

## Tropical sprue\*

Tropical sprue is an enigmatic malabsorption syndrome which occurs among people living in the tropics.<sup>1</sup> Symptoms of chronic diarrhoea, malaise, fatigue, and weight loss associated with malabsorption of fat, carbohydrates (glucose and d-xylose), folate, and vitamin B<sub>12</sub> represent the classic form of the disease. However, milder forms of this syndrome are probably more common<sup>2</sup> and may occur even in well nourished individuals.<sup>3</sup>

Certain features suggest that this disease is associated with an abnormal small intestinal bacterial flora. The onset can often be traced to an episode of acute gastroenteritis.<sup>4</sup> There are reports of epidemic tropical sprue following acute diarrhoea in prisoner of war camps<sup>4</sup> and villages in South India.<sup>5</sup> Members of the same household may simultaneously contract the disease.<sup>6</sup> Furthermore, the symptoms and absorptive defects often respond dramatically to antimicrobial drugs.

The small intestine in normal individuals, whether in tropical or temperate areas, generally contains low numbers of Gram-positive microorganisms.<sup>7</sup> Coliforms and obligate anaerobes are confined to the distal small bowel and colon. Recent studies indicate that the jejunum may become contaminated with colonic bacteria in tropical sprue.<sup>8</sup> Although the characteristics of intestinal bacterial clearance are poorly understood, effective peristalsis,<sup>9</sup> gastric acid,<sup>10</sup> and mucosal antibacterial factors<sup>11</sup> are important in experimental situations. The finding of colonic bacteria in the jejunum of sprue patients suggests that these protective mechanisms are disturbed.

One possible explanation for the failure of bacterial clearing is a mucosal injury incurred during single attacks or, more probably, repeated episodes of acute gastrointestinal infection. Colonization of the upper small intestine is known to occur in children<sup>12</sup> and adults<sup>13</sup> with acute diarrhoeal disease in temperate areas of the world. Similar findings in Calcutta<sup>14</sup> have shown that these alterations may accompany acute tropical gastroenteritis associated with *Escherichia coli*, *Shigella*, *Vibrio cholerae*, or a variety of 'non-specific' enteric microorganisms. Furthermore, bacterial contamination of the jejunum was found to persist in these patients for periods up to four months after the original infection. Intestinal physiology may also be altered by acute diarrhoea. Studies in East Pakistan<sup>15</sup> and India<sup>16</sup> have indicated that transient malabsorption of fat, vitamin B<sub>12</sub>, and xylose can be found in the acute and early convalescent periods.

It is apparent that intestinal bacteriology and absorption is altered for a variable period after acute gastroenteritis. Whether a patient goes

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on to develop tropical sprue may be determined by two factors: (1) the microorganism causing the acute episode and (2) the susceptibility of the intestinal mucosa to injury and its ability to recover.

Since acute gastroenteritis does not invariably disturb the small bowel microflora,<sup>13</sup> it is possible that only specific microorganisms which cause mucosal injury can initiate these alterations. This injury could be mediated by bacterial metabolic products or by the release of an enterotoxin. Toxins from enteropathogenic strains of *E. coli*<sup>17</sup> and other bacteria associated with diarrhoea can cause anatomical and physiological defects in the rabbit and dog intestine;<sup>18, 19</sup> similar changes have also been observed in non-specific diarrhoea in man. Such substances could play a role in the development of tropical sprue in a susceptible individual.

A critical factor in the pathogenesis of tropical sprue may be the ability of the intestinal mucosa to deal with noxious agents. There is circumstantial evidence to suggest that deficiencies of folate, vitamin B<sub>12</sub>, and/or protein may favour the development of sprue, possibly by rendering the mucosa more susceptible to injury. Additional factors such as diet and genetic predisposition may explain the unique geographical distribution of tropical sprue.<sup>20</sup> Although knowledge of these factors is limited, it is possible that the intestinal mucosa of certain individuals may be selectively susceptible to the development of tropical sprue in the setting of an acute mucosal injury.

Recent investigations have delineated the role of intestinal microorganisms in blind loop syndrome malabsorption.<sup>21</sup> Similar absorptive defects are associated with an abnormal intestinal bacterial flora in tropical sprue.

Vitamin B<sub>12</sub> malabsorption is present in most patients with tropical sprue.<sup>1</sup> Although gastritis is often present, intrinsic factor production is adequate.<sup>22</sup> Antibiotic treatment generally improves vitamin B<sub>12</sub> malabsorption immediately coinciding with reduction in intestinal bacteria.<sup>8</sup> In the blind loop syndrome vitamin B<sub>12</sub> is unavailable for absorption due to the binding of this substance by intraluminal microorganisms.<sup>23</sup> A similar mechanism may be responsible for vitamin B<sub>12</sub> malabsorption in tropical sprue.

Although vitamin B<sub>12</sub> absorption is frequently improved by antibiotics, it may not return to normal levels despite prolonged therapy.<sup>24</sup> There may be, therefore, a coexistent mucosal lesion as previously described in *E. coli*-contaminated rats<sup>25</sup> and small intestinal diverticulosis in man.<sup>26</sup> However, although the mucosal mechanism may explain the slow return to normal vitamin B<sub>12</sub> levels, the rapid initial improvement on antibiotics indicates that the major component of vitamin B<sub>12</sub> malabsorption in tropical sprue is most probably direct binding by intraluminal bacteria.

Steatorrhoea is a frequent finding in tropical sprue. Its irregular identification in the past may be partly due to inadequate dietary fat intake during the period of faecal fat measurement. A low fat diet,

common among indigenous tropical populations and anorexic patients, is known to reduce faecal excretion to normal levels.<sup>27</sup>

Since fat is maximally absorbed in the jejunum, the morphological abnormalities at this site have been thought to cause steatorrhoea. Against this concept is the lack of correlation between the dissecting microscopic features of jejunal biopsies and the incidence of fat malabsorption. Steatorrhoea correlates best with vitamin B<sub>12</sub> malabsorption but poorly with folate or d-xylose malabsorption, substances which are absorbed maximally in the jejunum.<sup>2</sup> Moreover, similar jejunal pathology may occur in asymptomatic individuals<sup>28</sup> and in protein-calorie malnutrition without steatorrhoea.<sup>29</sup>

On the therapeutic side, steatorrhoea responds poorly to folate or vitamin B<sub>12</sub> therapy.<sup>30, 31</sup> (Improvement over long periods may be difficult to distinguish from the natural remissions which occur in this disease.) In a careful balance study in Puerto Rico,<sup>30</sup> folic acid had no effect on fat or d-xylose absorption when given to 12 patients for nine to 44 days, although it did produce improvement in well being and a haematological response in folate-deficient subjects. However, antibiotic treatment in at least two studies has reduced steatorrhoea to normal levels within two to four days.<sup>32, 33</sup> This immediate response can best be explained by the elimination of intestinal microorganisms responsible for impaired fat absorption. The occasional relapse or recurrence after treatment may be due to recolonization of the small intestine by antibiotic-resistant bacteria.

Rapid reduction in steatorrhoea after antibiotic therapy also occurs in the blind loop syndrome.<sup>21</sup> Recent studies in this disease have shown that small intestinal bacterial overgrowth interferes with fat absorption by splitting bile acids.<sup>34</sup> In this circumstance, the concentration of conjugated bile acids in intraluminal fluid may be reduced below the critical concentration essential for effective micellar formation.

Another factor affecting bile salt metabolism which may be pertinent to tropical sprue has been demonstrated in patients with ileal diseases. During the normal enterohepatic circulation, conjugated bile salts are efficiently reabsorbed in the ileum and less than one gram per day passes to the colon. Ileal pathology or resection are associated with a diminished bile salt pool apparently by restricting reabsorption.<sup>35</sup> As a result, conjugated bile salts in the upper jejunum are reduced below the critical micellar concentration.<sup>36</sup>

A reduction of conjugated bile salts in the upper jejunum has been observed in tropical sprue; deconjugation was absent in the upper and mid-jejunum but could be detected in the lower jejunum and ileum.<sup>37</sup> This suggests that ineffective ileal reabsorption, possibly related to deconjugation at this site, could reduce the bile salt pool in patients with tropical sprue. In this respect tropical sprue may differ from the classic blind loop syndrome associated with gastrectomy or jejunal diverticulosis. In the latter conditions, bacteroides and split bile acids are found at all levels of the small bowel. On the other hand, in tropical

sprue, abnormalities appear to be limited to the lower small bowel which resembles a 'distal' blind loop syndrome as seen in Crohn's disease and ileal strictures. Definitive studies of bile salt metabolism in tropical sprue will be necessary to confirm these preliminary observations.

D-xylose malabsorption usually accompanies tropical sprue, and appears to persist in over 50% of patients despite long-term therapy with folate, vitamin B<sub>12</sub>, or antibiotics.<sup>1</sup> Experimental studies in mice and rats indicate that microorganisms within the intestinal lumen can reduce d-xylose absorption.<sup>38</sup> This reduction was related to morphological changes in the lamina propria induced by the presence of bacteria. On the other hand, studies in man suggest that bacterial contamination may not be the determining factor in d-xylose malabsorption. This absorptive defect is frequently found in tropical communities with<sup>39</sup> and without<sup>20</sup> tropical sprue. It can be induced by protein depletion,<sup>40</sup> dietary restrictions, and normal senescence,<sup>41</sup> and is often undisturbed in the blind loop syndrome even when associated with heavy bacterial overgrowth. Furthermore, treatment of tropical sprue with antibiotics generally produces a sluggish response in d-xylose absorption.<sup>24</sup> These observations suggest that an underlying mucosal abnormality is largely responsible for d-xylose malabsorption in the tropics. In support of this, Kent and Lindenbaum<sup>42</sup> have shown a clear correlation between the severity of the mucosal pathology and the degree of d-xylose malabsorption in tropical diarrhoeal disorders.

Variable degrees of histopathology are present in jejunal and ileal mucosa in tropical sprue. Similar abnormalities have been reported in tropical areas where sprue is not encountered and in other tropical diseases unassociated with steatorrhoea.<sup>29</sup> Many workers have been impressed with the non-specific nature of the mucosal lesion which occurs in the tropics.<sup>42</sup>

Folate and vitamin B<sub>12</sub> therapy may improve the abnormal epithelium in tropical sprue in three to six days with reversion of nuclear alterations, an increase in mitotic activity, and redevelopment of villi.<sup>43</sup> However, it is unlikely that folate or vitamin B<sub>12</sub> deficiency *per se* is fully responsible for the morphological changes since residual abnormalities may remain for months or years, apparently unresponsive to prolonged therapy.<sup>44</sup> Furthermore, experimental and nutritional folate and vitamin B<sub>12</sub> deficiency in temperate zones is unassociated with these histological changes in the jejunum.<sup>45</sup>

The duodenum and upper jejunum in tropical sprue may show severe histological derangement in the absence of abnormal bacterial populations at this site. The mucosal pathology usually reverts slowly towards normal but may still be grossly disturbed at a time when antibiotics have induced resolution of fat and B<sub>12</sub> malabsorption.<sup>24</sup>

Another indication of the underlying mucosal disorder is the alterations in water and electrolyte transport which have been observed in patients with tropical sprue. Marker perfusion studies have demon-

strated secretion of water and electrolytes in the jejunum and ileum. Following antibiotics, the ileum rapidly returned to normal absorption but the jejunum often continued to show a persistent secretory defect.<sup>8</sup>

Finally, the presence of colonic bacteria in the upper small bowel in sprue patients suggests that mucosal antibacterial mechanisms are impaired. The derangements in mucosal morphology, delay in complete recovery of B<sub>12</sub> absorption, and alterations in d-xylose, salt, and water transport are convincing evidence for a primary mucosal lesion.

The pathogenesis of tropical sprue can now reasonably be viewed in two parts, a defect in the intestinal mucosa accompanied by bacterial contamination. Although the mucosal abnormality may underlie the disorder, certain manifestations can be related to the presence of enteric microorganisms in an abnormal location within the small intestine.

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