> described a case of edema in a patient with tuberculosis enteritis; special studies showed slight elevation of the capillary blood pressure and a marked diminution of the osmotic pressure of the serum proteins. Blood transfusions were followed by marked subsidence of edema and a rise in the level of the serum protein.

In a more recent study of the serum proteins in a large variety of diseases, Bruckman and Peters<sup>1</sup> stated that non-inflammatory edema which could not be ascribed to cardiac or renal disorders is found only when there is obvious malnutrition. They found that there is no correlation between edema and the concentration of globulin, and that *edema was observed in patients with malnutrition only when serum albumen is below the normal level*. Edema almost invariably develops when the level of serum albumin falls below 3 per cent, is seldom found when the amount of albumin exceeds 4 per cent. These workers concluded that malnutrition edema appears to be referable to a deficiency in serum albumen caused by wastage of body protein as the result of disease or an inadequate diet.

Beriberi is a rare disease today. It is most unusual to see the condition in this country, although a few sporadic cases have been reported. That a diet deficient in vitamin B, if taken for a prolonged period, causes beriberi, is a generally accepted fact. Although vitamin B is quite widespread in the animal and vegetable kingdom, we know that meats, milk and fruit juices contain relatively small amounts of it, and when the diet is otherwise deficient, relatively large amounts of these foods must be consumed in order to prevent the development of beriberi. Vitamin B is found in abundance in whole grain cereals, brewer's yeast, egg yolk, dry prunes, spinach, and the lentils. It is relatively heat stable, but is destroyed in the heat used in sterilization. Vedder,<sup>11</sup> in an excellent monograph on the subject, stated that in sporadic cases some anti-beriberi vitamin usually is ingested, but should the amount be insufficient for normal body metabolism, the patient, after a prolonged depletion period, may develop beriberi in as severe a form as though the diet were strictly vitamin-free. He said that experimental work on scurvy and beriberi has demonstrated the fact that the body is unable to store up any reserve of vitamin, that when a diet deficient in vitamins is adopted, impairment begins at once. Degenerative changes occur in the nerves of fowls within seven days, when they are fed only decorticated rice; however, this impairment does not lead to symptoms at once. The depletion period as shown by various human feeding experiments usually occurs in man within 90 to 120 days. In the case under discussion there were no symptoms for about a year and a half, the patient apparently feeling well until the sudden onset of edema and weakness caused him to seek medical advice.

The cause of edema in beriberi has always been obscure. McCallum<sup>7</sup> expresses the opinion that protein shortage is the probable cause of starvation dropsy and that wet beriberi may be an expression of two specific dietary lacks, protein starvation and deficiency of vitamin B. With the discovery that plasma proteins are reduced in cases of nephrosis and other edemas it was thought that some light might be thrown on the mechanism of the production of edema in beriberi. However, no confirmatory reports are to be found in the literature. Kabayaski<sup>3</sup> reported the serum proteins normal in beriberi while Shigeari and associates<sup>9</sup> observed low values during the edematous stages which rose to normal or above after the disappearance of the edema.

Nakazama and co-workers<sup>8</sup> reported serum albumen values seldom below 4 per cent and colloid osmotic pressure of only 1 per cent below normal. They found the molecular weight of albumen greater in the edematous forms and suggest the hypothesis that

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the blood building mechanism is disturbed in beriberi. McCarrison<sup>6</sup> found that the adrenals of fowls suffering from "B" avitaminosis are considerably enlarged, and that the secretion of adrenalin by these enlarged glands is proportionally increased. He suggested that the edema may be due to circulatory changes resulting from this increased secretion of adrenalin. Vedder<sup>11</sup> stated that there is considerable experimental evidence to indicate that two vitamins are deficient in the diet that produces beriberi and suggested the possibility that the deficiency of one, the anti-neuritic vitamin, produces degeneration of the nervous system and the symptoms of dry beriberi, while deficiency of the second vitamin produces generalized edema and the syndrome, wet beriberi. Sargent<sup>9</sup> pointed out that in the wet form of beriberi an affection of the vasomotor nerves produces edema while in the dry form paraplegic manifestations are produced and palsy and atrophy of muscles occur.

The pathologic findings in wet beriberi, to quote the older pathologists are "water here, water there, water, water everywhere." McCarrison<sup>6</sup> reported that all organs suffer atrophy except the adrenals which are hypertrophied. Cameron<sup>2</sup> found hyperemia of the adrenals and hypertrophy of the islands of Langerhans in the pancreas. The peripheral nervous system shows typical Wallerian degeneration. Hypertrophy and dilatation of the heart is present in most cases that come to necropsy.

The treatment of beriberi obviously consists of supplying the patient with the factor missing in his diet, namely, vitamin B. This may be done by an adequate diet rich in vitamins or by supplying the deficient factor in the form of vitamin "B" extracts, wheat germ, or yeasts. The liquid extract is the more palatable of the various products on the market and is particularly potent in the vitamin B<sup>1</sup> (anti-neuritic) factor. The edema usually clears up rapidly with proper treatment. If neuritis is present recovery is much less prompt as regeneration of nervous tissue always is slow.

The prognosis in beriberi is most favorable.<sup>‡</sup> Death seldom occurs in cases in which appropriate treatment is administered. The very high percentage of fatalities in some reported instances has occurred in circumstances where the adequate diet could not be administered.

### SUMMARY

A young man exhibited generalized edema and weakness following a generally inadequate diet, deficient in vitamin B. Laboratory tests, including a study of the plasma proteins and of the inorganic constituents of the blood were entirely normal. The complete disappearance of the edema and general symptoms, after a course of

treatment consisting of the administration of vitamin B and an adequate diet, is proof that the condition was a deficiency disease, a B avitaminosis or wet beriberi.

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