A CONSIDERATION OF THE DEFICIENCY FACTOR IN DISEASES OF THE GASTRO-INTESTINAL TRACT*

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Four factors are operative in the production of deficiency disease.

1. The diet may be deficient in the food elements.

2. The diet may be sufficient, but a deficiency may exist because digestion has not prepared the food properly for utilization by the body.

3. The diet may ordinarily be sufficient but a relative deficiency may exist because of poor absorption from the gastro-intestinal tract, or from rapid loss of food substance through prolonged vomiting or diarrhea.

4. In some conditions such as pregnancy and hyperthyroidism, an increased demand by the body may cause a relative deficiency.

When it was recognized that certain diseases were caused by the lack of certain unknown substances in the diet, the first factor in the production of deficiency disease was self-evident. The recognition of this important fact immediately opened the large problem of what diseases are due to deficient diet, what substances are necessary to the human economy, what are the sources of these substances in natural foods, can they be artificially prepared and what quantity of these substances is necessary to prevent disease. Many of these problems have been answered, and today it is recognized that many diseases are definitely due to deficiency, many more are suspected, and undoubtedly others will eventually be added to this group. The general public has been so enlightened by what has been learned about the nature, source and quantity of these substances which are necessary to prevent disease, that, barring economic factors, it is rare to find the diet of the normal individual deficient in the known needed substances. But if for any reason, the individual subjects himself, or it is necessary for his physician to subject him to a dietary regime, certain precautions then become necessary to prevent a state of deficiency.

The whole problem, however, became much more interesting and complicated with Castle's discovery that pernicious anemia was a deficiency disease, not because of the usual conception of a deficient diet, but because the gastric secretion was deficient in an unknown digestive principle which, in the normal person, produced a substance in the digestion of food that was essential to the proper maturation of the red blood cell in the bone marrow. This work led to the second factor in the conception of deficiency disease; namely, that disease

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of the gastro-intestinal tract may cause a deficiency state even in the presence of a normal diet.

Observations of patients who were treated for pernicious anemia by the oral route soon led to the discovery that absorption from the gastro-intestinal tract was also a factor in the production of deficiency disease. Many patients would not respond with extremely large amounts of liver by mouth, but would make a normal response when liver was administered parenterally. This could lead to only one conclusion; namely, that the gastro-intestinal tract was not absorbing the essential substance present in the liver, and thus factor number three was added to complicate the picture of deficiency disease. With the renewed interest in deficiency disease occasioned by these observations, another factor was soon recognized. Diseases exactly similar to known dietary deficiency disease were observed in patients who suffered from long continued vomiting or diarrhea. The explanation was soon apparent, and it was seen that these conditions were the same as dietary deficiency with the exception that the deficiency resulted from such rapid loss of food substance that absorption could not take place.

The fourth factor—that of increased demand, lies more in the realm of theory than of fact. It appears, however, that in the presence of pregnancy, infections, hyperthyroidism, etc., more of the protective substances are necessary than under normal conditions.

It is apparent, therefore, that in every disease and functional disturbance of the gastro-intestinal tract, one or all of these factors may be in operation. If a careful search is made, evidence of mild and sometimes of severe deficiency disease is observed frequently enough in these patients that I believe a deficiency state should be considered a potential complication of all chronic gastro-intestinal diseases. The responsibility for the occurrence of such complications will rest largely upon the physician to whom these patients come for treatment. The ease with which most deficiency states can be prevented emphasizes the responsibility of the physician to anticipate their possible development. In order to anticipate and prevent these deficiency diseases by means other than the indiscriminate and expensive practice of administering the essential foods in a wholesale manner, the following questions become pertinent:

1. What are the most important essential food elements, what is the best source of these substances, the best mode of administration, the quantity needed for cure and continued prevention of deficiency diseases?

2. What diseases related to the gastro-intestinal system and the diets commonly used in their treatment especially predispose to deficiency states?

3. What deficiency diseases are most likely to occur in the presence of such diseases and diets, and what food elements should be supplied liberally for protection?

4. What are the earliest symptoms and signs that one should look for to detect incipient deficiency disease?

5. What examinations should be done that will give helpful clues to preventive therapy?

6. What consideration should one give to possible hypervitaminosis and the expense of supplying unnecessary and excessive vitamins?

7. What may we learn about still unknown deficiency diseases by careful observation of patients with chronic gastro-intestinal disease?

It is not the purpose of this paper to take up these points individually and to discuss them fully. They will be touched upon briefly, but other sources should be consulted for more detailed information.

In a consideration of the diseases of the gastro-intestinal tract which predispose to deficiency disease, it will not be necessary to consider them individually, but they can be grouped according to their symptomatology, pathology and customary treatment.

In one such group, a common finding is hyperacidity. Here we find such conditions as gastric and duodenal ulcer, disease of the gallbladder, nervous indigestion and irritable colon. No matter what the difference in the details of treatment, a special diet is prescribed and treatment with alkalies is instituted in practically all cases. If the condition is severe and chronic, the diet may necessarily be rather strict and long continued. Fresh fruits and vegetables, especially citrus fruits, are forbidden. This may lead to a deficiency of vitamin C. Frequently I have seen soft, spongy, bleeding gums develop in these patients, and these responded promptly to treatment with an increase of vitamin C. Although a serious scorbutic condition probably would never develop, these patients should be protected against this mild deficiency, because other still unknown conditions may result from a deficiency in vitamin C. Dental caries has been attributed by one school of observers to a deficiency in vitamin C. Adequate protection can be given without difficulty to the patient, and this is usually best done by giving lemon juice well diluted in warm water. Orange juice and tomato juice can be taken in small amounts, but amounts sufficient for protection are likely to produce digestive symptoms.

Vitamin A usually is not considered a potential deficiency in this group because butter and cream are supplied in large amounts. However, where alkalies are used extensively and for a long period of time,

the urine becomes strongly alkaline, and this causes precipitation of crystals in the urine. Deficiency of vitamin A results in keratinization of the epithelium in various parts of the body including the renal pelvis and ureters. If the epithelium of the urinary system, especially of the renal pelvis, is not in perfect condition, these crystals may collect on the impaired epithelium and produce stones. Higgins has emphasized the parts played by acidification of the urine and vitamin A in the solution of urinary calculi. O'Conner in discussing Higgins' paper was favorably impressed by the use of vitamin A in the prevention of urinary calculi in patients for whom alkaline therapy had been prescribed, and in whom he had noticed previously a very high incidence of stones. This evidence strongly suggests the need for a high vitamin A intake in this group of patients.

Special consideration of the vitamin and mineral content of the diet must be given in that large and heterogeneous group of patients who have anorexia or who eat very little for one reason or another. The appetite is impaired by so many conditions that only a few of the more common ones can be mentioned. These are the general systemic diseases, especially the chronic infections; the asthenic states due to nervous and physical exhaustion; the psychic disorders; numerous gastro-intestinal diseases; the anorexia of high strung children and young adults, especially young women; and the arteriosclerotic and myocardial degenerations found in the aged. In this group, the mineral deficiencies appear more pronounced than the vitamin deficiencies. As a rule, people with poor appetites have a distaste for meat and milk, and the iron and calcium intake is low. Iron deficiency anemia is almost the rule in such cases. Calcium deficiency is seldom demonstrable either clinically or by blood calcium studies, but very frequently, a brilliant therapeutic response follows large doses of calcium. Vitamin D may possibly help in the utilization of the calcium. Vitamins A, C and D are only too frequently oversupplied, due to the extensive propaganda of those who have something to sell, but even in those patients who do not take concentrated vitamins, I have seldom seen a case of outspoken vitamin deficiency disease in this group. The anorexia itself, the nervous symptoms and the atonic colon which is found so frequently, however, are suggestive evidence of vitamin B deficiency. The normal modern diet is so low in vitamin B that this deficiency should be expected if the diet is limited for any reason. Because of its insidious onset and slow response to treatment, vitamin B should be supplied empirically in large quantities over a long period of time, even though the clinical response does not seem to justify its continued use. Iron, calcium and vitamin B should be considered the

more important potential deficiencies in the diet of the patient with anorexia.

The third group to be considered as potentially subject to deficiency disease is that in which the patients have achlorhydria. If special examinations other than an ordinary test meal are made and a complete achylia gastrica is found, there is all the more reason to suspect the future development of deficiency disease. In such instances, deficient preparation and deficient absorption of the food are both potentially present. Past history would seem to indicate that all clinical conditions which are commonly found in association with achlorhydria should be suspected of being deficiency diseases until they are proved otherwise. It is only necessary to recall the story of pernicious anemia and hypochromic anemia to make this possibility more impressive. Quite a high percentage of patients who have pellagra and sprue also have achlorhydria. May this not mean that many of the disabilities of the last half of life, at which time achlorhydria becomes increasingly prevalent, are due to deficiency? In atrophic or rheumatoid arthritis, a very high incidence of association with achlorhydria and hypochlorhydria is seen, and irrespective of other factors which are involved, the rôle of deficiency disease must not entirely be disregarded as a predisposing factor.

The inference is clear that if achlorhydria is found during an examination, it is important that protection be afforded against future deficiency disease. A careful examination of the blood for microcytosis or macrocytosis may suggest whether it is more important to concentrate on iron or liver therapy. The age and sex of the patient is important. Idiopathic hypochromic anemia practically never develops in the male. Therefore, in males, attention should be concentrated on the protection afforded by liver and vitamin B. Hypochromic anemia is especially prone to develop in young women, and these patients should be urged to take plenty of iron in the diet, and watched carefully to see if large doses of iron should be supplied in other ways. In older women, it is important to supply the extrinsic factor of pernicious anemia and vitamins B_1 and B_2. It is not sufficient to watch these patients for the first signs of pernicious anemia. The value of prophylactic protection was forcibly impressed upon me when I saw two patients recently who had fairly marked subacute and combined degeneration of the spinal cord without any evidence of primary anemia. Both had previously been told that they had achlorhydria and as both improved on liver therapy, I believe it would have been possible to prevent the cord degeneration by prescribing the regular use of liver at the time of finding the achlorhydria. I am happy to say that no responsibility

exists for this unfortunate complication as the achlorhydria had been found in the days when liver was five cents a pound. Today, a physician should not have a very easy conscience if he should fail to advise adequately against the development of such complications. It is true that many patients will not heed the warnings, but that is another problem.

From this viewpoint, a gastric analysis is a highly important routine examination, especially in patients past 40 years of age and the finding of a subacidity or achlorhydria should be the signal to prescribe iron, liver and vitamins B_1 and B_2.

Patients who have chronic liver disease, especially cirrhosis of the liver, will frequently be found to have a macrocytic type of anemia. Some of these patients have achlorhydria, and some do not. In the former, the anemia is due to a lack of absorption and storage of the anti-anemic factor of pernicious anemia. This suggests that such patients should be supplied with this factor, and this should be given by the parenteral method to insure adequate absorption.

Chronic alcoholic addicts must be considered in a special group because they frequently have all the conditions mentioned in the last three groups. As a rule, they eat sparingly, frequently they have an alcoholic gastritis and associated achlorhydria, and in addition, they may have a cirrhotic condition of the liver. It may be years before the latter can be diagnosed clinically by palpating a large liver, but functional impairment of the liver must exist long before this stage is reached. The stage is well set for a deficiency state, and its actual occurrence is not rare as is so well shown by Spies' observation on the relation of pellagra to chronic alcoholism. Alcoholic neuritis is also a deficiency disease.

Chronic alcoholics are frequently seen in every day practice while they are still in a state of good health, but it is important that large quantities of vitamins B_1 and B_2 be given to prevent serious complications, because it is very doubtful if the use of alcohol will be discontinued.

Persistent vomiting from various causes such as neurotic vomiting, vomiting of pregnancy, severe migraine, labyrinthian disease, pyloric obstruction and partial intestinal obstruction is prone to cause such rapid loss of vitamins and minerals that serious deficiency disease results. A state of alkalosis develops from the loss of chlorides, and if this loss is not replaced by large amounts of chlorides by the parenteral groups, the patient rapidly becomes toxic with a high blood carbonate and urea. It is extremely important that the blood chemistry be studied and the alkalosis cleared up, especially before any surgery is attempted

in the obstructive cases. The vomiting in this whole group frequently is persistent only because of the presence of the toxic condition of alkalosis.

Peripheral neuritis is not infrequently seen as a complication of the vomiting of pregnancy. It is possible that, in addition to the loss, an increased demand may be placed on the body during gestation. An adequate supply of vitamin B is indicated and should be given parenterally if the vomiting is severe. Incidentally, iron and calcium should also be supplied liberally to offset anemia, dental decay and other calcium deficiencies. Not only the vomiting of pregnancy, but vomiting from any cause requires the same protection. I have observed two cases of peripheral neuritis due to pyloric obstruction.

The chronic diarrheas act in a similar manner to loss by vomiting, and some diarrheal conditions appear to be due solely to vitamin deficiency. Calcium loss may occur to an extent sufficient to cause rather severe hemorrhagic states. It is very interesting that in one such case which we observed, the calcium was down to 5 mg. per 100 cc., but at no time was tetany observed. The diet is so frequently restricted in fruits that vitamin C should also be watched. As in vomiting, however, lack of vitamins B_1 and B_2 cause the more serious complications and demand more immediate attention.

Extensive resections of the stomach also require special consideration of the anti-anemic factor of pernicious anemia, and the blood should be checked at intervals to determine the need for iron.

In the presence of extensive food allergy where the diet at times is greatly limited, appropriate vitamin protection should be afforded according to the foods which are restricted. Patients on strict diets for obesity, hypertension and nephritis should receive appropriate protection. We observed a very interesting patient at the Cleveland Clinic who had dieted voluntarily because of obesity. A marked edema soon developed which was thought to be due to nephritis. He was treated for this with a strict diet, and the condition became worse. The urinary findings and kidney functional tests did not suggest the presence of nephritis, and he responded immediately to large doses of vitamin B. I have been impressed by the condition of edema of the feet in warm weather which occurs in many stout women who eat lightly, and I have wondered whether it possibly is not a deficiency syndrome.

Many other specific needs for vitamin and mineral protection could be cited, but if the more common conditions mentioned above are kept in mind, the adequate protection of all patients becomes a routine matter. Certain tests have been mentioned that give clues to incipient deficiency states. A gastric analysis should be a routine procedure

in the presence of gastro-intestinal disorders. When an achlorhydria is found, a careful study of the blood for macrocytosis or iron deficiency should be made. Roentgen evidence of dilatation of the colon suggests vitamin B deficiency. Examination of the blood with regard to chlorides, carbon dioxide and urea is indicated when alkaline therapy has been used for a long time. Careful inquiry concerning slight attacks of renal colic may give a clue to the passage of small crystals, and roentgenograms and studies of the urine will give further confirmation.

Clinical symptoms and signs which suggest early deficiency disease should be searched for carefully. Unusual nervous conditions and mild psychic disorders, skin and nail changes, glossitis and atrophic tongue, bleeding gums and dental caries, paresthesias and peripheral pains all suggest early deficiency. Adequate therapy should be given before the more definite deficiency syndromes develop.

The known dangers of hypervitaminosis are relatively rare. I do believe too much vitamin D has been used in the elderly patients with the attendant danger of calcification of the arteries. Vitamins are expensive however, and pharmaceutical houses have specialized on concentrating them and making them attractive and easy to take. Unless there is special need for more than can be supplied naturally in the diet, as in some of the conditions mentioned above, these concentrated expensive products should not replace those in their natural form. Many mild and sometimes severe disorders which complicate gastro-intestinal disease and interfere with treatment are pure deficiency states, and appropriate replacement as outlined above will often be found to be of inestimable value in the solution of very puzzling problems.

From this brief summary of the potential dangers of deficiency disease in the presence of gastro-intestinal disorders, one cannot help but speculate that much can and will be learned about still unrecognized clinical syndromes of deficiency states by a study of the many complicating symptoms and signs that so frequently accompany chronic disease of the gastro-intestinal tract.

In conclusion, I wish to emphasize how important it is to think of disease as possibly resulting from negative agents as well as from positive agents. The only method for combating such diseases is an adequate supply of the missing agent. An even better field for preventive medicine is offered than in diseases due to bacterial origin. In this country where a deficient diet is not common, the prevention of such diseases lies chiefly with those patients who complain of gastro-intestinal disorders.