The possible role of dietary factors in the aetiology and pathogenesis of sprue, coeliac disease and idiopathic steatorrhoea

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The cardinal features of the malabsorption syndrome are generally regarded as the passage of abnormal stools, loss of weight or failure to thrive, and the occurrence of various signs and symptoms attributable to more specific nutritional deficiencies. Any situation that delays or prevents the absorption of the main nutrients may lead to the development of the malabsorption syndrome. The three forms of the malabsorption syndrome discussed in this paper are associated with interference with the function of the small intestine.

Sprue occurs in certain tropical and subtropical areas; coeliac disease and idiopathic steatorrhoea are more widely distributed and they have been mainly studied in countries in the temperate zones. Coeliac disease occurs in children; idiopathic steatorrhoea is a similar condition observed in adults. Some patients with idiopathic steatorrhoea are known to have suffered from coeliac disease in childhood, but it does not seem to be so in others. However, it is difficult to exclude a condition on the basis of retrospection made many years later. The patients with sprue described in this paper developed the disease in the Far East, usually in Hong Kong; some reference will also be made to studies in Puerto Rico, where the disease is similar, but may not be identical.

Main features of sprue, coeliac disease and idiopathic steatorrhoea

The essential features of these three conditions are summarized in Tables 1, 2 and 3. Though none of the features shown are in themselves specific, the overall picture is sufficiently characteristic for a provisional diagnosis to be made with some confidence. Other enteropathies, such as regional enteritis (Crohn's disease), lymphadenopathy (Whipple's disease), exudative enteropathy, postoperative surgical conditions, or constitutional disease with intestinal complications, can usually be recognized by characteristic features of the history or the gastro-intestinal situation. Study of the features described also provides a satisfactory basis for assessment of the effects of therapy.

Table 1. *Characteristics of stools in the malabsorption syndrome*

Characteristic	Normal	Malabsorption syndrome
Volume	150–200 ml	Increased up to 1 l. or more
Colour	Brown	Pale yellow
Odour	Normal faecal	Offensive
Consistency	Formed	Semi-formed or fluid
Short-chain fatty acids	<1 g/24 h	Increased up to 10 g/24 h or more
Long-chain fatty acids	<5 g/24 h	Increased up to 20 g/24 h or more
Nitrogen	<2 g/24 h	Increased up to 4 g/24 h or more

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Table 2. *Gastro-intestinal situation in coeliac disease, idiopathic steatorrhoea and sprue*

Characteristic	Normal subjects	Patients with coeliac disease, idiopathic steatorrhoea or sprue
Gastric secretion	Normal	Commonly hypochlorhydria or achlorhydria
Pancreatic enzymes	Normal	Normal
Biliary secretion	Normal	Normal
Absorption rate:		
Glucose	Maximum increment >40 mg/100 ml	Depressed (less than 40 mg/100 ml maximum increment)
Xylose	20% or more in urine in 5 h	Depressed (less than 20% in urine in 5 h)
Fat	Chylomicrograph: peak 150 particles per standard field	Depressed (less than 150 particles per standard field)
Radiography:		
Flocculable medium	Feathery pattern	Clumped
Non-flocculable medium	Feathery pattern	Dilated appearance: 'stacked coin' pattern
Biopsy	Normal	Abnormal

Table 3. *Some other features of the syndrome observed in coeliac disease, idiopathic steatorrhoea and sprue*

Characteristic	Coeliac disease	Idiopathic steatorrhoea	Acute phase of sprue	Chronic phase of sprue
Area	Temperate zone	Temperate zone	Tropical and subtropical	Tropical and subtropical
Age incidence	Childhood	Adult life	Adult life (? childhood)	Adult life
Abdominal distention	Marked	May occur	May occur	May occur
Anorexia	Marked	May occur	Marked	May occur
Loss of weight	May occur	May occur	Marked	May occur
Stunted growth	Marked	Not relevant	Not relevant	Not relevant
Anaemia	Common: microcytic	Common: macrocytic or microcytic	Common: macrocytic	May be absent
Ulcerated mouth	Not observed	Common	Usually marked	May be absent
Tetany	Not observed	May occur	Rare	Rare
Osteomalacia	Not observed (rickets may occur)	May occur	Rare	Rare
Skin pigmentation	Not observed	May occur	May occur	May occur

There are certain differences between sprue, coeliac disease and idiopathic steatorrhoea which are summarized in Table 3. The possible significance of some of these differences will become more apparent later in this paper.

Effect of diet on the features of the malabsorption syndrome

It has been recognized for many years that certain modifications in the diet can affect some of the features of the malabsorption syndrome. Thus, a low fat intake will commonly cause reduction of the fat content of the stools. A similar effect is sometimes observed with severe anorexia. The level of fat in the stools, therefore, is not a reliable guide to the severity of the condition; a fat balance study may be more reliable, but even it can be difficult to interpret.

Considerable attention has been paid to the carbohydrate intake, especially starch. (Howland, 1921; Parsons, 1932; Andersen, 1947; Sheldon, 1949; Lowe & May, 1951). Many of the features of the stools—bulk, pallor, semi-fluid consistency, offensive nature and presence of large amounts of short-chain fatty acids—are probably related to fermentative changes; they are likely to be aggravated by a high starch intake and may be improved by restriction or change in the type of carbohydrate ingested, or by an increase of protein intake. Thus, diets containing less starch and more protein (Fairley, 1936), or those in which special foods, such as bananas (Haas, 1938), were a major component, have been found to be helpful in the management of these patients. It is also likely that these dietary changes resulted accidentally in other modifications, such as reduction in bread intake, which may have had a more specific effect than was appreciated at the time. In addition to these general dietary measures, specific therapy has been used to correct deficiencies. In this category we must place treatment with iron, calcium, individual vitamins and liver extract.

Though some of these measures may still have a place in the treatment of these conditions, the whole situation has changed during the last 10 years because of the increasing knowledge about dietary factors that may play a more specific part in aetiology and pathogenesis. This paper is concerned with three of these factors—wheat gluten, folic acid and oxidized fats. The main information about each of them will be reviewed and their possible significance in the aetiology and pathogenesis of sprue, coeliac disease and idiopathic steatorrhoea will be discussed.

Wheat gluten

The beneficial effect of wheat gluten-free diet. The appreciation of the importance of wheat gluten in the aetiology and pathogenesis of coeliac disease has developed from the observations of Dicke (1950). It has been shown that almost all patients with coeliac disease improve when placed on a diet free from wheat gluten. The children begin to thrive, all the clinical features of coeliac disease disappear, and the patient may become normal except for the fact that the reintroduction of gluten into the diet may cause a return of coeliac signs and symptoms (Anderson, Frazer, French, Gerrard, Sammons & Smellie, 1952; Dicke, Weijers & van de Kamer, 1953; Ross, Frazer, French, Gerrard, Sammons & Smellie, 1955). Precisely similar effects may be observed in many adult patients with idiopathic steatorrhoea. The recovery in adults may be rather slower, but it can also be complete (Anderson, Frazer, French, Hawkins, Ross & Sammons, 1954).

Patients in whom all the signs and symptoms of coeliac disease or idiopathic steatorrhoea disappear on a gluten-free regimen and in whom an unequivocal increase of the faecal fat to abnormal levels is caused by the reintroduction of wheat gluten, may be conveniently classified as suffering from gluten-induced enteropathy.

There are some patients, however, who show improvement on a gluten-free diet, but not complete remission of all signs and symptoms. Thus, faecal fat levels may stay elevated, there may be repeated bouts of folic acid deficiency, or the intestinal mucous membrane may remain abnormal. One possible cause of this type of

response is failure to maintain a strict gluten-free regimen. The establishment of such a diet is not a simple matter and it is not easy to maintain it effectively under home conditions (Fletcher & McCririck, 1958). An alternative explanation for the failure to obtain complete recovery in this group of patients is that there is some other important aetiological factor involved in addition to gluten. This possibility is being further studied. These patients may be described as gluten-intolerant.

There are a few patients included in the group of coeliac and idiopathic steatorrhoea patients who do not show any benefit from a gluten-free diet. One such patient in our early series had a malabsorption syndrome due to lack of bile salts (Ross *et al.* 1955). It should be noted, however, that the beneficial effect of a gluten-free régime may be prevented by other complications, such as water and electrolyte imbalance. It is important that such complications, which commonly arise in patients with chronic diarrhoea, should be corrected at the beginning of the investigation; otherwise interpretation may be extremely difficult.

Patients with acute sprue do not appear to benefit from a gluten-free diet. It must be admitted, however, that it is difficult to assess this effect with certainty in an ill patient. In long-standing cases of sprue, gluten intolerance has been demonstrated (Rodriguez-Molina, Asenjo & Cancio, 1960). It seems likely that this is a secondary effect.

Nature of the deleterious agent or agents in wheat gluten. Both wheat and rye are deleterious to patients with gluten intolerance, but other cereals are not. Discussion in this paper will be restricted to wheat gluten, since it has been used in almost all the studies discussed. The deleterious effect of fractions derived from gluten is assessed by giving them to patients with gluten-induced enteropathy who are in remission on a gluten-free diet. The faecal fat level should be in or near the normal range and without large daily fluctuations; a positive response consists of a significant increase of faecal fat to abnormal levels (Frazer, Fletcher, Ross, Shaw, Sammons & Schneider, 1959).

Complete hydrolysis or deamidation of wheat gluten removes its deleterious effect on patients with gluten-induced enteropathy. However, treatment with pepsin and trypsin, ultrafiltration of the hydrolysate and autoclaving do not materially alter the deleterious action. The mixture may contain more than one deleterious agent. Incubation of the active hydrolysate with extract of mucous membrane from the small intestine renders it innocuous. This detoxicating effect of mucous membrane extract is heat labile; it may be enzymic (Frazer *et al.* 1959).

The effect of the deleterious agent in wheat gluten. Three effects on the intestine are evident. There is an increase in mucus secretion, damage to the mucous membrane and hypomotility. All three effects disappear on a gluten-free régime and return when gluten is reintroduced into the diet.

Mucosal damage has been particularly studied by Rubin, Brandborg, Flick, Parmentier, Phelps & van Niel (1961) and it is also under investigation by us and by several other groups of workers. However, the mechanism by which it is produced remains unknown. It has been suggested that it might be some type of allergic response (Frazer, 1953). This might explain the extensive plasma cell infiltration

often observed and might also account for the transient beneficial effect of cortisone (Taylor, Wollaeger & Comfort, 1952; Jones, 1953; Adlersberg, Colcher & Wang, 1953). It would also be compatible with our observations that gluten intolerance persists for periods up to several years, but may eventually disappear if a strict gluten-free regimen is maintained. If this is the mechanism by which mucosal damage is caused or maintained, the allergen in patients with gluten-induced enteropathy as described above would appear to be gluten, or a derivative of gluten; in other gluten-intolerant patients a different protein may be acting as the damaging allergen, either primarily or secondarily. Further investigation of this aspect of the problem is urgently needed.

Particular attention has been paid by us to an effect of gluten fractions on intestinal motility. It has been shown that the peptic–tryptic hydrolysate and certain fractions derived from it will cause inhibition of the peristaltic reflex in the isolated small intestine of the rat. This effect is only brought about if the substance is made to short-circuit the mucous membrane and the effect is removed by incubation with mucous membrane extract. This inactivation effect is thermo-labile. Pharmacological analysis has revealed that the action of this substance is due to interference with acetyl choline release in the intestinal wall (Schneider, Bishop, Shaw & Frazer, 1960).

Why are these patients intolerant? The possible relationship of these observations to gluten-induced enteropathy is still under investigation. Samples of mucous membrane obtained by biopsy can be tested for their ability to inactivate the inhibitory effect of a standard gluten fraction on the peristaltic reflex, by means of the isolated intestinal preparation of Bülbring, Crema & Saxby (1958). In the studies made so far, biopsy material from normal subjects and from those that are not gluten-intolerant rapidly destroys the motility-inhibiting factor; biopsy material from patients with gluten intolerance is unable to inactivate the motility-inhibiting factor. Thus, it is possible that changes in motility in these patients may be due to the action of this inhibitory agent, which is inactivated in normal people, but may not be inactivated in those that are gluten-intolerant. The inactivating mechanism in mucosal extracts is heat labile and may be enzymic in nature.

The barrier function of the small intestinal mucosa. It can be seen from these studies that various effects can be caused by gluten and certain gluten fractions, all of which are prevented by incubation with extract of mucous membrane from the small intestine. Thus, the mucous membrane of the small intestine might be regarded as a barrier that normally prevents any of these deleterious agents from causing an effect in the body. Reduction in the efficacy of the mucosal barrier might be expected in those patients in whom severe mucosal damage is evident, but the exact relationship between visible damage and faulty barrier function is not established. It is also possible for the barrier function to be defective or ineffective without visible mucosal damage, especially if the mechanism by which the barrier operates is enzymic.

In the conditions under consideration there is further evidence suggesting that the barrier mechanism is faulty. Thus, peptides can often be demonstrated in the circulating blood in these patients (Weijers & van de Kamer, 1955, 1960; Frazer, 1956; Alvey, Anderson & Freeman, 1957; Payne & Jenkinson, 1958; Gruettner,

Mellin & Bromstedt, 1959). Berger (1958, 1959) has demonstrated that a complement-fixing reaction occurs in gluten-intolerant patients when they are given gluten or gluten fractions. The fractions that cause this effect follow the same pattern as the other deleterious agents already described. Thus, a peptic–tryptic digest is effective, but inactivation occurs after incubation with extract of mucosa from the small intestine. Patients with severe mucosal damage may also have sucraemia after the administration of sucrose.

In patients with gluten-induced enteropathy, gluten maintains the syndrome, and for a long time after remission gluten will again initiate the enteropathy. This does not mean, however, that gluten alone started the condition in the first place. It could be that some other damaging effect, such as enteritis, temporarily reduced the barrier function of the mucosa and thus allowed the deleterious agents in wheat gluten to operate. Once the gluten-induced enteropathy has been firmly established, a vicious circle might be set up that could only be broken by the introduction of a strict gluten-free regimen. Another possibility is that the failure to handle the deleterious agents in gluten is genetically determined. There is some evidence that genetic factors may be involved in coeliac disease (Thompson, 1951; Boyer & Andersen, 1956; Carter, Sheldon & Walker, 1959). If a genetic mechanism were operative, it might be expected that gluten intolerance would be permanent. Present evidence suggests that gluten intolerance lasts for a long time in patients on remission on a strict gluten-free regimen, but there are indications that tolerance to gluten may be regained after a period of 5 years on a strict gluten-free diet. The answer to this question can only be obtained from further long-term follow-up studies. Both types of patient may well exist and secondary gluten intolerance resulting from mucosal damage caused by other agents than gluten has been described. The importance to the dietitian of a more complete understanding of the barrier function of the mucosa of the small intestine is apparent.

Folic acid

Deficiency of folic acid is rare in children with coeliac disease; it is common in adults with idiopathic steatorrhoea, but it may be absent; it seems to be a constant feature in our sprue patients from Hong Kong. There are certain differences between the folic acid deficiency observed in adult patients with gluten-induced enteropathy and those with sprue as encountered in Hong Kong (Frazer, 1958*a*). In gluten-induced enteropathy, the folic acid deficiency tends to be a relatively late phenomenon; in sprue, it is one of the first changes observed. In gluten-induced enteropathy, it is possible to treat the folic acid deficiency effectively by appropriate replacement therapy without greatly affecting the steatorrhoea, which will persist until a strict gluten-free regimen is introduced. In other patients, if the folic acid deficiency has not already been corrected, rapid remission may occur on a gluten-free diet without folic acid supplementation. These observations suggest that the folic acid deficiency in gluten-induced enteropathy is secondary to the enteropathy caused by wheat gluten. The reason for the rarity of folic acid deficiency in coeliac disease remains unknown.

There is a further difference between the folic acid deficiency in gluten-induced enteropathy and that associated with sprue. In gluten-induced enteropathy, the folinic acid excretion may be below normal, but it is only reduced approximately in proportion to the reduction in folic acid excretion; in sprue, on the other hand, there appears to be a more marked decrease of folinic acid excretion. This observation has been reported by Cintron-Rivera (1960) in Puerto Rico and there are indications that a similar situation may be present in the few patients from Hong Kong who have been studied in this way.

Folic acid deficiency will interfere with cell turnover, which might have some significance in the intestine. Studies on folic acid-deficient animals do not reveal any marked effect on the absorption of fat or other nutrients (Woodruff, 1950, 1952; Frazer, Fletcher, Sammons & Williams, 1958). On the other hand, recent studies indicate that treatment with aminopterin may interfere with absorption; this drug blocks conversion of folic into folinic acid. Even if folic acid deficiency does not in itself interfere with intestinal function to a significant extent, the combination of a damaging agent and folic acid deficiency might be significant. Repair of the intestinal mucosa is likely to be embarrassed by concomitant folic acid deficiency. The administration of folic acid causes dramatic improvement in the sprue patients with acute sprue; there is a rapid return of appetite and absorption may be considerably improved. Some of the sprue patients recover completely on folic acid therapy combined with treatment in hospital. The importance of this latter factor is difficult to assess; it may be significant, especially if a local dietary factor is involved. However, some patients on folic acid therapy do not completely recover. In spite of disappearance of the signs and symptoms of folic acid deficiency, great improvement in the gastro-intestinal situation and rapid increase in body-weight, steatorrhoea may return and persist. These patients may be effectively treated with antibacterial agents (Frazer, 1958*b*). This aspect of the chronic phase of sprue will not be further considered here, since, except for the development of a secondary gluten intolerance in some patients, it does not appear to be directly concerned with the dietary factors under discussion. Although, as first pointed out by Spies, Milanes, Menendez, Koch & Minnich (1946), folic acid is an important therapeutic agent in sprue, the condition cannot be attributed solely to folic acid deficiency. A number of other factors are involved in its aetiology and pathogenesis.

Oxidized fats

One of the outstanding questions in connexion with the sprue patients studied in Hong Kong is the cause of the acute folic acid deficiency. These patients are mainly service men or women, taking normal rations, who, within a few weeks or months, may change from healthy young men or women to patients with severe sprue. The diet in Hong Kong may be somewhat deficient in folic acid, but it is difficult to believe that this factor could be the cause of sprue in these patients. The effect is so rapid and differs from the folic acid deficiency seen in adults with gluten-induced enteropathy, a deficiency that is probably due to a simple deprivation consequent upon faulty absorption.

For many years it has been known that sprue has a peculiar geographical distribution, being common in the Far East, India and the Caribbean, but rare in Africa. In the sprue endemic areas the distribution is also patchy. The disease is seen in Hong Kong, but it is rare in Singapore; it is common in Puerto Rico, but almost unknown in Jamaica. It used to be common in Ceylon, but is now said to be rare. It is observed in Army or Air Force personnel in Hong Kong, but not in those of the Navy. It tends to occur in people living in certain houses, or in particular groups. There is, thus, a strong indication that some local factor plays a part in aetiology. This might be infective, and the existence of such a factor cannot be excluded at the present time; it might also be dietary.

It has been suggested that the use of certain fats for cooking might be relevant to this problem. Seed fats tend to be unsaturated, and if they are used for deep frying, oxidation readily occurs. Such fats are used in Hong Kong and at one time were used in Ceylon; unsaturated fats are also used quite extensively in Puerto Rico for this purpose. In Singapore, Jamaica and Africa, palm oils, especially coconut oil, are used for frying. These oils are more saturated and do not undergo extensive oxidative changes on repeated heating. The Navy revictual their ships from Singapore and use coconut oil for frying. Many of the patients developing sprue in Hong Kong have had a high intake of fried food before developing signs of the disease, but this is not invariably so. A survey of the cooking fats in Hong Kong eaten by sprue patients revealed some significant levels of oxidation. Thus, there is a considerable amount of circumstantial evidence indicating a possible relationship between the consumption of oxidized fats and the aetiology of sprue in Hong Kong. It cannot be said, however, that a correlation has yet been satisfactorily established.

We may, however, briefly examine this problem from another angle. Much work has been done on the toxic effects of oxidized fats. In general, polymerization products are relatively harmless, although they may not be well absorbed. Secondary oxidation products are more toxic and have been shown to cause tissue damage, including effects on the small intestine (Greenberg & Frazer, 1953). Oxidized fats also destroy a number of vitamins. However, the levels required to cause these effects are rather high and a direct toxic action of this nature would not explain the rapid development of folic acid deficiency observed in these patients, or the differences between the deficiency in sprue and gluten-induced enteropathy. The hydroperoxides and peroxides have been considered to be relatively harmless (French, 1949). However, their absorption into the body might not be directly toxic, but might lead to interference with metabolic activities that are dependent upon a reducing medium. One such reaction is the conversion of folic into folinic acid. As already mentioned, urinary excretion of folinic acid may be markedly reduced in sprue patients. Blocking the conversion of folic acid into folinic acid by the administration of aminopterin interferes with intestinal absorption. It may also be significant that the blood tocopherol levels in sprue patients may be extremely low (Darby, Cherrington & Ruffin, 1946), suggesting interference with the oxidation–reduction situation in the body. It is apparent that interference with folic acid metabolism by oxidized fats is at

present hypothetical. However, there are sufficient indications to make the point worthy of further study and of potential interest to dietitians.

Summary

1. Coeliac disease, idiopathic steatorrhoea and sprue are forms of the malabsorption syndrome in which enteropathy can be demonstrated. The features of the enteropathy can be adequately characterized and studied, so that the effects of various dietary factors on the course of these conditions can be investigated.

2. The importance of wheat gluten in the aetiology and pathogenesis of coeliac disease and idiopathic steatorrhoea can be demonstrated by the improvement that results from the institution of a strict gluten-free regimen.

Patients that recover completely on a gluten-free diet, and in whom a return of the enteropathy can be demonstrated after reintroduction of gluten, may be regarded as suffering from gluten-induced enteropathy.

Patients that are improved, but do not recover completely, may be regarded as suffering from gluten intolerance, which may be secondary to intestinal damage from some other cause than inability to handle wheat gluten. However, some of these patients may not have strictly adhered to a gluten-free diet; this could account for their continuing disabilities. A few patients with coeliac disease or idiopathic steatorrhoea do not benefit from a gluten-free regimen, nor do patients with acute sprue, according to present evidence. Some patients with sprue of long standing may benefit.

3. The deleterious agent or agents in gluten appear to be unaffected by peptic–tryptic digestion, autoclaving and ultrafiltration. They are inactivated by incubation with extract of mucosa from the small intestine; this property of mucosal extract is thermolabile.

4. An agent in wheat gluten has been shown to inhibit the peristaltic reflex of the small intestine owing to interference with acetyl choline liberation. Mucosa obtained from subjects who are gluten-tolerant inactivates this agent; mucosa from gluten-intolerant patients does not. The relationship of this agent to the production of mucosal damage and steatorrhoea, which have also been demonstrated, is under investigation. There may be several deleterious agents present in the active gluten fractions.

5. The possible significance of the barrier function of the small intestine is discussed.

6. Folic acid deficiency is observed in adults with gluten-induced enteropathy and in patients with sprue; it is rare in children with coeliac disease.

Differences in the folic acid deficiency observed in gluten-induced enteropathy and in sprue are described. Deficiency of folic acid in gluten-induced enteropathy appears to be secondary to the changes in the small intestine brought about by gluten. It is possible that there may be interference with conversion of folic into folinic acid in sprue. Folic acid deficiency alone does not account for the aetiology and pathogenesis of sprue.

7. The existence of a local factor in the aetiology of sprue is discussed; it may be related to diet.

8. The consumption of oxidized fats might play a part in the aetiology of sprue. Such materials may contribute to tissue damage, but the effect of hydroperoxides and peroxides may be more important. They might interfere with the conversion of folic into folinic acid. This possibility is still under investigation.

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