Malabsorption Syndrome: Pathogenesis

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The term "malabsorption syndrome" has attained great popularity since it was first introduced by Cross et al. in 1953.[1] Although it excludes from consideration one of the more common conditions of poor absorption, pernicious anaemia, it has directed attention to the small intestine, a poorly studied area of the body. For reasons which I have given elsewhere,[2] the term is misleading. The common factor between the various conditions is the presence of excess fat in the stools, a sign which is pathognomonic of disturbed function of the small intestine.

It is by no means certain, however, that some types of disorder included under the term malabsorption syndrome necessarily have steatorrhoea as a constant feature. These can be categorised into three groups: (1) those in which there is a disturbance of the digestive processes within the intestinal lumen, (2) those in which the intestinal wall is involved in defined pathologic processes and (3) those in which constitutional and systemic factors appear to be involved. It excludes patients with jaundice and acute diarrhoeal disorders.

The first group is that in which the processes of digestion are disturbed. The simplest disturbance of digestion is pancreatic dysfunction leading to an increased loss of fat and nitrogen in the faeces but not necessarily to disability; it is not associated with any haematologic abnormality and provided intake is adequate, there is no systemic upset of protein metabolism.

More complicated is the clinical picture of marked malnutrition, anaemia and steatorrhoea produced in some patients following gastrectomy. Among the factors concerned here is the mechanical factor of an inadequate stoma or afferent loop, which is too long, leading to insufficient mixing of the pancreatic and duodenal juices with food. In others an associated pancreatic disorder may exist while there are still unknown factors produced by the stomach which are necessary for normal digestion and absorption of fat and protein.

Another important factor is upset in iron absorption, which is slightly impaired following gastrectomy,[3] and subsequently the total body stores are gradually depleted over the years, the time needed varying from one case to another from one to many years. Although it has been claimed that chronic intestinal blood loss is the major cause in these cases[4] this seems to be unlikely except in the occasional patient. It is also to be expected that with resection of a portion of the stomach vitamin B_{12} deficiencies may become apparent. In some patients this will be due to loss of intrinsic factor. It has, however, been shown by Witts[5] and his colleagues in Oxford that the experimentally produced iron deficiency in rats leads to low serum B_{12} levels and impaired absorption of vitamin B_{12} which can be corrected by the administration of iron alone. This same phenomenon can take place in man (Fig. 1).

This observation of course is not new. Hartfall and Witts[6] suggested it in 1932 and the literature contains many observations on iron deficiency anaemia preceding the development of pernicious anaemia. It is not yet clear, however, whether this vitamin B_{12} deficiency is due to the temporary suppression of intrinsic factor or to the effect of chronic iron deficiency on the mucosal cells in the distal portion of the small intestine. It seems probable that either may take place. In the investigation of vitamin B_{12} absorption after gastrectomy reported by Lowenstein,[7] it is worth noting that the only patients who did not absorb vitamin B_{12} were three with severe

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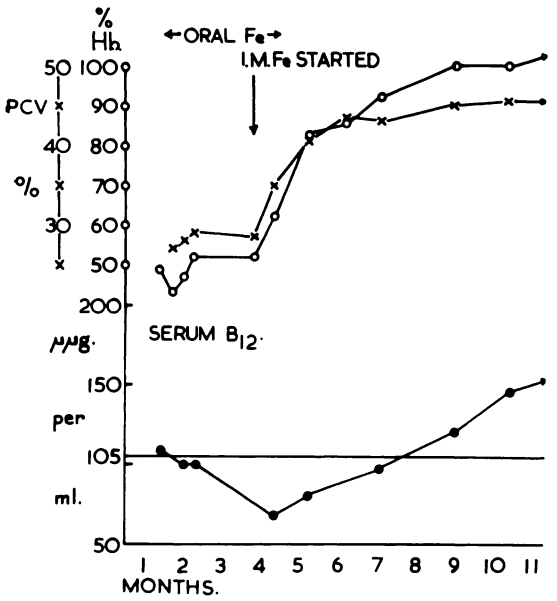

FIG. 1. A fifty year old man. Four years after gastrectomy there is a lack of effect of oral iron therapy with decreasing serum vitamin B_{12} levels and restoration of normal blood picture and vitamin B_{12} levels with intramuscular iron therapy.

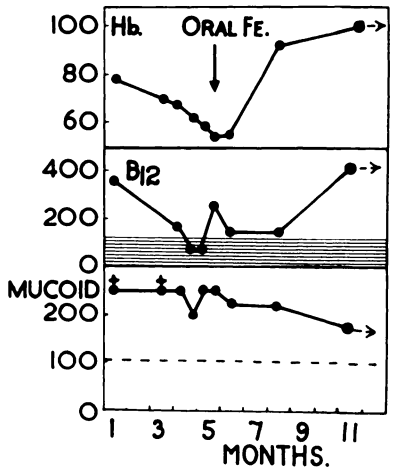

FIG. 2. An eighteen year old boy with regional enteritis. Note the effect of oral iron therapy on the serum levels of vitamin B_{12}. Serum iron at the start of therapy was 26 μg. per 100 ml. Levels maintained subsequently for eighteen months on oral iron therapy.

hypochromic anaemia. It also remains to be shown just what part chronic iron deficiency may play in aggravating the degree of steatorrhoea through changes in the cellular metabolism of the ileum.

Changes in the intestinal milieu may also be brought about by changes in the intestinal flora. In particular this applies to the gastrojejunocolic group in which the small intestine is continually soiled by colonic bacteria. In this group, the degree of steatorrhoea can be considerably lessened temporarily by the administration of antibiotics. To a lesser extent, the same phenomenon is seen in the enteroenterostomies lower down the bowel. Whether the same considerations hold good in intestinal diverticulae is not so clear. Girdwood[8] has claimed that bacteria isolated from such diverticulae produce significant amounts of folic acid. There is certainly no conclusive evidence that folic acid deficiency is ever produced in such cases, although patients in both these last two groups become deficient in vitamin B_{12} readily. It has been assumed that intestinal bacteria utilise the available vitamin B_{12} in preference to the host.[9]

The administration of antibiotics certainly cures the anaemia. It remains to be proved that this is direct action on the bacteria and not a systemic effect, since it has been observed that some antibiotics which are poorly absorbed do not have this effect.[9,10]

The second group of conditions are those in which the wall of the bowel is affected, such as regional enteritis, enterocolitis, tuberculosis, amyloid and carcinoma. As an example, regional enteritis may be considered. The clinical picture produced will depend upon the area of the gut involved. Some patients may simulate a primary malabsorptive state, as in extensive jejunoileitis. Jejunitis may exist without any significant increase in fat excretion while lesions and resections of the lower part of the ileum are associated with a degree of steatorrhoea. This is somewhat contrary to the findings of Börgstrom and his colleagues.[11]

The defects that I wish to consider particularly are those of iron, vitamin B_{12} and folic acid. Little attention has been paid to the incidence of iron deficiency in regional enteritis but it is high, and in a consecutive series of thirty-nine patients who had not had recent treatment with iron, the mean level was 51.3 per cent, range 12 to 107 μg./100 ml. To some extent this low level varies inversely with the degree of activity

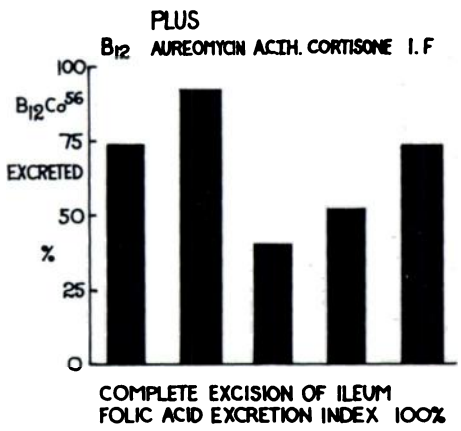

FIG. 3. Note the effects of therapy with aureomycin, ACTH, cortisone and intrinsic factor on the faecal excretion of radioactive vitamin B_{12} in a seventy-five year old man with excision of the ileum for regional enteritis.

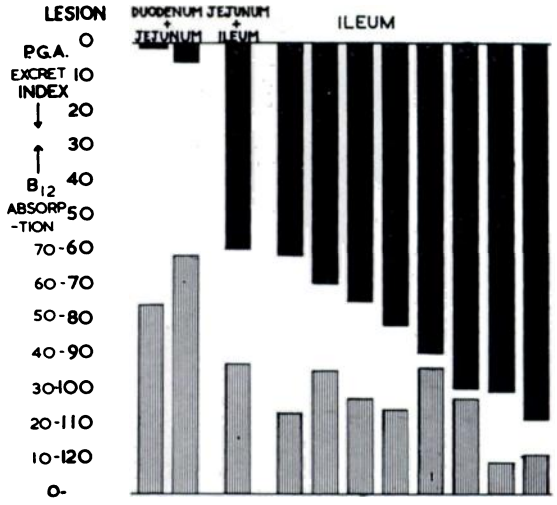

FIG. 4. Data on eleven patients with regional enteritis arranged according to the area of bowel involved. There was good absorption of vitamin B_{12} in the upper portion of the small intestine and poor absorption in the lower portion. At the same time there was a poor response to the folic acid excretion test in patients with jejunal involvement and a normal response when the ileum was involved or resected.

of the intestinal lesion. It may be partially due to the upsets in iron metabolism associated with chronic infection but in most patients it is probably due to chronic blood loss from the intestinal lesion. In one such patient under treatment without effect upon the haemoglobin (about 60 per cent) the average daily loss was 30 ml. of blood. Such chronic iron loss can have an effect upon the serum levels of vitamin B_{12} as is demonstrated in this patient (Fig. 2). However, the incidence of poor absorption of vitamin B_{12} (between 50 and 60 per cent) in chronic regional enteritis is too great to be accounted for by this mechanism alone. The deficiency in some patients may be accounted for by the actual length of intestine resected but such instances are few; in the majority it would appear to be due to involvement of the ileum with either macroscopic or microscopic lesions. Absorption is not improved by the administration of intrinsic factor or antibiotics but it is improved by the administration of steroids (Fig. 3).

Actual folic acid deficiency is rare in regional enteritis. Tissue unsaturation without clinical manifestations may occur through pure dietary inadequacy but actual haematological manifestations will only be found when the upper part of the jejunum is involved. By use of the folic acid excretion test[12,13] it can be shown that the site of absorption for folic acid is in the upper portion of the intestine (Fig. 4).

In this group of secondary malabsorptive conditions, it will be seen that, apart from steatorrhoea and any deficiencies that may accrue from this, iron deficiency is common, vitamin B_{12} absorption is frequently disturbed, and sometimes vitamin B_{12} deficiency may follow prolonged iron deficiency; folic acid deficiency is not common.

There remains to be considered non-tropical sprue, idiopathic steatorrhoea or adult coeliac disease, as I prefer to call it. Adult coeliac disease is characterised by chronicity with relapse and remission, constitutional and familial features, certain variable vitamin deficiencies, variable haematological features and histologic changes in the jejunum which may be characteristic. Although in the past interest has been focused on the intestinal difficulties, it is now shifting to within the intestinal cell and to enzymatic defects in the body as a whole. Since the metabolism of the intestinal cell is the second highest in the body, it is not surprising that changes show up there. In the untreated patient with coeliac

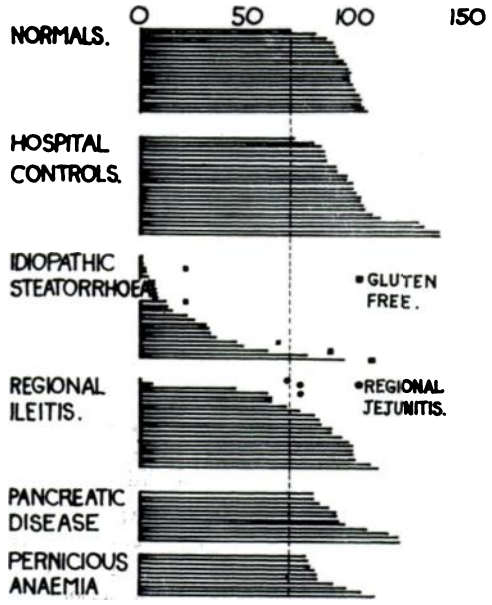

FIG. 5. Note the result of the folic acid excretion test. (Folic acid excretion index =

$$\frac{\text{Excretion after oral dose}}{\text{Excretion after previous intramuscular injection}} \times 100$$

The dotted line indicates lower limit of normality.

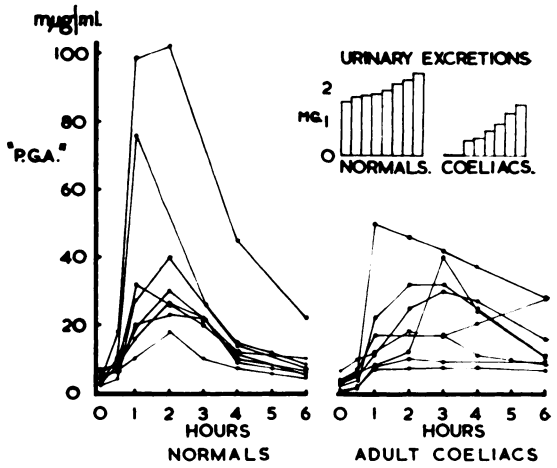

FIG. 6. Results of folic acid absorption test in eight patients with adult coeliac disease compared with those in six medical students and two hospital control subjects.

disease, there is a failure of iron absorption which is partially or completely corrected by adherence to a gluten-free diet or by the administration of steroids.[14] In patients with coeliac disease, iron deficiency anaemia is common but later in life macrocytic anaemias make their appearance and in about 40 per cent of adult patients there is interference with the absorption of vitamin B_{12}. In the majority of patients, this is not affected by the administration of intrinsic factor or antibiotics, but it is improved by the administration of steroids. It should be noted that in a few patients improvement does occur with the use of intrinsic factor.

Arising from our observations on the secondary malabsorptive conditions, two points should be considered. Is the tendency to chronic iron deficiency one of the factors responsible for the mucosal changes leading to the variable incidence of vitamin B_{12} deficiency in this disorder? My colleagues and I believe that this is a distinct possibility.[15] If so, the second question arises, can chronic iron deficiency cause sufficient cellular change to produce steatorrhoea? Again we believe that it is possible to separate a group of middle-aged and elderly women with hiatus hernia, long-standing menorrhagia or other source of chronic blood loss, in whom iron deficiency, vitamin B_{12} deficiency and steatorrhoea respond to iron therapy. In general, such patients appear to be well built and relatively well nourished.

We believe that iron and vitamin B_{12} deficiencies are essentially secondary features in adult coeliac disease. To us, folic acid would appear to be in a much more important and possibly key position. Girdwood[12] introduced a test in which the urinary excretion of folic acid following an intramuscular injection of folic acid is compared with that following an oral dose. We[13] have found that this test gives consistently abnormal results in adult coeliac disease (Figs. 5 and 6).

Girdwood[8] has encountered two patients with normal test results and stated that in 111 of 118 cases recorded, test results have been found to be abnormal. In our group one patient, a doctor in whom the results of the test were quite normal, proved to be sensitive to folic acid either whether administered orally or by injection. This patient, however, had taken the precaution to take antihistaminics at the time of the test. When the test was repeated without these drugs, the results were

abnormal. Three other patients with adult coeliac disease with similar sensitivity to folic acid are now under investigation. The results of the test, as applied to other conditions which may give rise to difficulties in diagnosis, are shown in Figure 5. The results seem clear-cut.

Girdwood implies that an abnormal test result signifies poor absorption of folic acid. We have preferred to call it an excretion test, believing that the evidence is insufficient as yet to attribute it to malabsorption in conditions other than those in which there is definite jejunal involvement, such as jejunitis. Although Spray and Witts[16] have published absorption curves showing poor blood levels following oral administration of folic acid, we have not been able to repeat these observations.

There is not a great deal of difference between absorption curves of the patients with adult coeliac disease and those of the normal control subjects: the lowest blood curve of the patients produced the highest excretion of folic acid in the urine. Chanarin, Anderson and Mollin[17] have found that when folic acid is administered intravenously it disappears much faster in adult coeliac disease than in other conditions. They have attributed this to folic acid deficiency in the tissues. We,[18] however, have called attention to the malutilisation of ascorbic acid that occurs in steatorrhoea which we were unable to attribute to poor absorption. Recently we[19] have been able to show that when ascorbic acid is administered intravenously to patients with adult coeliac disease it disappears more rapidly than in other conditions even when the plasma levels are normal and the patient's tissues are saturated with folic acid. The rapid disappearance of folic acid demonstrated by Chanarin may well be similar and may represent malutilisation of folic acid. This may also be related to the upset in tyrosine metabolism which we have demonstrated.[18]

It is of significance that test results have remained abnormal in patients on a gluten-free diet for periods up to four years even though there was clinical cure, no steatorrhoea and essentially normal haematologic findings. This is in contrast to the results reported in tropical sprue and in the few patients that we have been able to test. We therefore consider it possible that there is a fundamental defect in folic acid metabolism in patients with adult coeliac disease.

It has also become strikingly evident that gluten has a significant quantitative effect in adult coeliac disease. Children, however, can acquire tolerance for gluten, as Sheldon[20] has demonstrated, although the period of gluten free-diet necessary is at least eighteen to twenty-four months. The fraction of gluten concerned has been shown to be a polypeptide of unknown nature, and it is possible that certain other proteins may be implicated in rare cases. At present it does not seem possible to progress much further until the actual offending substance is isolated or synthesised.

It has been shown that a rise in blood glutamine occurs following the administration of gluten and, although this seems to be a somewhat inconstant feature, the question of the formation of a peptide-pteroylglutamate complex must be considered. That such a complex might act as a blocking agent in the folic acid cycle is suggested by the rapidity of haematologic response that may occasionally follow the administration of a gluten-free diet, a response comparable to that of a specific haematinic.[21] I have not considered other factors that might act as blocking agents, the clues to which may be found perhaps on chromatography of the urine.[19,22] I will conclude with a speculative hypothesis that adult coeliac disease is due to a constitutional enzymatic defect which is closely allied to folic acid metabolism and which is made evident by administration of gluten. In some patients this defect is so gross that it cannot be corrected even by a diet completely free of gluten.

More will be said later concerning tropical sprue. It does not appear to respond to a gluten-free diet and despite this does seem able to remit completely. I believe that it is a condition different from adult coeliac disease and much more closely related to jejunitis.

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