Gastrointestinal Disease

PATHOPHYSIOLOGY • DIAGNOSIS • MANAGEMENT

Second Edition

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Acute Stress Erosions and Ulceration
Tropical sprue is a syndrome of unknown cause. It should not be considered as a single disease entity. All residents of or visitors to tropical regions who have malabsorption of at least two unrelated substances, such as xylose and vitamin B12, and in whom no specific cause can be found for the malabsorption are considered to have tropical sprue. Histologic examination reveals jejunal mucosal abnormalities in the majority of such patients, but the absence of such abnormalities does not preclude the diagnosis. It must be emphasized that the many other diseases which give rise to malabsorption in temperate zones may also be found in the tropics, and it is essential to exclude these by careful evaluation before the diagnosis of tropical sprue is accepted in the individual patient.

HISTORY

A wasting disease associated with chronic diarrhea was known to the physicians of India from at least 600 B.C. In Charaka...
Epidemiology

Tropical sprue has a peculiar geographic distribution. It supposedly does not occur in Africa south of the Sahara. Although widely prevalent in the Caribbean, it has not been reported in Jamaica. These geographic differences are as yet unexplained. Much of the early literature implied that the disease was confined to Caucasians visiting the tropics. It is now recognized that the disease is prevalent in indigenous populations, and malabsorption and associated malnutrition are major public health problems in developing countries. As a result of the speed and availability of modern travel and large populations of emigrants in temperate zones, some patients with tropical sprue are being seen by physicians in nontropical areas.

Epidemic and endemic forms of the disease are recognized. This differentiation is only epidemiologic, because the clinical manifestations are identical. All age groups are affected, although the attack rate appears significantly higher in adults. Both sexes are equally affected. Accurate figures are not available regarding the prevalence of endemic tropical sprue in indigenous populations. A high prevalence of xylose malabsorption and of minor morphologic changes in the jejunal mucosa has been documented in asymptomatic subjects studied in several tropical areas. This pattern of abnormalities has been termed "tropical enteropathy." The relationship of this to tropical sprue is any, is not clear. Nearly two-thirds of a small number of asymptomatic subjects selected from a hospital population in Haiti were found to have malabsorption of xylose and vitamin B12. It is not certain that this reflects the prevalence of tropical sprue in the community. It has been estimated by studies carried out on a random sample from a rural population in southern India that three out of every 100 adults may have subclinical tropical sprue. The available data are incomplete, and the exact prevalence of tropical sprue is not known.

Several large epidemics of tropical sprue have been reported from southern India. In one large epidemic during 1960 to 1962, it was estimated that 100,000 people were affected and at least 30,000 of them died. Such epidemics occur without any seasonal pattern, and in any one affected village new cases continue to appear over a period of several months. The overall attack rate may be as high as 40 per 100. Diet, type and source of drinking water, and environmental factors such as housing and sanitation did not appear to influence the occurrence of these epidemics. The isolation rate of enteropathogenic bacteria from those affected in the epidemics was the same as that in control populations, and no etiologic role could be ascribed to bacteria. Virologic studies using limited techniques have also been unsuccessful in isolating an etiologic agent. However, several epidemiologic factors suggest that these epidemics are due to an infectious agent. The strongest evidence for this hypothesis is that in any given epidemic adults are symptomatically affected earlier than young children. When a village that has been affected in an epidemic is kept under surveillance, the age distribution of new cases changes, with younger age groups being most affected as the epidemic progresses.

Epidemic tropical sprue was also a major problem in the Burma theater during the Second World War. It apparently accounted for at least as many repatriations to Britain as the casualties of war!
Pathology

Intestinal mucosal pathology was first illustrated in autopsy material over 50 years ago.4 These findings were later confirmed in material obtained at laparotomy. The wide availability of peroral biopsy instruments in the last 15 years has made it possible to undertake a systematic study of the intestinal mucosal morphology.

Interpretation of the mucosal pathology in patients is complicated by the presence of changes, in jejunal mucosal biopsies obtained from asymptomatic residents of the tropics, that would be considered abnormal when compared with “normal” biopsies in temperate zones. These changes consist of broadening and thickening of villi, an increase in the height of the crypts, and increased infiltration of the lamina propria and the epithelium with mononuclear cells (Fig. 68-1). Up to 40 per cent of such normal control subjects have minimal malabsorption, especially of xylose. On the other hand, only shortening of villi in a patient with biphasic malabsorption caused by tropical sprue is shown in Figure 68-2. However, the morphologic changes do not correlate well with the severity of the absorptive abnormalities and may be present in subjects without evidence of malabsorption. These morphologic changes in asymptomatic subjects have been designated tropical jejunitis, but their pathogenesis or functional significance is not known. These geographic differences in what should be considered “normal” are important when evaluating biopsies from individual patients.

In patients with established tropical sprue, the overall thickness of the mucosa is usually within normal limits, but the villi are shortened and the crypt height is increased (Fig. 68-3). The surface epithelial cells may show severe abnormalities; cells vary in size and shape from low columnar to cuboidal, and pseudostratification may be present (Fig. 68-4). In general, surface cell alterations are much less severe than those seen in patients with untreated celiac sprue. The basement membrane is usually thickened, and fine droplets of fat may be present in both the basement membrane and surface epithelial cells even after 12 to 18 hours of fasting. The most consistent abnormality is a marked increase in the mononuclear infiltration between surface epithelial cells and in the

![Image 68-1. Jejunal mucosal biopsy from an asymptomatic Southern Indian adult. The thickness of the crypts is increased, and the number of lymphocytes in the lamina propria and the epithelium is increased. The subject was normal for 2nd vitamin B12 absorption but a slightly decreased absorption of D-xylose. X100.](image-url)
lamina propria. These changes, although present in the majority of patients, are not specific for tropical sprue and resemble changes seen in a wide variety of pathologic states, including mild celiac sprue and certain parasitic infestations. Occasional patients with clinical evidence of tropical sprue have a normal or near-normal appearing jejunal mucosa on biopsy. Ultrastructural changes have been demonstrated in intestinal epithelial cells both in the crypts and in the surface epithelium. These changes are characterized by abnormalities of the microvilli, marked increase in lysosomes, increase in intracellular fat, and degenerative changes in rough endoplasmic reticulum and mitochondria. Degenerating cells, taking up a pale stain similar to cells in

Figure 68-2. Biopsy of the duodenojejunal mucosa from a patient with a milder lesion of tropical sprue. Villi, structure is preserved, but the villi are shorter than normal. The cellularity of the lamina propria is increased, and the epithelium is infiltrated with mononuclear cells. × 95.

Figure 68-3. Jejunal mucosal biopsy from a patient with tropical sprue. The villi are reduced in length, with increase in the thickness of the crypts. Some of the surface epithelial cells are flattened. There is a marked increase in the number of lymphocytes in the lamina propria and epithelium. × 100.

Figure 68-4. Biopsy of the biopsy closely resembles that in m the zone of ext

Figure 68-5. El of crypt epithelium. Jejunal biopsy of a bi of sprue. A pale cell with normal-lookin cells seen in section.
the zone of extrusion at the tips of villi, are found on the sides of villi and in the crypts (Fig. 68-5). The specificity and significance of these pale-staining degenerating cells are not understood, although they are probably an index of mucosal damage. The basement membrane region shows an amorphous deposit with many collagen fibers and fat droplets.

The gastric mucosa is often characterized by atrophy and inflammation. Moreover, hypochlorhydria and diminished secretion of intrinsic factor are present in many patients.

ETIOLOGY AND PATHOGENESIS

Epidemiologic and clinical evidence suggests that the syndrome of tropical sprue is the result of damage to the intestinal mucosa.
The cause of this damage to the mucosa is not known, but the following have been suggested: (1) that it results from a nutritional deficiency; (2) that it is due to a dietary toxin, or (3) that it is due to a transmissible infectious organism.

The high prevalence of severe deficiency states in patients with chronic tropical sprue has led to the suggestion that it is primarily a deficiency disease. At present there is no evidence to support this claim. Tropical sprue afflicts people with no evident nutritional deficiency. The prevalence and extent of nutritional deficiency states in a group of patients increase with increasing duration of illness, suggesting that these deficiencies are secondary to persistent malabsorption. The correction of deficiency states in patients with chronic sprue, although accompanied by improved general status, is not paralleled by an improvement of the intestinal absorptive capacity. Severe protein deficiency can damage the intestinal mucosa in experimental animals, but there is as yet no evidence that a similar situation occurs in adult humans. It is, however, possible that antecedent deficiency states may increase susceptibility to the damaging agent.

Occasional cases of celiac sprue have been reported from the tropics. However, tropical sprue is not improved by the institution of a gluten-free diet. Epidemiologic studies so far have not revealed any evidence in favor of a dietary toxin as an etiologic agent.

An infectious cause for tropical sprue was suggested as early as 1905, but no causal agent, bacterial, viral, or parasitic, has so far been identified. The evidence in favor of an infectious hypothesis is primarily epidemiologic. That patients develop their initial symptoms within a week of arriving in endemic areas suggests a brief incubation period. The apparent first appearance of the disease in individuals many years after leaving endemic areas suggests that factors similar to those noted in herpetic infection may play a part. The geographic differences could be explained on the basis of the prevalence of the agent or its dependence on environmental factors.

Predisposing factors may enhance susceptibility of the mucosa to the damage of the agent, which other factors may perpetuate, producing chronic malabsorption. Nutritional deficiency, especially lack of folic acid and vitamin B12, may retard healing of the lesion. Bacterial colonization of the small bowel has been demonstrated in some patients with tropical sprue. These bacteria may perpetuate malabsorption by the production of toxins that interfere with fluid and electrolyte fluxes across the mucosa. Coliform organisms isolated from midjejunum aspirates of 10 of 11 patients with tropical sprue studied in Puerto Rico produced an enterotoxin that stimulated fluid secretion in rabbit ileal loops. The toxin-producing bacteria also produced alcohol, which could be identified in the jejunal aspirate. Such toxin-producing bacteria may be related to the pathogenesis of malabsorption in these patients, but the primary factors that lead to colonization of the jejunum are not understood.

However, several patients have been shown to have normal bacterial flora, and even when abnormal colonization is present, no consistent pattern of microbial flora has been observed. Therefore it appears at present that bacterial colonization of the small bowel, when it occurs, is probably a secondary phenomenon, although it may play a part in the perpetuation of malabsorption.

**CLINICAL FEATURES**

**HISTORY**

The majority of patients complain of diarrhea, anorexia, and abdominal distention. In addition, the symptoms associated with nutritional deficiency, especially pallor, weakness, sore tongue and mouth, edema of the legs, and night blindness, are also present. A few patients may present with only isolated sequelae of malabsorption, such as anemia, without any antecedent history of significant diarrhea.

Patients affected in epidemics and even some of the endemic patients can often name the day and sometimes the hour of onset of their symptoms. A day or two of fever, malaise, and anorexia precede the onset of diarrhea in about a quarter of such individuals. The further course of the illness can be divided into two stages. In the first stage the symptoms are predominantly gastrointestinal, varying among patients. In more than half, the stools are watery at the onset and become less fluid with the passage of time. Flecks of blood are

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PHY:
Some mucus are noted in the stools of a few patients. Nausea and vomiting, although present during the early course of the disease, tend to disappear, whereas anorexia and abdominal distention persist. In the early stage of the illness some loss of weight is common, but abdominal pain is usually not present. The second stage is characterized by the development of nutritional sequelae of persistent malabsorption in addition to continued diarrhea. The diarrhea may persist throughout the course of the illness in some patients, but, more characteristically, the course is marked with repeated remissions and relapses. Abdominal pain, usually mild, is noted by over half the patients at some point during the course of the illness. Very likely, however, the patient has severe colicky pain which can suggest intestinal obstruction when associated with vomiting and hyperactive bowel sounds. Anorexia, abdominal distention and marked weight loss usually persist. The classic picture of tropical sprue in earlier textbooks described multiple nutritional deficiencies in the patient at this stage. The time required for such deficiencies to develop and their severity are dependent on the antecedent nutrition of the patient. Night blindness, glossitis, stomatitis, xerophthalmia, cutaneous and mucosal hyperpigmentation, pallor, and edema are the major symptoms of the deficiencies. Hypocalcemic tetany is rare.

PHYSICAL FINDINGS

In about half the patients there may be some abdominal distention, and when the abdominal wall is thin, peristalsis is visible. The bowel sounds are usually loud and very regular. When the diarrhea is severe, patients may present with dehydration, acidoses, and shock.

In the chronically ill patient, the findings of abdominal examination are still minimal. Minimal hepatomegaly is present in less than 10 per cent of patients. However, at this time the signs of nutritional deficiency dominate the picture. Pallor and mild icterus are found in patients with severe megaloblastic anemia. Over half the patients have glossitis and/or stomatitis. Cutaneous hyperpigmentation associated with vitamin B_{12} or folate deficiency is noted in one-third of the patients. The characteristic distribution of this hyperpigmentation is on the dorsum of the hands, especially over the metacarpophalangeal and the interphalangeal joints, the terminal phalanges, and sometimes the nail beds. The pigmentation may be present in other parts of the skin or in the mucous membrane. Appropriate correction of the nutritional deficiencies leads to the rapid clearing of the hyperpigmentation. Edema of the dependent portions of the body is present in about one-third of patients and is associated with hypoproteinemia. Exfoliation of the skin and thin disfigured hair associated with protein deficiency are found in only a very small number of patients.

On proctosigmoidoscopic examination the rectal mucosa appears normal in over half the patients, but in others some mucosal erythema and edema may be present. Internal hemorrhoids are present in a significant number of patients with chronic diarrhea and may produce bloody streaking of the stool.

LABORATORY FINDINGS

In each patient suspected of having tropical sprue the absorptive capacity of intestine should be evaluated, and the consequences of the observed malabsorption should be assessed.

Stool Examination. The stools are usually liquid or semi-formed, and the 24-hour stool volume is increased. The prevalence of intestinal parasites such as E. histolytica, G. lamblia, and S. stercoralis in patients with tropical sprue is the same as in the general population. Surveys in tropical regions have shown that pathogenic bacteria such as Salmonella, Shigella and enteropathogenic E. coli can be isolated from the stool in about 10 per cent of the adult population. The isolation rates of similar bacteria from patients with tropical sprue is no higher. Capillaria philippinensis is an important pathogen associated with malabsorption in the Pacific region.

Tests of Intestinal Absorption. The absorption of water, fat, protein, carbohydrates, vitamin B_{12}, folic acid, polyglutamates, vitamin A, and several other substances as measured by perfusion, balance studies, and tolerance tests have been found to be reduced in clinically ill patients. However, in the clinical situation, the testing of fat, xylene, and vitamin B_{12} absorption is adequate. Malabsorption of at least two of
these substances should be present for the diagnosis of tropical sprue to be considered.

Steatorrhea is reflected by the presence of excessive numbers of fat droplets on a stool smear stained with Sudan III, a useful test for screening patients. Chemical determinations have shown that over 90 per cent of patients have steatorrhea, but the amount of fat in the stool is seldom as high as in clinically obvious exocrine pancreatic insufficiency. Since at least 40 per cent of the asymptomatic adults in the tropics have xylose malabsorption, its presence does not establish the diagnosis of tropical sprue, even though xylose malabsorption is present in 99 per cent of patients. In the rare patient who has xylose absorption may be normal. The prevalence of vitamin B12 malabsorption shows some geographic differences. In Caucasians with tropical sprue and in native populations in the Caribbean area, over 90 per cent of patients have vitamin B12 malabsorption, whereas in southern India only about 60 per cent appear to have this defect. In the majority of patients the absorption of vitamin B12 is not improved when additional intrinsic factor is given. In a small number of patients vitamin B12 malabsorption improves or becomes normal when intrinsic factor is added to the test dose.

Assessment of Nutritional Status. Dehydration associated with hypokalemia, hyponatremia, and acidosis is a frequent complication of diarrhea. Although severe dehydration is associated with hemococoncentration, hypernatremia is seldom found in these patients. The hematologic sequelae of malabsorption are frequent and led to the disease being considered of primary hematologic origin for many years. Anemia may be the result of different degrees of iron, folic acid, and vitamin B12 deficiency. The relative importance of vitamin B12 and/or folate deficiency in the pathogenesis of megaloblastic anemia is present in over 60 per cent of the patients, differs according to the nutritional background and the pattern of malabsorption.

Nutritional iron deficiency is widespread in the tropics, and it is difficult to assess the additional role malabsorption in tropical sprue plays in the production of iron deficiency anemia. In temperate zones iron deficiency anemia is less common than megaloblastic anemia, unlike the situation in celiac sprue.

A prolonged prothrombin time correctable by parenteral vitamin K is found in a large number of patients. The prevalence of hypo-protidinemia correlates well with the duration of illness. In addition to malabsorption, protein-losing enteropathy has been shown to play a role in the pathogenesis of this deficiency (see pp. 354 to 363).

**RADIOLOGY**

Dilatation of loops of small intestine, a coarse mucosal pattern with “transverse barring” or a “cog wheel” appearance, slow peristalsis with disordered forward propulsion, and flocculation of stabilized barium preparations are the major features that have been described (Fig. 68-6). When large series of patients are studied, a correlation between the degree of abnormality found radiologically and the degree of malabsorption is noted. However, these abnormalities are nonspecific in nature, and in the individual patient the importance of the radiologic

![Figure 68-6. Barium meal with follow-through. The upper loops of jejunum are dilated. Edema of primary mucosal folds produces a coarse mucosal pattern. Ninety minutes after the meal, the head of the barium has progressed very little, indicating slow peristalsis.](image-url)
Examination is to exclude anatomic abnormalities which can lead to secondary malabsorption.

**INTESTINAL BIOPSY**

The morphologic changes have been described under Pathology. These changes are nonspecific and are not by themselves diagnostic of tropical sprue. In a large series of patients, there was significant correlation between the severity of malabsorption and the degree of mucosal abnormality as measured by several parameters such as villous architecture, height, and degree of infiltration of the epithelium by mononuclears. The chief reason for examining jejunal biopsy specimens is in helping to exclude diseases with specific biopsy findings such as giardiasis, Whipple's disease, and lymphoma.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

In the tropics the diagnosis of tropical sprue should be suspected in all patients with chronic diarrhea, malnutrition, or megaloblastic anemia. A history of having visited endemic areas is necessary before this diagnosis is entertained in temperate zones. The confirmation of the diagnosis requires establishing the presence of malabsorption and excluding the many other diseases which can give rise to intestinal malabsorption.

Acute bacillary dysentery or nonspecific diarrheal illnesses should be considered as important in the differential diagnosis in early cases in epidemic situations. The early detection of epidemics of tropical sprue is important because of the high mortality when treatment is not instituted. The diagnosis can be suspected on epidemiologic and clinical grounds such as the higher attack rate in adults early in the course of the epidemic and the absence of the recognizable patterns of common diarrheal epidemics. Bacteriologic and parasitologic surveys should be done to exclude these causes of diarrhea. Although patients affected with epidemic tropical sprue have malabsorption even in the first week of illness, the lack of suitable tests of absorption for use in field situations makes it necessary to admit to hospital some of those affected for detailed study before the diagnosis can be confirmed.

In a patient presenting with chronic diarrhea the diagnostic problems are different. Parasitic diseases such as amebiasis can be diagnosed easily by the detection of the amebae or by the presence of appropriate serum antibodies. Parasitic diseases that are of particular importance because they are associated with malabsorption are giardiasis, strongyloidiasis, and capillariaisis. These parasites are present in the upper small bowel, and examination of aspirates of jejunal juice or of jejunal biopsy specimens may be necessary to exclude them. Rapid improvement following treatment of parasitic infestations helps exclude the diagnosis of tropical sprue (see pp. 1154 to 1180).

Tuberculosis of the intestines with stricture formation is still probably a most important differential diagnosis in many areas of the tropics. Careful radiologic examination of the small bowel is essential in excluding this and other causes of the stagnant bowel syndrome with bacterial overgrowth (see pp. 1094 to 1102).

With the introduction of wheat to many traditionally rice-eating populations of the tropics, celiac sprue has become an important differential diagnosis (Table 68–1).

When a history of eating wheat is obtained, failure of response to a gluten-free diet is essential before celiac sprue can be excluded. Intestinal biopsy is of particular importance in excluding conditions such as diffuse infiltrative lymphoma and Whipple's disease.

Primary disaccharidase deficiency can be differentiated from tropical sprue by low mucosal disaccharide levels in the face of a morphologically normal mucosa.

**TREATMENT**

The treatment of tropical sprue consists of controlling diarrhea, correcting nutritional deficiencies, and using measures aimed at curing the intestinal lesion.

**Control of Diarrhea.** This can usually be achieved by simple measures, using Lomotil (2.5 to 5.0 mg, three or four times a day) or mixtures containing belladonna and opium, peregoric, and bismuth salicylate. The exact medication and dosage must be adjusted to the individual patient. Controlling diarrhea
### Table 68-1. COMPARISON OF TROPICAL SPRAE AND CELIAC SPRAE

<table>
<thead>
<tr>
<th></th>
<th>Tropical Sprue</th>
<th>Celiac Sprue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Tropical climate, especially Caribbean, Indian subcontinent and S.E. Asia;</td>
<td>Temperate zone; increased incidence in families and in blood group O Rh positive</td>
</tr>
<tr>
<td></td>
<td>epidemics</td>
<td></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>? Deficiency state; ? Infection</td>
<td>Sensitivity to gluten fraction of gluten</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Usually partial villous atrophy; surface epithelial cells less affected;</td>
<td>Usually total villous atrophy; surface epithelial cells more affected;</td>
</tr>
<tr>
<td></td>
<td>correlation with degree of malabsorption</td>
<td>correlation with degree of malabsorption</td>
</tr>
<tr>
<td></td>
<td>Often poor</td>
<td>Often poor</td>
</tr>
<tr>
<td><strong>Extent of disease</strong></td>
<td>Uniform small bowel involvement</td>
<td>Proximal small bowel most involved; distal small bowel less involved or normal</td>
</tr>
<tr>
<td><strong>Clinical and laboratory findings</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Macrocytic anemia</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>B₁₂ deficiency</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Folic acid deficiency</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Signs and symptoms of</td>
<td>Prominent</td>
<td>Prominent</td>
</tr>
<tr>
<td>anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B complex</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypokalemia</td>
<td>Uncommon</td>
<td>Usually present (variable)</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Urinary 5HIAA</td>
<td>? Normal</td>
<td>Usually slightly elevated</td>
</tr>
<tr>
<td>Treatment</td>
<td>Vitamin B₁₂, folic acid, antibiotics</td>
<td>Gluten-free diet; corticosteroids in refractory cases</td>
</tr>
<tr>
<td>Response to therapy</td>
<td>Generally good, but may relapse if drugs not taken long enough</td>
<td>Usually excellent if diet remains free of gluten</td>
</tr>
</tbody>
</table>

*Compiled by Dr. Stephen Herr.

may reduce the occurrence of fluid and electrolyte abnormalities, but it is unlikely that these measures have any effect on shortening the duration or the course of the disease. 

**Correction of Deficiency States.** Dehydration, acidosis, hypokalemia, and hypovolemia associated with severe diarrhea can often lead to death, especially in the tropics. Severe fluid and electrolyte deficiencies must be corrected by parenteral supplementation. In the majority of cases if the diarrhea can be controlled and an adequate intake of a simple solution containing the essential electrolytes is maintained, major problems do not arise. By using these measures in epidemic situations, the mortality has been reduced to less than one per 100 (see p. 1083).

Specific deficiency states such as megaloblastic anemia and iron deficiency should be appropriately treated. In the individual patient the determination of the hematologic parameters should determine therapy. Orally administered iron and folic acid appear to be adequately absorbed. Vitamin B₁₂ should be given parenterally, because malabsorption of this substance is frequent.

The appropriate diet for these patients has been the subject of debate for many years. Many ingeniously devised diets have had their proponents in the past. None of them have been shown to be of particular value. A diet ensuring at least 3000 calories and about 1 g of protein per kilogram body weight is adequate. In the individual patient any specific item of diet that seems to worsen his symptoms should be avoided. The ideal diet, of course, is one on which the patient gains weight. The majority of patients gain weight even when malabsorption is persistent.

**Attempts at Specific Therapy.** Since the agent that damages the mucosa is not known, no rational method of therapy is available. Vitamin B₁₂, folic acid, and antibiotics have all been credited with altering the course of the disease. It must be emphasized, how-

The effect of the administration of the antibiotics on the course of the disease is not certain. A sho bedside test for the detection of the pathogenic organism is often helpful. If a specific organism is isolated from the gut, antibiotic therapy may be aimed at the specific organism. If the patient fails to respond to antibiotic therapy, a change in the antibiotic should be considered.
Tropical Sprue

It used to be considered that repatriation to temperate zones was necessary for those affected in the tropics. More recently, the study of epidemics in India has shown that a large majority of those affected appear to recover spontaneously even in endemic zones, but sufficient data are not available to fully characterize the natural history of the disease. Longer periods of follow-up of patients treated with various regimens are necessary before prognosis can be accurately determined. It is, however, clear that if the diarrhea is controlled and nutrition is ensured, patients can lead a normal life.

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