CLINICAL NUTRITIONAL DEFICIENCY DISEASE

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It is increasingly evident to clinicians that a lack of necessary specific nutritional elements often leads to definite symptoms and syndromes. Certain deficiency diseases such as scurvy and beriberi resulting from a total lack of such elements have long been recognized but are seldom seen in this country. Mild symptoms, however, due to an inadequate supply of nutritional factors occur frequently. We should think of a nutritional deficiency state as a combination of different symptoms and signs resulting from the disturbed nutrition of tissue rather than as a definite "disease." Often, more than one specific element is lacking, thus further complicating the picture. A nutritional deficiency results from a deficient supply or use of a specific nutritional element at the point of normal utilization. The element may be brought by the blood stream to the point of normal utilization and still be unused. Thus, in certain conditions such as lead poisoning, iron may be supplied in adequate amounts without influencing an iron deficiency anemia because the tissues are unable to utilize the iron offered in the building of hemoglobin. Similarly, absorption may be interfered with so the nutritional element is of no more value so far as the tissue needing it is concerned than if it had not been taken into the gastro-intestinal tract. It is apparent also that vomiting and diarrhea cause a mechanical loss of elements before absorption can take place.

All the specific nutritional elements must be ingested as such or formed in the gastro-intestinal tract from ingested food. The vitamins and mineral salts are taken in preformed, while other elements represent altered food constituents. Thus, the substance protective against pernicious anemia is formed by the interaction of something supplied by the stomach, the intrinsic factor, on something contained in ingested food, the extrinsic factor. Further study will probably reveal other factors similarly formed from intrinsic and extrinsic factors, but the erythrocyte maturing factor is the only one so far proved. The more important specific nutritional elements now known are: (1) calcium, (2) iron, (3) vitamin A, (4) vitamin B_1, (5) vitamin B_2 complex, (6) vitamin C, (7) vitamin D, and (8) the erythrocyte maturing factor (EMF) protective against pernicious anemia.

I have summarized in the following table the now accepted essential functions of the more important specific nutritional elements and indicated the "disease" recognized as due to a total lack of each element. We are especially interested, however, in the minor symptoms of the deficiency "state" rather than the fully developed deficiency diseases (Table I).

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TABLE I
NUTRITIONAL FACTORS WITH A SPECIFIC FUNCTION

Factor	*Specific Function*	*Clinical Signs of Deficiency*	*Clinical Syndrome ("disease")*
Calcium	Necessary for the normal function of bone and nerve tissue.	Increased nerve irritability.	Tetany.
Iron	Necessary for the formation of hemoglobin and erythrocytes.	Anemia of hypochromic and often microcytic type.	Hypochromic anemia
Vitamin A	Necessary for the integrity of epithelial tissue.	Epithelial defects.	Ophthalmia; urinary calculi; night blindness.
Vitamin B_1	Necessary for the integrity of nerve tissue.	Anorexia; neuritis; edema.	Beriberi; multiple neuritis.
Vitamin B_2 complex	Necessary for the integrity of dermal tissue.	Glossitis; dermatitis; neuritis; mental disturbances.	Pellagra?
Vitamin C	Necessary for the integrity of the endothelium of blood vessels.	Hemorrhage due to vascular defects.	Scurvy.
Vitamin D	Necessary for the normal metabolism of bones and teeth.	Softening of bone; decay of teeth.	Rickets; dental caries.
Erythrocyte maturing factor (EMF)	Necessary for the maturation of erythrocytes in bone marrow.	Glossitis; diarrhea; anemia of macrocytic type; degeneration of spinal cord.	Pernicious anemia; subacute combined degeneration of spinal cord; sprue.

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The formation, absorption or use of specific nutritional elements in the body is influenced greatly by numerous conditions, the more important of which are:

(1) Insufficient intake of food.
(2) Absence of some digestive factor necessary for the formation of a specific nutritional element for food (as the intrinsic factor lacking in pernicious anemia).
(3) Excessive loss of gastro-intestinal contents by diarrhea or vomiting.
(4) Increased need, as in pregnancy and lactation or states of overactive metabolism as hyperthyroidism.
(5) Presence of any toxic state impairing absorption and utilization such as malignancy or poisons as from lead, renal insufficiency, or infection.
(6) Anemia in which there is a deficient interchange between oxygen and food and tissues.
(7) Achlorhydria which affects the absorption or production of specific factors from food.
(8) Lowered metabolism in which the tissues are working at an abnormally low speed.
(9) Impaired glucose tolerance which seems to increase the need or impair the use of at least some of the nutritional elements.
(10) Disturbed circulation.

This is a large group of influencing factors, but each must be evaluated in any consideration of "deficiency" disease.

Illustrative Cases

Edema Due to Vitamin B Deficiency

Case 1: An attorney, 27 years of age, complained of edema beginning one week before admission without other significant symptoms. The gain in weight during this week had been 16 pounds. During the preceding two years, the patient had reduced his weight from 165 to 105 pounds by diet restriction for furunculosis. The diet consisted with very little variation of grapefruit and a small portion of meat daily and lettuce occasionally.

On examination, the weight was 127 pounds. The edema was generalized. There was no muscle weakness, change in tendon reflexes, or sensory disturbance. The pulse rate was 60, the blood pressure 100 mm. of mercury systolic and 64 diastolic. There was no anemia, and repeated urinalyses revealed no abnormalities except a low specific gravity. The urea clearance test showed 67 per cent of normal and the phenolsulphonphthalein excretion was 65 per cent in 2 hours. It was evident from the examination that no cardiac or renal factor was responsible for the edema. A hypoproteinemia was also excluded since the total blood proteins were 6.74 per cent with 3.97 per cent albumin and 2.77 per cent globulin.

The clinical diagnosis was edema due to vitamin B deficiency, and a high vitamin diet with a vitamin B concentrate was prescribed. In three weeks, the edema entirely disappeared with a loss in weight of 16 pounds. The patient had been symptom-free for four months when the edema recurred following discontinuance of the concentrate. The serum protein at this time was 8.3 per

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cent. The edema again disappeared. With a normal diet, the patient has been symptom-free for three years.

In this case, the important element in the development of the deficiency state was evidently the deficient intake of protective foods. At the time of the original examination, the basal metabolic rate was minus 26 per cent. This has been observed repeatedly and always found to be low. The lowered rate was probably an influencing factor in the development of the disease.

Weakness Due to Vitamin B Deficiency

Case 2: A housewife, 38 years of age, complained of weakness and shortness of breath on exertion for four years and weakness of the left leg for two years. She had been perfectly well until the birth of a third child (weight 11 pounds) five years before this examination. She had always been very active, but now noticed extreme weakness and dyspnea which permitted her to walk only one or two blocks without resting. For two years, the left leg had been very weak and for the past few days, the patient had been unable to get out of bed without assistance. She had consulted many doctors without relief. There were no other significant points in the history except marked constipation which had been present for years. She had lost 20 pounds in weight during the preceding six months.

Examination revealed that the patient weighed 152 pounds (the normal for her age and height being 138 pounds), the blood pressure was 120 mm. of mercury systolic and 90 diastolic. There was no infection. A complete general examination and a special neurological examination showed no objective findings except absent Achilles tendon reflexes. The tongue was smooth and rather atrophic. A gastric analysis made before admission had shown an achlorhydria. The basal metabolic rate was plus 2 per cent, the Wassermann test gave a negative reaction, and the blood sugar tolerance curve was normal. Roentgen examinations of head, chest, and gastro-intestinal tract all gave negative findings except for the colon. This was enormously dilated and very redundant. There was no anemia.

During observation in the hospital, the pulse rate was rapid and after walking only 30 seconds it rose to 160. The temperature was normal. The weakness was so extreme that the patient could not step on a scale platform without help. With no other treatment except a high vitamin, low carbohydrate diet and added vitamins, improvement was rapid so that she could walk the length of the corridor without assistance within two weeks. Two months later, she returned to show that all symptoms had disappeared entirely. Her weight was 140 pounds, all the deep tendon reflexes were normal, and a barium enema showed a great decrease in the size of the colon.

So far as could be ascertained from the history, this patient had followed an average normal diet. Her symptoms followed a pregnancy. She had an achlorhydria and a very abnormal colon. The abnormality of the gastro-intestinal tract was probably an important factor in the impaired absorption or use of the protective foods, although McCarrison[1] has shown experimentally that loss of tone and dilatation

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of the gastro-intestinal tract occurs commonly in the presence of vitamin B deficiency, so this may be a result rather than a cause.

Kidney Stone Due to Vitamin A Deficiency

Case 3: A man, 49 years of age, gave a history of passing renal calculi for 18 years, and several attacks of hematuria had occurred during the year preceding our examination. He had limited his food for a long time on account of indigestion. His diet for years had been as follows: breakfast—coffee and whole-wheat toast; lunch—soup, tea, and lemon; dinner—meat and two vegetables in small amounts. This patient weighed 170 pounds and his height was 69 inches.

The general examination was entirely negative. The blood pressure was 140 mm. of mercury systolic and 94 diastolic. A roentgenogram of the kidney showed a small stone in the right kidney pelvis. There was no anemia. Examination of the urine showed a few red cells and a trace of albumin, but there was no gross blood. It was alkaline in reaction with a pH of 7.8. The retinal sensitivity as measured by the biophotometer test was much diminished. Following use of the acid-ash high vitamin A diet, the pH of the urine fell to 4.8.

Atypical Scurvy Due to Vitamin C Deficiency

Case 4: A man, 58 years of age, was seen at the Clinic in October, 1933, with a typical history of duodenal ulcer, and gastric retention was demonstrated by roentgen examination. The patient had followed a stringent Sippy regime for two years and had taken no fruits except prunes, although he had been instructed to drink juice of citrus fruits. All the gastric symptoms disappeared, but two years later, the patient returned because a large hemorrhage had developed about the elbow and another in the lip without apparent cause or injury.

The general examination was negative except for one infected tooth. There were no petechiae although the tourniquet test was positive. A special examination of the blood for hemorrhagic disease showed no anemia or abnormality of the white cells. The platelets numbered 280,000 with normal clot retraction. The bleeding time was one and one-half minutes. The coagulation time was 20 minutes (normal 5-10 minutes). With a diet high in vitamin C, all symptoms disappeared rapidly.

Peripheral Neuritis Due to Lack of Vitamin B_1 and Hypochromic Anemia

Case 5: A woman, 46 years of age, was first seen because of menorrhagia which had been present during the preceding six months and which was found to be due to a cancer of the cervix. She tired easily, was dyspneic on exertion, and had edema of the feet. The examination was entirely negative except for the malignancy and a marked anemia. The red blood cells numbered 3,130,000 and the hemoglobin content was 45 per cent. The cancer responded to radium therapy and there had been no sign of recurrence or metastasis. While the patient was in the hospital, iron was given and the hemoglobin content of the blood had risen to 68 per cent six weeks after admission.

Eight months later, the patient returned complaining of severe pain in the hands and feet which had been severe enough to wake her at night. Neurologic

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examination revealed no paresthesia or other abnormality. She had gained 11 pounds in weight at the time she had edema of the feet. No further blood loss had occurred since the radium therapy. She had always taken very little meat and had eaten excessively of sweets.

She now showed marked atrophy of the tongue, blue sclerae, and the spoon nails characteristic of idiopathic hypochromic anemia. The blood count showed 4,760,000 red cells with 46 per cent hemoglobin and a volume index of 0.6 per cent.

Peripheral Neuritis, Dental Caries, and Hypochromic Anemia Due to Deficiency in Vitamin B_1 and Iron

Case 6: A woman, 22 years of age, was admitted in the sixth month of the fifth pregnancy in five years. Six months previously, numbness and weakness of the hands and feet developed and this progressed to complete motor paralysis of all extremities. The deep reflexes were absent and no sensory changes were found. There was marked muscle atrophy. The tongue was smooth and red. Edema was absent. There were marked dental caries. The spinal fluid was normal. Free acid was absent in the stomach and the total acidity was only 31. Examination of the blood showed: red cells, 3,950,000; hemoglobin, 68 per cent; color index, 0.84.

This patient was the wife of a steel mill worker and her diet had been limited for economic reasons. Five pregnancies had occurred in rapid succession and with each, she had had marked vomiting. With a balanced diet to which vitamins and iron were added, the pregnancy proceeded normally and the patient has made a complete recovery.

Sprue, Peripheral Neuritis, Macrocytic Anemia, Tetany, Deficiency in Erythrocyte Maturing Factor (EMF), Vitamin B, and Calcium

Case 7: A man, 26 years of age, had been treated for pernicious anemia for two years. On admission, he had a constant diarrhea with large stools, excessive formation of gas, and weakness. For one year he had had marked numbness of the hands and feet.

On examination the tongue was smooth and a test meal showed no free hydrochloric acid. There were no neurologic findings of significance. Examination of the blood showed a macrocytic anemia with a volume index of 1.44. The red cells numbered 2,940,000 and the hemoglobin content was 78 per cent. With intramuscular liver therapy, the diarrhea ceased and the blood returned to normal. While in the hospital, a typical carpopedal spasm of tetany developed which was relieved by the intravenous injection of calcium. The blood calcium was as low as 8.64 mg. per 100 cc.

This patient had a macrocytic anemia and sprue due to a deficiency in the erythrocyte maturing factor, a deficiency neuritis, and a calcium deficiency, all of which were relieved following liver therapy.

Pellagra and Pernicious Anemia (Deficiency in Vitamin B_2 and the Erythrocyte Maturing Factor)

Case 8: A single woman, 60 years of age, had been losing weight for three months and had become increasingly weak and mentally dull. She had been confined to bed for one week. Pallor and dryness of the skin had been noticed

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for some time. On admission, the patient was confused and answered questions with difficulty. She was obese; the face and legs were edematous and the dorsum of the hands showed marked wrinkling and scaly dermatitis. Over the elbows, the skin was markedly pigmented. There were no significant neurologic findings and no glossitis or stomatitis. The urine and blood proteins were normal. The blood showed a macrocytic anemia with a red cell count of 2,990,000, hemoglobin content of 65 per cent, and volume index of 1.21. The test meal showed an achlorhydria.

In the hospital, the patient had a daily rise in temperature to as high as 102° F. without apparent cause except the deficiency disease. With high vitamin feeding and the administration of liver extract intramuscularly, the edema disappeared and the mental state returned to normal.

This patient had a macrocytic anemia with achlorhydria typical of pernicious anemia and the skin and mental changes seen in well developed pellagra, and responded to liver therapy.

These case histories illustrate various phases and combinations of nutritional deficiency disease. Certain symptoms and signs should always suggest the possibility of a specific nutritional defect: a macrocytic anemia suggests a deficiency in the erythrocyte maturing factor (EMF) and a hypochromic anemia a deficiency in iron. Hyperirritability of the neuromuscular mechanism may be due to a lack of calcium. Night blindness, pyorrhea alveolaris, ophthalmia, and urinary calculi should bring to mind vitamin A insufficiency. Disturbances of the peripheral nerves suggest a vitamin B_1 deficiency just as dermatitis, pigmentation of the skin, glossitis, and stomatitis with mental disturbances suggest a vitamin B_2 complex deficiency. Rickets and dental caries suggest a vitamin D deficiency, while easy bruising and unexplained edema suggest a deficiency in vitamin C. It is most important to remember that deficiency disease may arise when the patient seemingly is ingesting a normal amount of the specific principle; this is due to interference with absorption or utilization by one or more of the numerous influencing factors mentioned above. To keep in mind the possibility of deficiency disease is often to solve an obscure clinical problem.

Reference

1. McCarrison, R.: Studies in Deficiency Disease, London, Henry Frowde, 1921.

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