

A Perspective on Tropical Sprue

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A diagnosis of tropical sprue, an infrequent affliction of inhabitants and travelers in tropical regions, should be considered in patients with a compatible history, malabsorption, and chronic diarrhea. It can occur in either endemic or epidemic form and can be preceded by acute gastroenteritis. The cause of tropical sprue is still unknown, although most data support an infectious etiology. Therapeutic experience is greatest with folic acid and tetracycline. Most patients can be expected to recover with proper nutritional support, although relapses and slow responses occur.

Introduction

Although tropical sprue may have been described as long ago as the later years of the Roman Empire, it remained subsequently unrecognized until the 18th century, when Hillary published a short treatise on diarrheal illnesses in the West Indies [1]. Manson introduced the term "sprue" in his 1880 work on diarrheal diseases in the Far East. Etymologically, "sprue" derives from the Dutch *sprouw*, used to describe an outbreak of celiac disease in the Netherlands in the 1600s and subsequently applied by Dutch physicians to what appeared to be a similar disease in the Dutch East Indies colonial empire. In succeeding years, sprue was recognized in India, Ceylon (now Sri Lanka), and Puerto Rico, although in many instances the diagnosis was confused with other causes of diarrhea and malabsorption. Ashford, a US Army surgeon stationed in Puerto Rico during the Spanish-American war, demonstrated hookworm infection (*Necator americanus*) to be the cause of epidemic macrocytic anemia. It is likely, however, that his most debilitated patients also suffered from tropical sprue, perhaps explaining the unusual severity of disease in his case series [2]. Between 1943 and 1945, as many as 10% of British soldiers evacuated from the China-Burma-India theater were diagnosed with tropical sprue. Since World War II, tropical sprue has been frequently recognized as a cause of persistent diarrhea, weight loss, and malabsorption among residents and travelers in the tropics. However, many aspects of this illness remain puzzling today.

Accurate characterization of this disease is further hampered by controversies in case definitions. The broad definition suggested by Klipstein and Baker [3], "malabsorption of two or more substances in people from the tropics when other known causes have been excluded," has since been refined. Klipstein [4••] now characterizes tropical sprue as jejunal morphologic abnormalities accompanied by malabsorption of two distinct substances, and having the following distinct features: 1) gastrointestinal symptoms; 2) relentless worsening unless treatment is instituted; 3) nutritional deficiency in all patients with advanced disease, regardless of dietary intake; 4) failure of the morphologic abnormalities to improve with emigration to a temperate zone; and 5) consistent response to folic acid and/or tetracycline.

Cook [5] suggests that an additional criterion be added: the presence of bacterial overgrowth in the jejunum. However, Indian researchers have not consistently found a greater incidence of bacterial colonization among patients with tropical sprue than among control subjects. In addition, response to folic acid and tetracycline is not necessarily diagnostic in the Indian experience. (*ie*, not all patients with tropical sprue respond quickly to these therapies). It should also be noted that, in the Indian experience, spontaneous remissions do occur, casting into some doubt the necessity of "relentless worsening" as a diagnostic criterion. Finally, although an episode of acute gastroenteritis is thought to precede most cases of tropical sprue, this is not reported by all patients; in a case series of 27 North American patients residing in Puerto Rico, five described a gradual onset of symptoms without acute gastroenteritis [6•].

The amended case definition of Klipstein [4••] helped differentiate between tropical sprue and the entity of subclinical tropical malabsorption (also called tropical enteropathy), a benign condition sometimes seen among both expatriates and natives in the tropics. Like tropical sprue, tropical malabsorption is characterized by jejunal morphologic abnormalities, and in some series it is also associated with bacterial overgrowth of the small intestine; however, tropical malabsorption does not have the clinical signs and symptoms of tropical sprue [7]. It is not entirely clear whether sprue is simply the most severe manifestation of tropical malabsorption, a syndrome for which tropical malabsorption is a predisposing factor, or an altogether unrelated illness [8]. Cook's preferred nomenclature, "post-infective tropical malabsorption," has been criticized as implying too much about what is currently

known of the cause of tropical sprue and has not gained widespread use [9].

Geographic Distribution and Epidemiology

Tropical sprue is endemic in Puerto Rico, Cuba, the Dominican Republic, and Haiti but is not reported in Jamaica or the other West Indies. It has been reported in Central America, Venezuela, Colombia, and parts of Mexico. In the Far East, tropical sprue has been reported in the Indian subcontinent, Myanmar, Malaysia, Vietnam, Indonesia, and the Philippines. It has been infrequently reported in the Middle East as well as in Africa. Additionally, Cooke *et al.* [10] described, among patients in England, an entity of small bowel malabsorptive disease, folic acid deficiency, and megaloblastic anemia, which Cooke named “temperate sprue”; this disease responded to folic acid supplementation. The relatively restricted geographic range of tropical sprue has been advanced historically as strong evidence of an underlying infectious cause.

The incidence of sprue appears to vary seasonally, with the highest in the winter months in some geographic areas [11]. One unexplained aspect of tropical sprue is its oft-cited predilection for expatriates (*ie*, colonists, soldiers, and travelers). Whether this reflects genetic and environmental differences among various populations in the tropics or selection/referral bias (based on availability of medical care) is unclear. Numerous authors have observed that tropical sprue is rarely if ever seen in the English-speaking islands of the Caribbean (despite Hillary’s original description of the disease in Barbados), although it is endemic in Haiti, Puerto Rico, and the Dominican Republic; the reason for this is unknown.

Tropical sprue has been described as occurring in both acute and chronic forms, and as having both an endemic and an epidemic pattern. Most cases seem to occur after a residency in the tropics lasting from months to years, although sprue can develop even after a relatively brief stay [12]. Hillary’s account of tropical sprue on Barbados includes a description of an epidemic of the disease. Epidemic tropical sprue has been best characterized in southern India, but also in Burma, Bangladesh, and the Philippines, usually as a sequela to an outbreak of infectious diarrhea. In the Indian epidemics described by Baker and Mathan [13•], over 100,000 people were affected. In households afflicted by tropical sprue, cases frequently followed each other by an interval of several weeks. Interestingly, in this series the Brahmin caste was almost entirely spared, despite the fact that there was no segregation between them and the other residents in the villages that were studied. Economic status did not seem to be significantly associated with risk for disease. Baker and Mathan [13•] report a fatality rate of nearly 30% in their study; and they speculate that the relatively poor nutritional status of the villagers may have worsened their

overall prognosis. They note, however, that the Harijan (“untouchable”) villagers, who had the worst diet, did not have a notably worse prognosis than the other patients. Household outbreaks have been reported in India as well [14]. Even in well-nourished populations, the attack rate of acute tropical sprue can be surprisingly high. One study reported an attack rate of 8% in a population of North American military personnel and their families, despite access to an adequate diet and medical care [6•].

Although numerous attempts have been made to link heredity with a predisposition for tropical sprue, the evidence is inconclusive [15]. A high-fat diet may be a risk factor. During World War II, British troops in the India–Burma campaign, as well as Italian prisoners of war in India, were frequently afflicted by tropical sprue; however, it was rare among American soldiers in the Pacific theater. This may reflect the relatively high-fat rations issued to British soldiers. Furthermore, certain types of cooking fats may predispose the jejunum to colonization with enteric gram-negative bacteria. Seasonal variations in diet may in part explain the temporal changes in disease incidence in Puerto Rico, where pork fat (rich in long-chain unsaturated fatty acids) is commonly used for cooking during the Christmas season. Cultural dietary differences may also partially explain the geographic distribution of tropical sprue [16]. Pre-existing folic acid deficiency is associated with a worse prognosis.

Some researchers have theorized that empiric treatment of traveler’s diarrhea may prevent the development of tropical sprue. Likewise, improved sanitation may decrease the incidence and prevalence of tropical sprue in a given population. Interestingly, children have a decreased risk of developing tropical sprue, despite their known propensity for gastrointestinal infections in general. In those children diagnosed with tropical sprue, the disease seems to be similar in all respects to that in adults [17]. The prognosis in children appears to be good if metabolic abnormalities and dehydration are rapidly addressed [18].

Pathogenesis

Despite aggressive investigation, researchers have never been able to identify a single pathogen responsible for the syndrome of tropical sprue. Indian researchers have reported the presence of coronavirus-like particles in jejunal biopsies and stool of patients with sprue; however, this was not found in all patients, and the finding has not been replicated in other studies [19•]. Nevertheless, there is strong circumstantial evidence of an infectious agent playing an important role. In particular, the fact that the disease can be acquired after travel to the tropics, that it can be demonstrated to occur in an epidemiologic pattern consistent with person-to-person spread, and that it responds to antibiotic therapy are all consistent with an infectious process. It is noteworthy, however, that most therapeutic trials in tropical sprue have used tetracyclines

as the antibiotic of choice. The possibility that the efficacy of tetracyclines is related to their recognized anti-inflammatory effect, rather than to direct antimicrobial action, has not been adequately addressed.

Although efforts to link tropical sprue to specific microorganisms have been unsuccessful, considerable evidence supports a relationship between tropical sprue and persistent bacterial colonization of the jejunum. Unlike the healthy host, patients with tropical sprue frequently have coliform colonization of the proximal small bowel [20]. Identified pathogens include *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. Other bacteria identified in the past include *Alcaligenes faecalis*, *E. aerogenes*, and *Hafnia* species. Although these are not cytotoxic or invasive organisms, they are capable of producing enterotoxins that stimulate fluid secretion when they are cultured in rabbit ileal loops [21]. This distinguishes tropical sprue from diseases caused by bacterial overgrowth, such as those seen in blind-loop syndromes, where the bacteria are usually obligate anaerobes and do not elaborate toxins. However, in at least some investigations, this relationship has not been confirmed; Indian researchers did not find that bacterial colonization of the jejunum was significantly more associated with tropical sprue in comparisons with control populations [22].

Fat malabsorption is a common finding in tropical sprue, but it may be as much a cause of the syndrome as an effect. Contrary to what one might expect, patients with tropical sprue tend to have prolonged small bowel transit times, when compared with healthy control subjects [23••]. Presumably, this is a result of fat malabsorption, which has been shown to retard intestinal peristalsis in experimental models. It is possible, therefore, that slowed small bowel transit time caused by fat malabsorption may prevent the clearance of pathogenic bacteria from the small bowel. Additionally, as noted previously, long-chain fatty acids may predispose patients to colonization of the small bowel by enteric bacteria by suppressing the growth of normal gram-positive commensal microflora. Unlike blind-loop syndromes, intraluminal bile salt deconjugation is not increased in patients with tropical sprue. Although the exact role of fat malabsorption remains undefined, it is noteworthy that steatorrhea is not universally found in patients with tropical sprue. Furthermore, increased small bowel transit time is not consistently reported [24].

The popularly accepted model of pathogenesis of tropical sprue, therefore, postulates that an acute or subacute episode of gastroenteritis leads to mucosal damage and colonization of the small bowel with toxigenic gram-negative bacteria. Gram-negative colonization, mucosal damage, and malabsorption create a vicious cycle, eventually leading to frank folic acid and other micronutrient deficiencies; fat malabsorption may cause steatorrhea. The exact role of factors such as diet (in particular, fatty acids) and derangements in gut motility remains unclear. Unfortunately, this explanation fails

to clarify why people with subclinical tropical malabsorption who have bacterial overgrowth and jejunal abnormalities on biopsy nevertheless remain asymptomatic. The restriction of the disease to the tropics (except in rare cases) is also left unexplained, as is the regional variability in disease (*eg*, between the Caribbean and the Indian subcontinent).

Clinical Presentation

On presentation, the patient typically relates a history that includes experience of traveler's diarrhea while visiting or living in an endemic area. In some cases there is no identifiable initial diarrheal event, particularly in the endemic setting. Unlike routine gastroenteritis, however, after the initial episode, bowel function never returns entirely to normal; characteristically, the patient notes soft, foul-smelling stool, frequently associated with cramping, bloating, and mild to moderate abdominal pain. Weight loss is common, primarily because of associated anorexia [25], and may be profound (some patients report losses of 30 pounds or more). Fever is uncommon in the Caribbean experience but is seen in about a quarter of patients in southern India [26•]. Steatorrhea is common but not universal. Some patients may experience spontaneous remission; in those who do not, as time goes by, evidence of nutritional deficiency becomes manifest, such as glossitis and stomatitis. Eventually, megaloblastic anemia develops, as the patient becomes increasingly deficient in folic acid (and in some instances vitamin B₁₂ as well). Magnesium and calcium deficiencies may also become apparent. Hypoalbuminemia (largely caused by decreased hepatic synthesis, and only secondarily by protein-losing enteropathy) and consequent edema may complicate severe cases, as well as dermatitis, peripheral neuropathy, and osteopenia. In the epidemic setting described by Baker and Mathan [13•] in southern India, mortality in acute tropical sprue can be significant (in excess of 20%).

In one small case series, Whitfield [27] reported an incidence of 0.27% among all deliveries at one hospital in the tropics, suggesting that tropical sprue might be symptomatically worsened in pregnancy because of the competing demands of the fetus for folic acid. This author noted that delivery did not necessarily result in resolution of megaloblastic anemia, glossitis, and other symptoms. The fact that radiologic studies and jejunal biopsy may be relatively contraindicated in pregnancy may make diagnosis difficult; furthermore, standard treatment with tetracyclines is likewise contraindicated.

As summarized in Table 1, tropical sprue described by Indian researchers seems to differ in significant ways from tropical sprue in other geographic locations. Although these differences may be due to variations in methodology, it seems likely that tropical sprue may be multifactorial in origin. How this possibility can be reconciled with the circumstantial data supporting an infectious agent remains unclear.

Table I. Indian versus Caribbean tropical sprue

Indian variant	Caribbean variant
Fever noted in 25%	Fever "rare"
No association with small bowel colonization	Association with small bowel colonization
Response to folic acid and antibiotics variable	Response to folic acid and antibiotics reliable
Spontaneous remissions common	Spontaneous remissions rare
High mortality	Low mortality
Same small bowel transit time as control subjects	Prolonged small bowel transit time compared with control subjects

Differential Diagnosis

As implied by the original case definition, tropical sprue in many ways remains a diagnosis of exclusion. Likely pathogens should be sought: *Giardia lamblia*, *Strongyloides stercoralis*, *Capillaria philippinensis*, *Isospora belli*, *Entamoeba histolytica*, *Cyclospora cayetanensis*, and *Cryptosporidium parvum*. This is especially important in view of the fact that certain pathogens, such as *Strongyloides* and *Giardia* species, are associated with histopathologic findings that are very difficult to distinguish from those typical of tropical sprue. In fact, some of the early case series of patients with tropical sprue may well have included patients infected with pathogens such as *Cryptosporidium* and *Cyclospora* species, which were not recognized at the time. Most of these pathogens can be identified through a combination of direct fluorescent antibody staining of the stool (*Giardia* spp), trichrome, and/or acid-fast staining of the stool (*Cryptosporidium*, *Cyclospora*, and *Isospora* spp), and direct microscopic examination for ova and parasites (three samples submitted, preferably on different days). The presence of eosinophilia may indicate a helminthic cause, or an infection by *I. belli* or *Dientamoeba fragilis*. *Yersinia enterocolitica* is also, on rare occasions, associated with chronic diarrhea in the returned traveler, and it requires special media for laboratory identification. Capillariasis should be excluded in patients from the rural Philippines. HIV should be at least considered as a possible cause or contributing factor in all patients with chronic diarrhea and wasting.

Lactose intolerance may present in a very similar manner to tropical sprue, and the distinction may be more difficult because tropical sprue can induce a disaccharidase deficiency. Celiac disease (non-tropical sprue) itself may mimic tropical sprue; however, the response to a gluten-free diet usually differentiates the two entities. Crohn's disease can result in malabsorption and chronic diarrhea. Intestinal tuberculosis, which classically involves the ileocecal area but can affect any site in the small bowel, is also associated with malabsorption; because most tropical areas are also regions of high tuberculosis endemicity,

this is a diagnosis that should not be overlooked. Irritable bowel syndrome may cause chronic diarrhea, although it should not be accompanied by nutritional deficiencies.

The presence of malabsorption and steatorrhea may be inferred on clinical grounds (wasting, edema, or the history of foul-smelling, greasy stools) and confirmed by a 72-hour fecal fat collection, a D-xylose absorption study, and/or measurement of vitamin B₁₂. Additionally, the patient should be evaluated for the presence of megaloblastic anemia, which may result from a deficiency in either folic acid or vitamin B₁₂.

Further work-up may include a radiographic evaluation of the small bowel to exclude Crohn's disease or anatomic deformities that might lead to short-bowel syndrome. The gold standard, however, is jejunal biopsy, which helps to exclude entities such as Whipple's disease, intestinal tuberculosis, celiac disease, or lymphoma infiltrating the small bowel. Small bowel biopsies of patients with Whipple's disease characteristically show large macrophages that stain for the presence of bacteria with periodic acid-Schiff stain. Rarely, more specialized techniques, such as electron microscopy of jejunal biopsy specimens and/or polymerase chain reaction to detect *Tropheryma whippelii* DNA, may be required. Characteristically, the villi of tropical sprue jejunal biopsies are thickened and blunted, with plasma cells, histiocytes, lymphocytes, and eosinophils in the lamina propria. The epithelial cells lose their characteristic columnar shape and become more cuboidal. The crypts are enlarged in both length and width, with an increased number of enteroblasts. One diagnostically useful finding is the presence of lipid accumulation in the basement membrane of the villous epithelium, which is not characteristic of celiac disease [19•]. Furthermore, the classic finding of celiac disease on small bowel biopsy, the flattening of the jejunal mucosa with loss of villous structure, is not characteristic of tropical sprue. However, if complete loss of villous structure is not apparent, the distinction between tropical and non-tropical sprue on histologic grounds may be difficult.

If diagnostic tests are consistent with sprue, a trial of folic acid supplementation with antibiotic treatment is reasonable. Rapid clinical response is considered strong confirmatory evidence of the diagnosis, although some patients may have lingering symptoms for months.

Treatment

The cornerstone of treatment for tropical sprue remains folic acid replenishment, with or without tetracycline. Most of the severe complications, including megaloblastic anemia and malabsorption, are ameliorated by adequate oral intake of folic acid [28]. On occasion, vitamin B₁₂ repletion is also necessary. Sheehy *et al.* [28] note that early administration of folic acid is associated with a more rapid return to normal. However, response may be incomplete; in one series, two thirds of the patients continued to

have gastrointestinal symptoms even after prolonged treatment and possibly required antibiotic therapy [29]. Patients should be given oral rehydration as needed, as with other diarrheal illnesses.

Tetracyclines remain the preferred antibiotics in the treatment of tropical sprue. Recommended regimens include tetracycline, 250 mg four times a day, or doxycycline, 100 mg twice a day, for 3 to 6 months. Interestingly, treatment with folic acid and tetracycline was not as effective in the setting of epidemic tropical sprue studied in India, again suggesting that the southern India variant may be pathologically distinct [30••]. Response to treatment may be dramatic, with suppression of bacterial growth and improvement in absorption within 24 hours [31]. However, both clinical improvement and jejunal morphologic changes may lag considerably. Although less is published on the use of antibiotics other than tetracyclines, the British experience with sulfonamides during World War II suggests that therapy targeted against enteric gram-negative pathogens is probably effective. It is possible, however, that at least some of the patients in those studies were suffering from protozoan infections with species such as *Cyclospora* and *Isospora*, which might respond to sulfonamide therapy. More recently, Maldonado *et al.* [32] demonstrated that sulfonamide therapy is effective in tropical sprue patients treated for 6 months. Interpretation of the published data on the treatment of tropical sprue with antibiotics is hampered by the lack of randomized, blinded, placebo-controlled trials, and the reported incidence of spontaneous remission varies widely.

Long-term follow-up suggests that a minority of patients treated with folic acid and tetracyclines may relapse, even after leaving a tropical area [33•]. The need for prolonged therapy with antibiotics in some patients and the potential for relapse highlight the possibility that antimicrobial activity alone may not be an adequate explanation of the effectiveness of these agents.

Conclusions

Despite over a century of scientific investigation, the exact cause, or causes, of tropical sprue remains elusive, along with the precise sequence of pathogenetic events that leads to clinical disease. As international travel increases in volume, physicians in the industrialized world will be faced with the challenge of diagnosing and treating many diseases that were hitherto rare in their experience. It is hoped that a greater awareness of tropical sprue as a clinical entity will lead to greater research interest, which in time may uncover the cause of this mysterious illness, as well as new methods of diagnosis and a wider range of therapies.

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