CHAPTER 10
TROPICAL SPRUE
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INTRODUCTION

'Tropical sprue' is a name used to describe a malabsorption syndrome of as yet unknown aetiology occurring in people who are resident in, or who have visited, the tropics (Baker et al., 1962). In non-tropical areas there are many disorders of known aetiology which can result in malabsorption (Booth, 1960; Wollaege and Scudamore, 1964; Dawson, 1965; Eisenstadt, 1966). As these conditions are also found in the tropics, they must be excluded before the diagnosis of tropical sprue can be substantiated in any given individual. Since there are probably a number of disorders of unknown aetiology which may result in malabsorption, tropical sprue must be considered a syndrome and it is to be expected that studies of patients in different parts of the world, and different groups of patients, may show some variations in the pattern of disease (Baker and Mathan, 1968a).

It is well known that visitors to the tropics are likely to suffer from numerous gastrointestinal upsets. In the past decade it has also been shown that, in tropical regions, there is a widespread incidence of subclinical gastrointestinal abnormalities (Baker et al., 1962; Sprinz et al., 1962; Banwell, Hutt and Tunnicliffe, 1964; Acosta-Matienzo, Coll-Cañaldez and Gintron-Rivera, 1966; Klipstein, Samloff and Schenck, 1966; Lindenbaum, Janiul Alain and Kent, 1966; Russell et al., 1966; Robins, García-Palmieri and Rubio, 1967). The relation of these episodes and their biopsy findings to tropical sprue is not yet clear. Klipstein (1967a) has suggested that they may be very closely related, but Baker et al. (1962) in South India and Troncalle et al. (1967) in Thailand found that the widespread minor histological changes were not necessarily associated with malabsorption. However, precise definition of this relationship, if any, must await further study.

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Epidemiology

Tropical sprue has long been considered to have a peculiar geographical distribution (Manson-Bahr, 1953). Although it is present in most parts of the tropics, it has been thought to be very rare or absent in Eastern, Central and Western Africa (Banwell et al., 1967). However, there are occasional case reports suggestive of tropical sprue from Eastern Africa (Harries, 1964) and in South Africa patients with megaloblastic anaemia have been found to have intestinal malabsorption of unknown aetiology (Hilt and Adams, 1963). A syndrome with some similarities to tropical sprue has occasionally been described in people who have never been in the tropics (Cooke et al., 1963). Whether or not such disorders are in fact related to tropical sprue cannot, at present, be decided.

The disease occurs in both epidemic and endemic forms (Baker and Mathan, 1968b). There is very little information available about the endemity of malabsorptive states in the indigenous populations of the tropics. The incidence of xylose malabsorption in the community ranges from 8 to 40 per cent in different regions (Mathan and Baker, 1968; Lindenbaum, 1968) but there are no reports of other tests of absorption carried out in large populations selected at random. It was previously considered that the disease was confined to adults, but it is now clear that both endemic and epidemic sprue can also occur in children (Sheehy and Floch, 1964; Mathan, Joseph and Baker, 1968).

Almost all reports of epidemics of tropical sprue are confined to India, Pakistan and Burma (Baker and Mathan, 1968b), although Hillary (1759), in his description of sprue, thought that the disease reached epidemic proportions in Barbados. Many of the epidemics described in the literature occurred in military personnel and affected mainly adult males. However, in civilian populations, the overall sex incidence is equal and all age groups are affected, although the attack rate is higher in adults (Baker, Mathan and Joseph, 1963).

Several epidemics of tropical sprue have been studied in South India since 1960. These appear to have a distinctive epidemiological pattern (Baker and Mathan, 1968). The onset is usually gradual with the peak incidence, in any given village, occurring a few months after the initial cases. However, occasionally it may be more explosive in nature involving a large percentage of the community within a few weeks of onset (Leishman, 1945; Mathan and Baker, 1968). The spread of the disease through a village shows a tendency to clustering of cases in time and space. (Mathan and Baker, 1968).
Within a given household there are often multiple cases occurring usually one after the other at intervals of a few days to a few weeks (Baker and Mathan, 1968b). This pattern of spread within a family was well demonstrated in an isolated household (Mathan, Ignatius and Baker, 1966).

Attempts to define the aetiological agent in epidemics have so far been unsuccessful (Baker, Mathan and Joseph, 1963; Mathan and Baker, 1968). It has not been possible to demonstrate any relationship between case incidence and diet, source of water supply, wealth, housing, occupation or environmental sanitation. However, there is circumstantial evidence to suggest that the epidemics may be infective in origin and much further work is needed to study this aspect.

CLINICAL FEATURES

The clinical features of the syndrome were described by Caraka two to three thousand years ago (Baker and Mathan, 1968b). Over the last 100 years there have been a number of papers describing the disease, but it is only with the advent of better investigative techniques that it has been possible to define the syndrome more exactly. The clinical features, as seen in different parts of the world, have been described in a series of recent papers: Klipstein (1964a)—Puerto Ricans in New York; Sheehy et al. (1965)—North Americans in Puerto Rico; Klipstein, Samloff and Schenk (1966)—Haitians in Haiti; Jeejeebhoy et al. (1966a, b)—Indians in Bombay; Misra et al. (1967)—Indians in Delhi; Baker and Mathan (1968a, b)—Indians in South India; and O’Brien and England (1966)—Britons in Singapore. Although diarrhoea is often considered the outstanding symptom, patients may have malabsorption without diarrhoea (Baker, 1957; Misra et al., 1967). It used to be thought that symptoms of deficiency states such as glossitis were essential for the diagnosis of the disease (Manson-Bahr, 1965). However, the deficiency states are secondary to the malabsorption and not primary symptoms of the disease (Baker and Mathan, 1968a, b; Mathan, Joseph and Baker, 1968).

RADIOLOGY

The radiological features of the small intestine in cases of malabsorption syndrome were well reviewed in the first volume of this series (French, 1952). Although this study was apparently based on cases of non-tropical sprue, similar findings are also seen in tropical sprue. The main abnormalities are flocculation of the barium, even
when 'non-flocculating' barium suspensions are used, dilatation of the intestine and a coarsened mucosal pattern (Paterson and Baker, 1956). On screening or cine-radiographic study, marked abnormalities of peristalsis may also be observed (Paterson, David and Baker, 1965). These changes in peristaltic movement are not as well recognized as they should be since they are a valuable diagnostic aid.

Floh, Caldwell and Sheehy (1962), Caldwell, Swanson and Bayless (1965) and Misra et al. (1967) found a broad correlation between radiological findings and other parameters of intestinal function. Paterson, David and Baker, (1965) in a series of 32 patients could detect no such correlation, but a recent analysis of the findings in over 300 patients in South India (Baker and Mathan, 1960) confirms the existence of such a correlation. However, since in a given individual marked radiological abnormalities may be present in the absence of obvious malabsorption (Paterson, David and Baker, 1965) the existence of an overall correlation is of little practical importance. When the typical abnormalities are present they suggest, but do not establish, the diagnosis and their absence does not exclude it (Paterson and Baker, 1958). The chief importance of radiology is in excluding other lesions of the gastrointestinal tract which may mimic tropical sprue, especially strictures, diverticula, blind loops, tumours etc. In this regard the techniques of small bowel enema and retrograde filling of the small intestine (Frizmann-Dahl, 1955; Miller, 1965) are particularly useful in demonstrating or excluding obstructive lesions.

HISTOPATHOLOGY

Previously histological study of the gastro-intestinal tract in tropical sprue was limited to either autopsy material (Bahrs, 1915; Suarez, Spies and Suarez, 1947) or specimens obtained at laparotomy (Milanes, Leon and Causa, 1951; Butterworth and Perez-Santiago, 1958). However since the introduction of the transoral biopsy tube (Wood et al., 1949) a number of studies have been reported.

From 60 to 90 per cent of patients with sprue show varying degrees of cellular infiltration and atrophy of the stomach and hypo- or achlorhydria (Floh et al., 1963; Vaish et al., 1965a). In some cases the changes may be so marked as to resemble those seen in classical pernicious anaemia (Baker and Rao, 1962). The aetiology of this gastric lesion is unknown but it may result from the same cause as the intestinal lesion.

When the jejunal mucosa is damaged the villus structure as seen
under the dissecting microscope undergoes a series of changes from 'finger-like' villi, which may successively be described as 'tongue-shaped', 'leaf-shaped', 'ridged', 'convoluted' and 'flat' (Holmes, Hourihane and Booth, 1961; Baker et al., 1962; Booth et al., 1962). In man these alterations appear to be the nonspecific end result of a variety of damaging agents (Collins, 1965; Ammann, 1965), and in the tropics, leaves, ridges and convolutions may be found in apparently normal people (Baker et al., 1962; Chacko et al., 1968). In a given person the nature of the villus architecture is of little diagnostic significance, but it can help in better interpretation of conventional histology, and in longitudinal studies in a given individual repeated observations may show a progressive return towards a more normal appearance. It is noteworthy that in patients with gluten induced enteropathy a flat mucosa is present in over 60 per cent of cases (Booth et al., 1962) whereas in tropical sprue it is very rare (Baker et al., 1962; Sheehy, Cohen and Brodsky, 1963; Jeejeebhoy et al., 1966b; England and O'Brien, 1966), suggesting that the severity of the mucosal damage is less in the latter condition.

Reported histological changes in jejunal biopsy material range from the 'normal' or 'almost normal' to the 'very abnormal' (Chacko et al., 1961; Sheehy, Cohen and Brodsky, 1963; Swanson and Thomasen, 1965; England and O'Brien, 1966; Misra et al., 1967). As with villus architecture the definition of the 'normal' has to be established with reference to the local population. Klipstein (1968) in his excellent review of tropical sprue raises the issue as to whether patients with 'normal' biopsies really have tropical sprue. This is to a considerable extent a matter of semantics. Patients with intestinal malabsorption of two or more substances may have biopsies indistinguishable from apparently healthy members of the local population when studied by conventional staining techniques (Baker et al., 1962; Dasai and Jeejeebhoy, 1967; Misra et al., 1967). Since the absorptive capacity of the mucosal cells is related to their molecular integrity, it is not to be wondered at if absorption is abnormal without there being any histologically demonstrable abnormality. Whether more refined techniques of histochemistry and electron microscopy will enable a better correlation of morphology and function to be made remains to be seen.

Quite a lot has been written about villus shape, but unless histological sections are correlated with dissecting microscopic appearances the estimation or measurement of villus width on a single section has no meaning, since leaves cut longitudinally will give the
appearance of broad villi, and when cut in cross section may show finger-like villi (Baker et al., 1962). In this respect the importance of correct orientation and the desirability of obtaining serial sections has been emphasized by Rubin and Dobbins (1965). Villus height is often reduced, and in severe cases may be markedly so (Chacko et al., 1961). This reduction in villus height is usually accompanied by an increase in depth of the crypts. Swanson and Thomassen (1965) have shown that there is an inverse relationship between reduction in villus height and increase in crypt depth, except in what they term 'atrophic sprue' where the villus height is greatly reduced with only a slight to moderate increase in crypt depth. Similar findings have been seen by England and O’Brien (1966) and Chacko, Mathan and Baker (1967). Swanson, Wheby and Bayless (1966) point out that some of this 'atrophy' may be the result of intestinal distension. However, this cannot be the whole explanation as this type of mucosa can be seen where intestinal distension is not a feature. Whether this atrophic stage is the end result of severe damage, or whether it has a different aetiology from those cases where glandular hypertrophy is marked, is not clear.

In normal people the lamina propria usually contains lymphocytes, plasma cells and histiocytes (Astaldi and Stroselli, 1960). In sprue these cells are usually present in increased numbers and similar findings are recorded in patients with coeliac disease (Fone et al., 1960; Rubin et al., 1960; Schenk, Samloff and Klopstein, 1965). Occasionally there are prominent collections of eosinophils especially around the bases of the crypts, unrelated to the presence of parasites (Butterworth and Pérez-Santiago, 1958; Chacko et al., 1961; Schenk, Samloff and Klopstein, 1965; England and O’Brien, 1966). The significance of the increase in the various cell types is not yet clear.

The mucosal cells may show no detectable changes. In other cases, especially in those with the most marked increase in crypt depth, the cells, instead of being tall and columnar, may be flattened or cuboidal. Cytoplasmic vacuolation is also common and at times may be very marked (Butterworth and Pérez-Santiago, 1958). This vacuolation may, in part, be an artefact (Wolf-Heidegger, 1940). In more severe cases the brush border of the mucosal cells may appear disorganized even on light microscopy (Sheehy, Cohen and Brodsky, 1963) although electron microscopic study is necessary for adequate evaluation. In cases where there is folate, and/or vitamin B₁₂ deficiency, the mucosal cells are macrocytic corresponding perhaps to changes seen in the bone marrow cells (Butterworth, Smith and Pérez-Santiago, 1960; Thijs Ten, 1963). The macro nuclei
return to a more normal size following therapy with folate or vitamin B\textsubscript{12}, but compared with the bone marrow the return to normal may take a much longer time (Swanson, Whobey and Bayless, 1966). A similar delay has been seen by Furoozan and Trier (1967) in the normalization of crypt cell nuclei in patients with pernicious anaemia in relapse following treatment with vitamin B\textsubscript{12}. Since the turnover of epithelial cells is a rapid process, measured only in days, the reasons for this delay are hard to understand. Mitotic figures, relative to the number of mucosal cells, may be increased in number. Swanson and Thomasen (1965) have shown that this increase is greatest in 'mild' cases, and is least marked in severe and 'atrophic' cases. An increase in mitotic figures can be interpreted either as an increase in the number of cells entering mitosis and/or an increase in the time taken to complete mitosis and it is not at present possible to distinguish between these.

'Infiltration' of the mucosal cells by small round cells may be seen in normal subjects (Astaldi and Strosselli, 1960) but in patients with sprue this may be very marked, especially towards the villus tip (Chacko et al., 1961). These cells are between, and not in, the mucosal cells (Meader and Landers, 1967; Mathan et al., 1968). The basement membrane is frequently thickened or reduplicated especially towards the luminal surface (Butterworth, Smith and Pérez-Santiago, 1960; Schenk, Samloff and Klipstein, 1965).

Mucus secreting goblet cells are often present in normal numbers but occasionally they may be increased (Chacko et al., 1961). The Paneth cells in subjects with sprue do not appear to have received much attention, but when mentioned they have been reported as normal (Schenk, Samloff and Klipstein, 1965) or as present but without granules (Chacko et al., 1961). Argentaffin cells are reported as being increased considerably in numbers (Swanson and Thomasen, 1965) but the significance of this finding is obscure.

There is now ample evidence that the main histological abnormalities seen in tropical sprue are non-specific in nature. Similar findings may be seen in some milder cases of non-tropical sprue (Shiner and Doniach, 1960; Thurbeck, Benson and Dudley, 1960) in kwashiorkor (Bruner et al., 1966) in bacterial diarrhoea associated with septicemia (Gottlieb and Brandborg, 1966) in sarcoidosis and lymphoma (Gjone, Myren and Refsum, 1965) and in various other situations (Townley, Cass and Anderson, 1964; Ammann, 1965; Collins, 1965). However, Rubin and Dobbs (1965) have suggested that plasma cells occur more frequently in the lamina propria in coeliac disease and lymphocytes in cases of tropical sprue. Also Schenk, Samloff and Klipstein (1965) have calimed that it is
possible to distinguish biopsies from patients with tropical sprue and
celiac disease on the basis of lipid staining. In the former they
find lipid in the area of the thickened basement membrane, whereas
in the latter it is predominantly in the supranuclear portion of the
epithelial cells. The frequency and specificity of these findings
awaits further study.

Histochemical studies have shown reduction in various enzymes in
tropical sprue (Spiro et al., 1964; Schenck, Samloff and Klipstein,
1965) but as yet these have contributed little to our understanding
of the disease. Hartman et al. (1960) describe an electron micro-
scopic study of the jejunal mucosa in tropical sprue. They found
distortion of the microvilli, fragmentation of intercellular mem-
branes and abnormalities of the nuclei. However, from their
account it is clear that the fixation was not satisfactory. Preliminary
electron microscopic studies in epidemic sprue have shown sparse
and irregular microvilli, fragmentation of the terminal web and a
marked increase in lysosomes. Degenerative changes were present
in the nucleus and cytoplasm of some cells even on the sides of the
villi, and in several cases there was marked thickening of the base-
ment membrane (Mathan et al., 1968).

Because of the relative ease of sampling most studies of mor-
phology have been based on jejunal biopsy material. However, the
ileum may also be involved with abnormalities similar to those seen
in the jejunum (Bahr, 1915; Suarez, Spies and Suarez, 1947;
Baker et al., 1962). At times, however, the ileal lesion may be less
severe than the jejunal lesion (O'Brien and England, 1966; Chacko,

Fat
One of the hall-marks of tropical sprue is steatorrhoea. However,
it is not a sine qua non for the diagnosis since an otherwise identical
clinical syndrome may occur in the absence of steatorrhoea
(Rodriguez-Molina, Asenjo and Cancio, 1957; Jeejeebhoy et al.,
1966b; Tandon et al., 1966; Miura et al., 1967). The presence and
degree of steatorrhoea is dependent to some extent on dietary fat
intake—a low fat intake will abolish the steatorrhoea (Asenjo,
Rodriguez-Molina and Cancio, 1958) and a high fat intake will
increase the total fat excretion. On a 50-60 g fat intake the majority
of patients excrete between 6 and 25 g of fat per day (Baker and
Mathan, 1968a).
The aetiology of the steatorrhoea is not clear. The digestion and absorption of food fats is a complicated process which may be interfered with at a number of points (Frazer, 1952; Dawson, 1967). Congenital absence of bile salts may cause steatorrhoea (Ross et al., 1955) and it is possible that in tropical sprue there is a reduction in the amount of bile salts available for fat absorption. It has been shown that there is an enterohepatic circulation of bile salts, and that the major site of bile salt reabsorption is the ileum (Tappeiner, 1878; Freilich, 1936; Baker and Searle, 1960; Lack and Weiner, 1961 and 1963). Resection of the ileum (Playoust, Lack and Weiner, 1965) and regional ileitis (Meitlhoft and Kern, 1968) result in bile salt malabsorption which produces bile salt deficiency and steatorrhoea. It may be that the lesion of the ileum in sprue interferes with bile salt reabsorption resulting in a depletion of the bile salt pool. Another possible mechanism is suggested by studies in the blind loop syndrome, where it has been shown that the bacteria in the small intestine cause degradation of conjugated bile salts (Donaldson, 1953; Draser, Hill and Shiner, 1966, Tabacchiali and Booth, 1966; Rosenberg, Hardison and Bull, 1967). This results in an intraluminal deficiency of conjugated salts which in turn gives rise to steatorrhoea which can be cured by feeding extra bile salts (Tabacchiali, Hatzicoannou and Booth, 1968). There is considerable circumstantial evidence that, at least in some cases of sprue, there is a bacterial invasion of the small intestine and it is possible that these bacteria may have an effect similar to that occurring in the blind loop syndrome. The results of detailed studies of bile salt pool size and enteric degradation in tropical sprue will be awaited with interest.

Pancreatic function is usually thought to be normal in tropical sprue (Romero-Burcelo, 1955). However, there are no published reports of quantitative pancreatic function studies using modern techniques.

Finally, impaired fat absorption may result from disease of the intestinal absorptive cell itself giving rise to defective entry into the cell, defective lipid metabolism within the cell, or defective egress from the cell. In vitro studies with biopsy specimens have demonstrated that in some patients with sprue there is both defective uptake of labelled stearic acid, and some depression of the conversion of the absorbed stearic acid to triglyceride (Baker and Rao, 1962). The histological preparations of Schenk, Samloff and Kilpatric (1963) also suggest that lipid transport through the basement membrane may be defective.

When medium chain triglycerides were substituted for the usual
dietary fat in Puerto Rican patients with sprue, steatorrhoea decreased or disappeared, serum lipids returned to normal and the patients gained weight (Cancio and Menendez-Corrada, 1964). This suggests that the major defect responsible for the steatorrhoea is one connected with the absorption and transport of the longer chain fatty acids. However, in South Indian patients we have been unable to confirm this effect of feeding medium chain triglycerides.

Glucose

A low rise in the level of blood sugar in the glucose tolerance test has long been known to be a common finding in patients with tropical sprue (Fairley and Bromfield, 1932). However, not all patients with sprue have a flat glucose tolerance test and an 'abnormal' result is found in a certain proportion of apparently normal people. Nevertheless, as a group, significantly more patients with sprue have a flat test than do comparable control subjects (Gardiner, 1956; Rajan et al., 1961; Sheehy, Anderson and Begg, 1966). Theoretically the flat glucose tolerance test could be due to either poor absorption or to rapid glucose utilization. However, utilization of intravenously administered glucose is normal (Vaish, et al., 1965b) so that the 'flat' glucose tolerance test does in fact represent defective absorption. The aetiology of the glucose malabsorption is unknown, but is presumably related to damage to the intracellular transport mechanism for glucose.

Xylose

Because of its simplicity the xylose absorption test (Fourman, 1948) has become popular as a test of intestinal function. Absorption may be followed by measuring blood levels or urinary excretion, but the latter, because of the ease of collection and estimation, is the most favoured method. Initial studies were usually carried out with a 25 g dose (Gardner and Perez-Santiago, 1956; Butterworth et al., 1959; Christiansen, Kirner and Abalaza, 1959). However, this frequently causes nausea and diarrhoea. With the demonstration by Santini, Sheehy and Martinez de Jesus (1961) that similar results could be obtained with a 5 g dose, without the unpleasant side effects, this smaller dose has come into widespread use. A critical study of the relationship between the dose administered and the amount excreted showed that the separation between normal subjects and patients with malabsorption was not as good with the 5 g dose as with the 25 g dose (Rinaldo and Gluckmann, 1964), nevertheless, because of its advantages, many workers still
prefers the lower dose. The majority of patients with sprue have an
abnormal urinary excretion of xylose following either dose (Peréz-
Santiago and Butterworth, 1957; Sheehy, Cohen and Brodsky,
1963; Paterson, David and Baker, 1965; Jeejeebhoy et al., 1966b;
Klipstein, Samloff and Schenck, 1966; O'Brien and England, 1969;
Baker and Mathan, 1960a). In some series all patients have had
abnormal xylose excretion, while in others there have been some
patients with normal absorption. While there is no a priori reason
to believe that all patients with sprue should have defective xylose
absorption, it is possible that where a normal result was found with a
5 g dose an abnormal result might have been obtained with a 25 g
dose. Sammons et al. (1967) have shown that a modification of the
5 g xylose test to measure excretion up to two hours and from two
to five hours will enhance the separation between people with normal
and abnormal intestinal function.

**Disaccharides**

Following the initial observations of Fox (1950) on sucrose mal-
absorption in 'sprue' patients, Santini et al. (1957) observed an
increased urinary excretion of sucrose in patients with tropical
sprue both in the fasting state and after an oral loading dose. Gray
and Santiago (1966), using the constant infusion technique, showed
that patients with sprue had impaired hydrolysis and absorption of
sucrose, lactose and maltose.

Several studies have demonstrated depressed levels of disacchar-
idasises in biopsy specimens from patients with tropical sprue (Santini,
Aviles and Sheehy, 1960; Bayless, Walter and Barber, 1964;
Sheehy and Anderson, 1965; Sheehy, Anderson and Baggs, 1965;
Desai et al., 1967). There are, however, some differences in the
reported results. For example, Sheehy, Anderson and Baggs report
low values of lactase, sucrase and maltase, whereas Desai et al.
report only depressed levels of lactase activity with maltase and
sucrase being relatively unaffected. Even in subjects without
sprue there are wide variations in the levels of lactase activity. Some
of these variations may be racially determined (Cook and Kajubi,
1966; Bayless and Rosenweig, 1966) but whether they are hereditary
or acquired is not known. The high incidence of lactase deficiency
in some population groups makes the role of sprue in producing such
deficiencies more difficult to assess.

It is not at present clear whether disturbances of disaccharide
absorption are related only to abnormalities of brush border
enzymes, or whether other factors are also involved.
Vitamin A

In a community where vitamin A intake is marginal the onset of tropical sprue may precipitate the appearance of signs of overt vitamin A deficiency (Baker and Mathan, 1968b). Studies of plasma levels of vitamin A following a large oral dose show a low rise (Gardner, 1938), but whether this is due to rapid clearance from the plasma or to defective absorption of lipid in general, or of the vitamin specifically, is not clear. In subjects with non-tropical sprue Fox (1949) showed that prior emulsification of the oily vitamin A greatly improved the absorption, suggesting that in those patients it was intraluminal lipid emulsification which was faulty. No such study appears to have been undertaken for tropical sprue.

Pyridoxin, Riboflavin and Thiamine

Although signs of multiple vitamin deficiencies are common there are very few reported studies of the absorption of these vitamins. The finding of increased excretion of xanthurenic acid after tryptophan loading suggests some disturbance of pyridoxin metabolism (Sigler et al., 1962); Girdwood (1956), using microbiological assays, studied the absorption of pyridoxin, riboflavin and thiamine in three patients with treated tropical sprue, and found no evidence of impaired absorption. Using tritiated pyridoxin the absorption of this vitamin, when given alone, was not impaired in most subjects with sprue (Baker and Mathan, 1968a).

Vitamin B12

The reported incidence of vitamin B12 malabsorption in tropical sprue differs in different series from a very low percentage (Gardner, 1938) to 80 per cent (O’Brien, 1968a and b). Similar variations in incidence have been seen among patients from different epidemics in South India (Baker and Mathan, 1968a). The reason for these variations is not known.

The vitamin B12 malabsorption results most commonly from an ileal lesion which prevents vitamin B12 absorption even in the presence of excess intrinsic factor (Baker, 1957; Mollin, Booth and Baker, 1957; Sheehy, Peréz-Santiago and Rubini, 1961; Rivera and Bernabe-Prida, 1962; Floch et al., 1963; Klipstein, 1964a; O’Brien and England, 1966; Klipstein, Samloff and Schenck, 1966; Jeejeebhoy et al., 1966b).

In some cases the administration of broad spectrum antibiotics appears to cure the ileal defect and vitamin B12 absorption returns to normal (Baker, 1957; Mollin, Booth and Baker, 1957; Tasker,
1961; Klipstein, 1964a; Guerra, Wheby and Bayles, 1965; O'Brien, 1968a, b). This improvement may start within 48 hours of the commencement of therapy (Baker, 1967) whereas in other cases response may not occur for a number of months (Booth and Mollin, 1964; Guerra, Wheby and Bayles, 1965). The early improvement in vitamin B₁₂ absorption is presumably related to the direct effect of the antibiotic on bacterial flora. However, the return to normality after months of chemotherapy is more difficult to explain in terms of bacteria and needs to be distinguished from the known tendency for spontaneous remission in the B₁₂ absorptive defect (Baker and Rao, 1962).

The reason why, in some cases, the ileal defect responds to antibiotics and does not in others is obscure. In South India a marked difference has been noted between patients from different epidemics in the response of the B₁₂ absorptive defect to short term tetracycline therapy, the response rate varying from 25 to 50 per cent (Baker and Mathan, 1968d). The reasons for these variations are not clear. Presumably those that respond to antibiotics are related to bacterial invasion of the ileum. In those that do not respond it is possible that the defect may be due to bacteria which are resistant to the antibiotics used. It has been shown in animals that the adsorption of the vitamin B₁₂-intrinsic factor complex to the intestinal mucosa is calcium dependent (Herbert, 1959). Roderiguez-Rosado and Sheehy (1961) tried the effect of added calcium in patients with sprue, but could demonstrate no improvement in B₁₂ absorption. Similarly it has been suggested that some intestinal factor may be necessary for normal vitamin B₁₂ absorption (Movit et al., 1963) but Baker (1963) could show no improvement with added normal intestinal juice. It is therefore probable that, in those cases which do not respond to antibiotics, the absorptive defect is related directly to some lesion of the ileum interfering with vitamin B₁₂ entry into, or transport through, the cells.

In some cases of tropical sprue there is decreased intrinsic factor secretion (Vaish et al., 1965a) and intrinsic factor assays show that it is very markedly diminished or absent in about 5 per cent of sprue patients (Baker and Mathan, 1968a). In such cases if the intestinal lesion returns to normal, leaving only the gastric lesion, patients may present a picture almost identical with that of pernicious anaemia (Baker and Rao, 1962).

Folic Acid

Interest in folic acid metabolism in tropical sprue was first aroused by the demonstration of its therapeutic efficacy (Spies
et al., 1946). With the advent of microbiological assays it has become clear that folate deficiency in sprue is very common, although the relative incidence of deficiency varies in different series (Klipstein, 1964a; O’Brien and England, 1964; Baker, 1965; Jeejeebhoy et al., 1966b; Sarin, Kaker and Mehta, 1966; Klipstein, Schenk and Samloff, 1966; Baker and Mathan, 1968b).

The role of malabsorption in the pathogenesis of the folate deficiency is not completely clear. Absorption of crystalline pteroylglutamic acid has been studied both by microbiological techniques and by the use of tritium-labelled material (Butterworth et al., 1957; Klipstein, 1963, 1964a and 1966; Paterson, David and Baker, 1965; Jeejeebhoy et al., 1966b and 1967; Baker and Mathan, 1968a). These tests give results which vary from practically 100 per cent of subjects demonstrating ‘folate malabsorption’ to those with a very low incidence of demonstrable ‘malabsorption’. In general the highest incidence of defective absorption has been found employing microbiological techniques. These involve the measurement of plasma levels or urinary excretion and, in some cases, preliminary saturation of the patient with folate. Whether these tests and those employing faecal balance techniques give comparable results has yet to be demonstrated. Nevertheless the findings of Sheehy et al. (1961), that patients with sprue and folate deficiency megaloblastic anaemia will respond to an oral dose of as little as 25 µg of pteroylglutamic acid a day, demonstrate that in those patients malabsorption of folic acid was not a major feature.

Folic acid in food is largely in the form of polyglutamates (Butterworth, Santini and Frommeyer, 1963) and it is probable that the absorption of pteroyl-glutamic acid bears little or no relation to the absorption of food folate. Using the double reticulocyte response it has been shown that food folate is not as effectively absorbed and/or utilized as is crystalline pteroyl-glutamic acid (Baker, 1968) but whether the same is also true for normal subjects is not clear. Jeejeebhoy (1968), studying the rise of folate in the blood, has produced evidence suggesting that the polyglutamates may not be so well absorbed in patients with sprue as they are in normal controls. It is assumed, but not proved, that polyglutamates are usually broken down before absorption. It is possible that in sprue there may be defective digestion of polyglutamates but Klipstein (1967b) could find no difference in the conjugase activity of duodenal aspirates of normal people and of subjects with tropical sprue.

Other factors may also contribute to the folate deficiency. Anorexia is often a feature of the disease, and will reduce folate intake. A preliminary study with labelled pteroyl-glutamic acid
also indicates that in some cases there may be increased gastro-intestinal losses of folate (Baker, 1968) but this aspect awaits further study. Finally, the vitamin B₁₂ deficiency which often occurs in sprue will also tend to deplete the body folate pool (Dawbarn, Hine and Smith, 1958; Girdwood, 1959).

Iron

In areas where iron stores are marginal, frank iron deficiency in tropical sprue is common (Baker and Mathan, 1968b). However, few studies on iron absorption have been undertaken. Gardner (1956), using an oral iron load, found a flatter iron tolerance test in a group of sprue patients compared with normal controls, suggesting defective absorption in the former. However, this type of test is rather difficult to interpret and also bears little relationship to the absorption of food iron. This subject needs further study with labelled iron and with foods in which the organic iron is labelled.

Calcium and Vitamin D

Haddock and Vazquez (1964 and 1966) demonstrated a low 'antiarachitic activity' in the serum of some patients with untreated tropical sprue compared with treated patients and controls. Whether this is related to defective vitamin D absorption, or to other factors, is not at present clear. It has, however, been demonstrated that calcium absorption is decreased in sprue (Schaaf, 1964) and serum calcium levels may also be decreased (Haddock, 1965; Klipstein, Samloff and Schenk, 1966), although tetany is rare (Rodríguez-Molina, 1955).

METABOLIC COMPLICATIONS

Fluid and Electrolytes

Black (1946) described dehydration and hyponatraemia associated with tropical sprue in military personnel, and concluded that these were due to excess faecal losses. Subsequently there has been very little written about this aspect of tropical sprue. However, in South India dehydration, hyponatraemia, hypokalaemia and metabolic acidosis are not uncommon in severe cases of sprue and are an important cause of death in untreated cases (Baker, 1957; Baker and Mathan, 1968a, c). The increased losses of fluid, sodium and potassium in the stool are obviously related to a failure of intestinal absorption and/or reabsorption. However, whether the lesion responsible for this state is primarily in the small intestine (as in
cholera) or in the large intestine, or is a combination of both, is not clear. The losses of fluid and electrolytes brought about by the diarrhoea may be greatly aggravated by vomiting and also by anorexia and nausea which prevent an adequate intake.

Protein and Amino Acids

A moderate degree of hypoproteinaemia, due to hypoalbuminemia, is a common accompaniment of tropical sprue (Lopez et al., 1949; Baker, 1957; Peréz-Santiago and Butterworth, 1957; Klipstein, 1966; Baker and Mathan, 1968a). Measurements of total exchangeable albumin show an even greater reduction than is indicated by the estimation of serum proteins alone (Vaish, Ignatius and Baker, 1965). This depletion of body protein may be the result of several factors. Anorexia often reduces protein intake. The assimilation of dietary protein in tropical sprue has not been studied in detail. Glycine absorption has been shown to be defective (Butterworth, Santini and Peréz-Santiago, 1958) and it is reasonable to suspect that the absorption of the products of protein digestion may also be defective. Such defective absorption has been demonstrated by Crane and Neuberger (1960) using \(^{15}\)N-labelled protein in cases of non-tropical sprue. Using \(^{51}\)Cr- or \(^{131}\)I-labelling of plasma albumin, it has been demonstrated that in a proportion of cases there is excessive loss of albumin into the gastro-intestinal tract, with consequent decrease in the half life of the circulating albumin (Rubini et al., 1961; Vaish, Ignatius and Baker, 1965). The mechanism by which protein enters the gastro-intestinal tract, either in normal subjects or in patients with sprue, is not clear, although there is some evidence that the jejunum rather than the ileum is the site of entry (Winawer et al., 1967). The increased loss is presumably related in some way to the intestinal damage, but the only observed parameter with which there was any correlation was the degree of steatorrhoea (Vaish, Ignatius and Baker, 1965).

The role of hypoanabolic states in the reduction of body protein needs further elucidation (Jecjebhoy, 1964). Such a state could theoretically arise from defective protein intake or absorption, or from interference with albumin synthesis by the liver from other causes. At least one of the cases described by Vaish, Ignatius and Baker (1965) had an anabolic rate below normal, while others had rates which, while normal or greater than normal, were still not adequate to meet the demands associated with the increased catabolism—in other words their reserve anabolic rate was reduced. Further study is still needed in this area.
Santini, Sheehy and Butterworth (1963) found that glycerine formed a relatively greater proportion of urinary amino acid nitrogen in sprue patients than in control subjects. They also found a reduction in creatinine excretion. Both free and bound urinary amino acid excretion was found to be quantitatively reduced in subjects with sprue, with the notable exception of hydroxyproline which was increased (Satwekar and Radhakrishnan, 1965). The significance of this increased excretion of hydroxyproline is not clear, but it is presumably related to a disturbance in collagen metabolism.

Haematological Disorders

One of the commonest complications of sprue is anaemia in which deficiencies of iron, vitamin B₁₂ and folic acid may play a part either alone or in various combinations. The incidence and aetiology of the anaemia varies in different series according to the definition of anaemia, the duration and severity of the illness, the nature of the absorptive defects and the dietary habits of the patients prior to and during the illness. Apart from the aetiology of the deficiencies, the anaemia does not appear to differ in any way from nutritional anaemia due to other causes. In those parts of the world where tropical sprue is prevalent, it may be the commonest cause of megaloblastic anaemia in non-pregnant adults (Baker, 1958 and 1965).

Hormonal Disorders

Fairley and Mackie (1926) pointed out that some subjects with tropical sprue have features suggestive of hypoadrenalism. Paniagua et al. (1950) and Rivas, Morales and Koppisch (1952) found diminished urinary excretion of 17-oestrogens in sprue patients. More recently it has been shown (Baker et al., 1968) that both 17-oestrogen and oestrogenic steroid excretion are reduced, although responses to both ACTH and metopirone stimulation are normal. The precise interpretation of these findings is difficult and further studies of plasma cortisol levels and cortisol production and destruction rates are needed to elucidate fully the problem.

TREATMENT

Until the cause of sprue is known, treatment of the disease itself must rest on a purely empirical basis. Since the condition is probably a syndrome, and not a single disease entity, it is not surprising if
different patients, and groups of patients from different parts of the world, respond differently to similar treatment. It is important to note that there is frequently a tendency to natural remissions and relapses, and even to spontaneous cure, with little or no treatment or change in diet, occupation, or environment (Keele, 1946; Baker, 1957; Webb, 1963; Baker and Mathan, 1968b). This makes the true assessment of the effect of therapeutic regimens on the course of the disease difficult or impossible without statistically controlled therapeutic trials which have not yet been reported.

Control of Diarrhoea

Control of the diarrhoea, by simple measures such as bismuth salicylate, belladonna and opium, kaolin etc., is important and may bring about a marked subjective improvement (Stefanini, 1948; Baker, 1957; Baker and Mathan, 1968c; Mathan et al., 1968) but it is not yet clear whether this has any ultimate effect in shortening the duration of the illness.

Correction of Deficiencies

Since fluid and electrolyte disturbances are one of the commonest causes of death (Baker and Mathan, 1968a) adequate correction of these disorders is very important (Black, 1946). In studies of epidemics in South Indian villages, control of the diarrhoea and maintenance of adequate fluid and electrolyte balance even with no other specific therapy reduced the mortality from 20 to 30 per cent to less than 1 per cent (Mathan and Baker, 1969).

Where deficiency of vitamin B₁₂, folic acid or iron, exist administration of these agents will produce an adequate therapeutic response. Because of the high incidence of vitamin B₁₂ malabsorption this is always better given parenterally, however orally administered folic acid and ferrous sulphate, in therapeutic doses, are readily absorbed (Gardiner, 1958; Baker and Mathan, 1968c). The effects of vitamin B₁₂ and folic acid administration are most obvious on the haemopoietic system but they will also cure glossitis, improve the appetite, and bring about a marked increase in the sense of well being. Swanson, Wheby and Bayless (1966) have also shown that these vitamins will produce some changes in intestinal morphology but abnormalities remain despite prolonged therapy.

At times, the administration of tetracycline to anaemic patients may induce a haematological remission. This is probably due to several factors such as the folate content of the tetracycline, improved absorption of folate following antibiotic therapy (Klipstein,
Potic Acid

The effect of vitamin \( B_2 \) and folic acid administration on intestinal function and on the course of the disease is much less clear than its effect on the haemopoietic system. Following folic acid therapy a number of investigators have noticed considerable improvement in alimentary function with decrease in diarrhoea and, in a proportion of cases, a reduction or disappearance of steatorrhoea and improvement in xylose absorption and biopsy findings (Spies, 1946; Lopez et al., 1946; Suarez, Spies and Suarez, 1947; Milanes et al., 1948; Gardner, 1956; Sheehy et al., 1962; Frazer, Schneider and Hayward, 1963; Klipstein, 1964a; Webb and Simpson, 1966). This improvement has occurred, in some cases, within a few days of starting therapy, while in others it has only occurred after months or years. Since many of these studies have been performed without the use of adequate control subjects, it is difficult to be certain that the improvement observed was definitely related to the folate therapy. Other investigators have found little or no effect of folic acid therapy on the steatorrhoea or the course of the disease (Ferguson and Calder, 1948; Woodruff, 1950; Baker, 1957; Rodriguez-Molina, Cancio and Arenjo, 1960; Baker and Mathan, 1966b; Mathan et al., 1968). The apparent variations in response to folate therapy in different centres may reflect differences in the aetiology of the sprue syndrome.

Antibiotics

Prontosil (Rogers, 1938) and sulphonamides (Elder, 1947; Walters, 1947; Stefanini, 1940) were found to produce some clinical improvement in subjects with sprue. French, Gaddie and Smith (1956) found marked improvement in the general condition and cessation of steatorrhoea in seven subjects following successive five day courses of sulphonamide, tetracycline and chloramphenicol. Clinical and biochemical improvement following antibiotics given for one to four weeks has also been noted by Klipstein (1964a), Klipstein, Schenk and Samloff (1966), O’Brien and England (1966), Jecsehboy et al. (1966b) and O’Brien (1968b).

However, not all patients respond to antibiotics. Sheehy and Pérez-Santiago (1961) treated 12 patients for two weeks with tetracycline and chloramphenicol. The steatorrhoea was reduced in only half of them and in none of six patients studied was vitamin
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B₄ absorption improved. Chuttani, Karthuri and Misra (1968) found that only about one-third of patients improved with sulphonamides or antibiotics. In South India half the patients treated with antibiotics for two to three weeks show some improvement in steatorrhoea but in only about one-fifth of them does the stool fat excretion return to normal and stay normal (Baker and Mathan, 1969).

There are two reports of long term antibiotic treatment. Klipstein (1964a) treated two patients with tetracycline for a number of months (14 and 25) and found some improvement in intestinal function though neither patient had returned to normal. Guerra, Whely and Bayless (1965) treated 17 patients with tetracycline for a period of six months, or more, and found marked clinical biochemical and histological improvement in nearly all. Nine of these were subjects who had previously been treated for months or years with vitamin B₄ and folic acid without improvement. Further controlled studies of prolonged tetracycline therapy should be undertaken.

Whether the different responses to antibiotics indicate differences in aetiology, or merely a difference in some secondary factor such as the degree and character of bacterial colonization of the intestine, remains to be determined.

AETIOLOGY

The aetiology of tropical sprue is still unknown. Any hypothesis regarding its aetiology must take into account the known facts about the syndrome such as its geographical distribution, its occurrence in endemic and epidemic forms, the available epidemiological data, and the curious fact that the disease may apparently first manifest itself many years after leaving the tropics (Booth and Mollin, 1964; Mollin, 1968).

Initiating Factors

From biochemical and histological studies, the initial lesion appears to be damaging to the intestinal epithelial cells, but the nature of the damaging 'agent' is unknown. Various possible 'agents' have been suggested such as a toxic factor in the food, a dietary deficiency, or a bacterial or viral infection. It might be thought that anything which damages the intestinal mucosa in a susceptible population could initiate sprue. However, studies of epidemics of diarrhoea have shown that this is not the case and
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that there is at least some specificity in the nature of the damaging 'agent' (Mathan and Baker, 1968).

Wheat and rye gluten are known to be responsible for producing the malabsorptive state associated with coeliac disease (Dicine, 1950). Coeliac disease occurs in the tropics (Baker et al., 1962; Miara, Kaushuri and Chattani, 1966; Walia et al., 1966) but sensitivity to wheat gluten cannot be the cause of tropical sprue as it occurs even in those who do not eat wheat or rye (Baker et al., 1962). Some cases of sprue are reported to improve on a gluten free diet and to deteriorate on reintroduction of gluten (Bayless, 1964). Whether such patients are subjects with tropical sprue with acquired sensitivity to gluten, or whether they are in reality cases of coeliac disease in the tropics, is not clear. French (1955) postulated rancid fats as a possible aetiopathological factor, but there is no evidence for this. Studies of epidemic sprue have so far failed to elicit any evidence in favour of a toxin (Baker, Mathan and Joseph, 1963; Mathan and Baker, 1968).

The frequent occurrence of severe deficiency states in patients with sprue has led to the suggestion that it is primarily a deficiency disease (Walters, 1947; Ayrey, 1948) but there is at present no evidence to support this. Since sprue can occur in well fed people with no evident nutritional deficiency, and since the incidence of deficiency states increases with increasing duration of illness (O'Brien, 1968; Baker and Mathan, 1969) it is more probable that the deficiencies are the result of the disease rather than vice versa (Gardner, 1956 and 1958; Baker, 1957; Sheehy et al., 1965). It is, however, possible that some deficiency state(s) may predispose to the occurrence of the disease though not in itself initiating it (Althausen, de Melendez and Pérez-Santiago, 1962; O'Brien and England, 1966; Baker and Mathan, 1968b). There is at present no evidence in favour of such a hypothesis which could best be proved by a prospective study among individuals at risk.

The question of the possible role of protein malnutrition in producing a form of malabsorption syndrome has recently been revived. Monkeys fed on a low protein or protein free diet develop chronic diarrhoea, atrophy of the intestines (Rao, 1942) and absorptive defects (Deo and Ramalingaswamy, 1964). However, in rams fed a protein free diet the intestine remains relatively unaffected (Hill et al., 1968). Jejunal biopsies in children with kwashiorkor have shown changes in villous architecture, increase in crypt: villus ratio and increased cellularity of the lamina propria (Burmarrd, 1965; Stanfield, Hutt and Tunnell, 1965). However, neither of these studies included comparable controls,
and Stanfield, Hutt and Tunnicliffe noted that the intestinal changes persisted despite apparent clinical and biochemical cure, suggesting that the intestinal changes noted may have been unrelated to kwashiorkor (Chacko et al., 1968). Brunner et al. (1966 and 1968) reported partial villous atrophy in children with kwashiorkor but not in children with marasmus. However, there is no evidence as to whether the changes noted by these authors in kwashiorkor were due to protein deficiency or to a superadded intestinal disease of differing aetiology.

In adults the situation is even more complex. Among prisoners of war and concentration camp victims, diarrhoea was very common (Edge, 1943; Burger, Sarstead and Drummond, 1945; Adelsberger, 1946) but it appears to have responded promptly to sulphonamides and/or vitamin B₁₂. Also, in seven prisoners of war from the Middle East, who had chronic diarrhoea, barium meal examinations were normal in all (Spillance, 1945) which is unlike the findings in malabsorption syndrome. In Japanese prisoner of war camps where the diet was very poor sprue was not noted (Gardner, 1958). Mayoral et al. (1967) on the other hand claim that severe protein malnutrition is capable of producing a mild to moderate malabsorption syndrome in adults. Unfortunately a number of criteria they employ for defining protein malnutrition do not help to distinguish between primary deficiency of intake and the secondary effects of tropical sprue. Further in their protein malnutrition group they include cases of strongyloidiasis which can cause intestinal damage and malabsorption (Steinmermann, 1967) and some of their subjects who were supposed to have responded to protein alone were given folic acid and all were given a high protein diet which must also have contained a fair amount of folic acid and other nutrients. Patients with severe hypo-albuminaemia due to a nephrotic syndrome do not usually have malabsorption (Jensen, Jarnum and Hansen, 1966), though it is possible that the metabolic defects of hypoalbuminaemia in the nephrotic syndrome may be different from those associated with defective protein intake. In summary it may be said that some of the animal experimental work suggests that protein deprivation may cause intestinal damage, but it has yet to be proven that protein deprivation per se, in man, produces a malabsorption syndrome.

The possibility of an infectious aetiology for sprue was postulated a number of years ago by Galloway (1905) and Bahr (1915). The occurrence of the disease in epidemics, the pattern of spread of the disease in a household (Mathan, Ignatius and Baker, 1966) and in a village (Mathan and Baker, 1968) and other circumstantial evidence
all point to a possible infective aetiology. Sabin (1956) has described a rectorrhoeic enteritis in children following a REO virus infection but this illness was of relatively short duration. So far attempts at identifying possible bacterial or viral agents have been unsuccessful both in endemic (Nadel and Gardner, 1956; Desai, Parekh and Jejeebhoy, 1966; Bayless, Guardiola-Roger and Wheby, 1966) and epidemic cases (Baker and Mathan, 1968b). It should, however, be noted that the techniques used in the search for an infective agent have been limited in their scope, and the negative results so far obtained may only mean that the techniques applied were inadequate.

**Perpetuating and Aggravating Factors**

Whatever the nature of the initial damage there seem to be certain predisposing, aggravating, or perpetuating factors (Baker and Mathan, 1968b). The pre-existing nutrition of the patients, as well as their nutrition during the course of the illness, has a profound effect on the rapidity with which they develop deficiency states (Stefanini, 1948; Gardner, 1958; Baker and Mathan, 1968b) and, therefore, markedly influences the mortality and morbidity of the disease.

In some cases there is circumstantial evidence in the form of the response to antibiotics, already discussed, and the increase in excretion of urinary indole derivatives (Haverback, Dyce and Thomas, 1966; O’Brien, 1968a; Baker and Mathan, 1968a), that bacteria in the small intestine may contribute to the malabsorption. Conventional bacteriological studies of the small intestinal flora have often failed to show any significant differences from normal controls (Nadel and Gardner, 1956; Rajan *et al.*, 1961; Desai *et al.*, 1966; Klopstein and Samloff, 1966; O’Brien, 1968a). However, the dominant organisms in the intestine are anaerobes (Eggerth and Gagnon, 1933) and in order to study adequately the intestinal flora specialized techniques are necessary (Drazer, 1967; Gorbach *et al.*, 1967). Application of these newer techniques should enable more information regarding the bacteriological flora and their role in sprue to be obtained.

**CONCLUSION**

Within the past decade great advances have been made in our understanding of the pathology and pathophysiology of the small intestine in general and of tropical sprue in particular. Nevertheless, there still remains a great deal to be learnt about intestinal structure.
and function in health and disease and continuing study of tropical sprue may be expected to help in the acquisition of this knowledge.

The major deficiency in our present understanding of tropical sprue is its unknown aetiology. There is some evidence to suggest that the condition as seen in different parts of the world, and even in the same area in different epidemics, may not be a single disease entity but a syndrome of multiple aetiology.

Until one or more of the initiating factors are positively identified all theories will remain interesting speculations and all attempts at categorizing cases in terms of the clinical picture, histological and biochemical lesions, response to treatment and prognosis, will be fraught with the greatest difficulty.

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