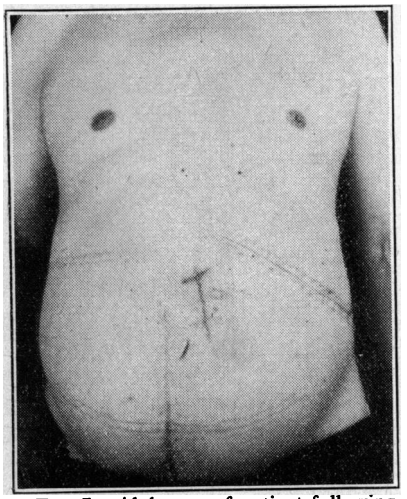

FIG. 7.—Abdomen of patient following closure of the colostomy. Partial hepatectomy for secondary deposits in the liver has been carried out through a left subcostal incision.

has completely healed. As soon as rectal examination reveals that the sinus opening into the bowel lumen is adherent to surrounding structures and admits no more than the tip of the little finger, repair of the colostomy can be effected (Fig. 7). Formed stools will then by-pass the small sinus (Fig. 8) and be evacuated through the anal canal.

It has been found that for some months after the operation rectal sensation is lowered and the patient is not always conscious that the pelvic colon and the rectal stump are loaded with faeces. Glycerin suppositories are of great help in aiding regular evacuation, and with these the patient rapidly procures the habit of normal bowel action.

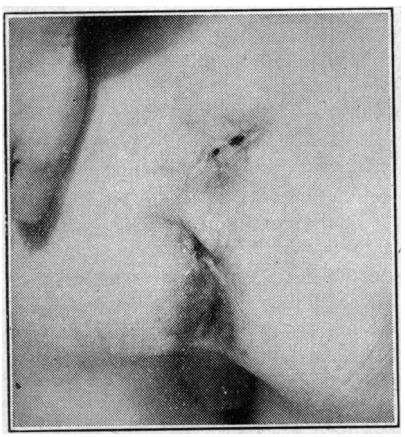

FIG. 8.—Healing perineal wound. A small sinus is still present at the lower end.

This operation is not advocated as a routine procedure for the treatment of carcinoma of the rectum, but it is suggested that in the type of cases described it is of value. So far as can be established by pathological investigation it is sound in its concept, and anatomically its boundaries of excision are wide. It seems to be well worthy of trial in selected cases, and especially for those to whom a colostomy would prove an intolerable burden.

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A NEW MECHANISM OF VITAMIN DEPRIVATION

WITH SPECIAL REFERENCE TO THE SPRUE SYNDROME

BY

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Vitamin deprivation may be of dietary, intestinal, or metabolic origin.

Dietary Deficiency of Vitamins.—Vitamin deprivation was originally based on the conception of dietary deficiency. The classical cases of scurvy which occurred in sailors on long sea voyages may be a true example of this type of deprivation. Beriberi and pellagra, on the other hand, can hardly be regarded as simple vitamin deficiencies (Williams, Mason, Wilder, and Smith, 1940; Meiklejohn, 1940), although some of the main features of each condition can be reproduced in animals by selective deprivation of thiamin or nicotinic acid. It is quite clear that the diets which usually induce beriberi or pellagra in human subjects are grossly deficient in many other dietary essentials. The selective dietary deficiency of one vitamin is not likely to occur under ordinary conditions of life, but such selective deficiencies may be induced by the destruction of vitamins during processing, cooking, or digestion of food. Thus, vitamin C is well known to be relatively heat-labile, and an otherwise adequate diet may be rendered deficient in this vitamin by faulty cooking methods. Again, vitamins A and E are readily destroyed by oxidation. Oxidative rancidity of fats included in the diet may destroy these vitamins, with consequent deprivation (Mattill, 1938; Whipple, 1936).

Intestinal Deficiency.—The signs and symptoms of vitamin deprivation may occur even though the diet contains an adequate supply of vitamins and in the absence of any evidence of destruction. This may be due to faulty digestion of the vitamins, or to their inclusion in unabsorbed residue. The latter may occur when large quantities of liquid paraffin are taken, resulting in absorptive deficiency of fat-soluble vitamins (Andersen, 1938). Alternatively, the mechanism of absorption of the vitamin may be defective. Thus, in obstructive jaundice, low blood prothrombin due to inadequate absorption of vitamin K may occur. Bile salts assist the absorption of this vitamin (Lord, Andrus, and Moore, 1940). The condition can be corrected by the parenteral administration of vitamin K.

Metabolic Failure.—Theoretically, faulty utilization of absorbed vitamins might occur. It is difficult to establish vitamin deficiency in such a condition, since even parenteral administration of the vitamin may give no response. Faulty utilization of vitamin A has been described in cases of alcoholic cirrhosis (Patek and Haig, 1939). Faulty phosphorylation was thought to account for certain riboflavin deficiencies (Verzar and Laszt, 1936), but the relationship of this deficiency to the adrenal cortex has not been substantiated (Nelson, 1940; Ferrebee, 1940). A second form of metabolic fault is defective synthesis. This may be observed in the case of vitamin D. The incidence of rickets was particularly high in smoky industrial towns in England and in negro children living in the northern part of the United States (Howe, 1920; Hess and Abramson, 1931). Sterol precursors of vitamin D can be synthesized in the body and vitamin activity induced by irradiation

with ultra-violet light. Absence of effective sunlight may thus be more serious than dietary deficiency of the vitamin, and vitamin deprivation in such cases may be at least partly metabolic in origin.

Vitamin Deficiencies in the Sprue Syndrome

Vitamin deficiencies have been studied and a number of relevant investigations have been made in a series of cases of defective fat absorption in Birmingham (Cooke, Elkes, Frazer, Parkes, Peeney, Sammons, and Thomas, 1946). The results of these studies may be briefly reviewed.

Relatively Transient Nature of Deprivation.—In chronic cases of the sprue syndrome the fat-absorption defect persisted more or less unchanged over long periods. From time to time, however, the patient might complain of an exacerbation of certain symptoms—especially diarrhoea, with large, bulky, fermenting stools, sometimes associated with a sore ulcerated tongue and sore eyes. The haematological changes also showed exacerbations and remissions. This group of signs and symptoms seemed to come and go—as though superimposed on a more constant underlying defect.

Nature of Deficiencies.—The commonest deficiency signs and symptoms were those affecting the tongue and eyes. The majority of cases of sprue showed signs of glossitis. From time to time the tongue became enlarged, sore, and ulcerated, scarlet-red or magenta in colour, the conjunctival vessels might be injected, and the eyes sore, with excessive lacrimation and photophobia ; cheilosis was also frequently seen. These changes were commonly associated with deprivation of riboflavin, nicotinic acid, and/or pyridoxin. Various haematological changes were also often observed. Macrocytosis was almost a constant feature of the sprue syndrome (Cooke, Frazer, Peeney, Sammons, and Thompson, 1948). These haematological changes were attributed to deficiency of folic acid and possibly other members of the vitamin-B complex. In occasional cases other vitamin deficiencies were observed.

Effects of Therapy.—In most cases of riboflavin, nicotinic acid, or pyridoxin deficiency in sprue parenteral administration of the appropriate vitamin fraction caused dramatic relief of the signs and symptoms of deprivation. Small doses were effective. In many cases very large doses of the vitamin were effective orally. It was not uncommon to find that the administration of one of the vitamin fractions by mouth might precipitate deficiency symptoms associated with some other fraction. Thus the administration of large doses of nicotinic acid might precipitate a classical ariboflavinosis. Increase of carbohydrate in the diet sometimes had a similar precipitating effect.

Relationship to Fat Absorption.—Relief of the signs and symptoms of vitamin-B deficiency was achieved in the sprue syndrome without alteration in the fat-absorption defect. Classical cases of ariboflavinosis have been observed in which fat absorption was normal. There seems no reason, therefore, to suppose that the vitamin-B deficiency is intimately related to the aetiology of the fat-absorption defect (Frazer, 1947).

Intestinal Flora.—A number of cases of the sprue syndrome have been intubated, using a technique devised by my colleagues Drs. J. M. French and M. D. Thompson, to minimize contamination. In hypochlorhydric cases thousands, and occasionally hundreds of thousands, of bacteria were observed per ml. of upper intestinal contents. In achlorhydric cases millions of viable organisms per ml. were demonstrated. The organisms were the usual inhabitants of the intestine, normally confined to the lower reaches. The type of predominating organism, the number of viable bacteria, and the level to which they reach will vary under differing environmental conditions.

Synthesis of Vitamins by Intestinal Bacteria.—Some attention has been paid to the question of bacterial synthesis of vitamins. In some cases of sprue the faeces contained more vitamins than the diet, in spite of a concomitant vitamin deficiency. Thus classical ariboflavinosis was observed in a patient passing three times more riboflavin in the faeces than was present in the diet—the amount in the diet being greater than normal requirements (Smart and Daley, 1946).

Effect of Antibacterial Agents.—Antibacterial agents may stop severe diarrhoea at least temporarily (Keele, 1949). The effect of antibacterial agents on vitamin deficiencies is unknown. An interesting observation was made using sulphasuxidine. Usually less than 10% of this drug was absorbed and the sulphathiazole level in the blood was negligible, <1–2 mg. per 100 ml. of blood. In two cases of sprue the administration of sulphasuxidine by mouth resulted in blood levels of sulphathiazole of 10.6 and 13.8 mg. per 100 ml.

Discussion

Dietary inadequacy is certainly not a common cause of vitamin deficiency in the sprue syndrome. It may account for the occasional case of vitamin-E deficiency, especially since oxidative rancidity of fats may be one of the precipitating causes in tropical sprue. It does not account for any of the common vitamin-B deficiencies. There is no evidence of any metabolic fault of vitamin-B utilization in the sprue syndrome. Parenteral administration of the appropriate vitamin fraction secures immediate relief in the vast majority of cases.

An absorptive defect due to interference from unabsorbed materials may account for the occasional vitamin-A or vitamin-D deficiency ; the latter is further complicated by changes in calcium absorption. Again, the common vitamin-B deficiencies are not due to a faulty absorptive mechanism, since large doses are often effective by mouth and the normal dietary intake is adequate in remission. There is no evidence of faulty digestion of vitamin precursors. It would seem, therefore, that the common vitamin-B deficiencies observed in the sprue syndrome do not fit into any of the known deprivation groups.

The selective nature of the vitamin-B deficiencies—nicotinic acid, riboflavin, pyridoxin, and folic acid—in sprue is very striking. The deficient vitamins are all essential growth factors for bacteria—particularly those bacteria which are known to be present in the upper part of the small intestine in sprue. Large numbers of these bacteria can be demonstrated in the upper small intestine by intubation, and their presence is also indicated by the results of sulphasuxidine administration: clearly, in the sprue syndrome the bacterial decomposition of sulphasuxidine is occurring within the absorbing area. It is well known that bacteria will first take up preformed growth factors and then synthesize more of these vitamins if necessary. In sprue the bacteria may synthesize further vitamins ; it is likely that they will take up as much preformed vitamin as possible before doing so. It is therefore suggested that in the sprue syndrome intestinal bacteria invade the upper small intestine from time to time in large numbers. This bacterial invasion may give rise to large, bulky, fermenting stools. It also results in competition between the bacteria and the host for common essential nutrients. In many cases the bacteria are the most successful competitors and the host consequently shows signs of deprivation.

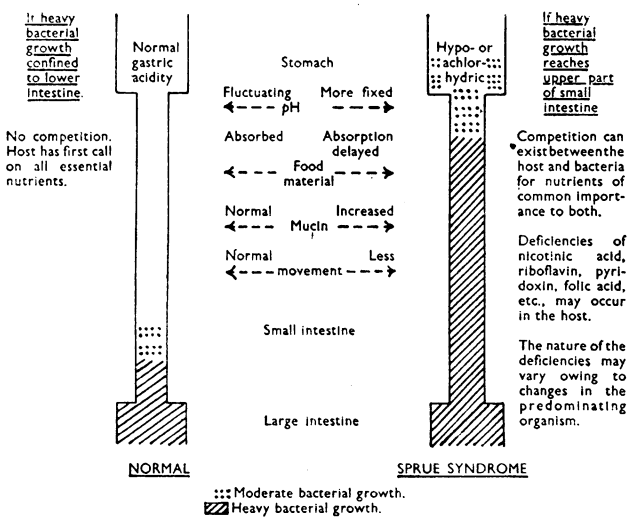
This competition hypothesis would account for the exacerbation of vitamin deficiencies and diarrhoea associated with heavy growth and high-level invasion of intestinal bacteria. This bacterial invasion may be related to fixation of *p*H as a result of achlorhydria, and possibly the presence of suitable food materials due to delayed absorption. The competition hypothesis would also account for the peculiar selective deficiencies observed in the sprue syndrome. It might also explain the administration of one vitamin precipitating the deficiency of another, since bacterial growth would be stimulated by the one and would increase the demand for the other. In oral administration of the vitamins, sufficient vitamin must be given to provide both

for the bacteria and for the host. Hence the large dosage required in oral therapy. It is also recognized that modifications of the dietary regime which are known to alter intestinal flora affect the sprue syndrome.

The part played by intestinal bacteria in vitamin synthesis in normal human subjects is obscure. It has been suggested that the modification of intestinal flora by sulphonamides or other antibacterial agents might result in faulty synthesis of vitamins and consequent vitamin deprivation. This conception of vitamin deprivation is mainly based upon experimental studies in animals and especially upon the phenomenon of refection (Kon, Kon, and Mattick, 1938). Rats and rabbits may not develop certain vitamin deficiencies when placed upon an appropriate vitamin-deficient diet. This can be shown to be at least partly due to the synthesis of B vitamins by intestinal bacteria.

The inclusion of certain types of starch in the diet and initial coprophagy are probably important factors in the establishment of refection. In some animals on a deficient diet prevention of coprophagy results in the development of vitamin deficiencies in spite of continued intestinal synthesis of the vitamins. The vitamins synthesized by intestinal bacteria can be utilized by the body only if they are released from the bacteria and absorbed from the intestinal tract. The formation of B vitamins in the large intestine in man and their continued inclusion in viable bacteria greatly limit their availablity. The conditions within the intestine in the refected rat may resemble to some extent those prevailing in the human intestine in the sprue syndrome; the possible importance of starch fermentation in both cases is of special interest. It seems clear, however, that the synthesized vitamins are much more readily available to the rat than to the human subject.

Vitamin synthesis by intestinal bacteria in the normal human subject is probably limited in extent and mainly confined to the large intestine—it is therefore unlikely to play a major part in the vitamin economy. In the sprue syndrome, synthesis may be greatly increased and the site of formation may now include normal absorbing areas. In spite of this, vitamin-B deficiencies now occur, which would suggest that the synthesized vitamins are not available for absorption, possibly owing to their retention within viable bacteria. The competition hypothesis is put forward here in its simplest possible form, but it is clear that many complexities may develop in individual cases. Some aspects of refection in rats might be usefully examined in relation to the changes in intestinal flora which can be observed in the sprue syndrome.



Diagrammatic representation of competition hypothesis of vitamin deficiencies in the sprue syndrome.

This paper is especially concerned with vitamin deficiencies in the sprue syndrome. Special consideration must be given, however, to the possible importance of intestinal bacterial competition in other conditions. A similar competition situation must arise in pernicious anaemia, in which vitamin-B deficiencies are well recognized—much of the haematological picture being ascribed to them. In this condition there is, however, apparently normal fat and glucose absorption, a normal radiographic pattern, and an absence of fermentative changes. These points serve to emphasize the lack of intimate relationship between the absorptive defects in the sprue syndrome and the changes in intestinal flora and consequent vitamin deficiencies. It is possible that the absence of absorptive defects in pernicious anaemia and consequent environmental differences may result in qualitative and quantitative modifications of the intestinal flora, with resultant differences in metabolic demands. The possibility of intestinal bacterial competition along the lines indicated in this paper should be investigated not only in the sprue syndrome but in various other conditions which are thought to be closely associated, such as pernicious anaemia, pellagra, and nutritional megalocytic anaemia (Manson-Bahr, 1940, 1941). The metabolic demands of a varying but essentially non-pathogenic flora may be the key to the problem of the multiple but selective vitamin deficiencies so commonly observed in these conditions.

Original observations reported in this paper have been made as part of a team-work study on fat absorption and the sprue syndrome which is being carried out with my colleagues, W. T. Cooke, J. M. French, T. L. Hardy, A. L. Peeney, H. G. Sammons, G. Thomas, and M. D. Thompson, at the Medical School and Hospitals Centre, Birmingham. We are indebted to the Medical Research Council and the Sir Halley Stewart Trust for financial assistance.

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The Ministry of Health states that more blood was given for hospitals in England and Wales in the second quarter of this year than in any comparable period since the war. New donors in the quarter numbered 36,847—the biggest response since the war—bringing the total strength of donor panels to 382,382. Hospitals are now using over 40 times as much blood as before the war, and the demand is still rising. To provide for these future needs it is estimated that over 190,000 more donors are wanted.