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Commentary

Tropical sprue: a riddle wrapped in a mystery inside an enigma

Tropical sprue was a major scourge afflicting tropical countries in the last two centuries. Characterised by profuse diarrhoea, steatorrhoea, abdominal distension, mouth ulcers and weight loss, it is a malabsorption syndrome the aetiology of which has never been conclusively identified. The phrase "A riddle wrapped in a mystery inside an enigma (Winston Churchill)" applies very aptly to tropical sprue. During the period of European colonialism in India and southeast Asia, tropical sprue was considered to primarily affect expatriates from Western countries who visited the colonies and for a long time thereafter it has continued to be viewed principally from that angle. In fact, sprue, or an illness remarkably similar to it, was described many centuries ago in the Charaka Samhita as *grahani vyadhi*[1]. In the 1960s, tropical sprue was recognized to be a major cause of malabsorption in Indians both in adults and in children[2-7]. Epidemic forms of the disease occurred in southern India during the 1960s and killed as many as 35,000 people in a single epidemic[8]. In recent years the disease has been on the wane in India. However, it remains a significant cause of adult malabsorption in many parts of India[9,10].

Studies in the last century elucidated the many ways in which gastrointestinal physiology was subverted in this disease[11-18]. The comparison of intestinal absorption and transport in patients with the disease and in appropriate controls resulted in significant advances in our understanding of digestive physiology. Studies of changes in organs outside the gastrointestinal tract, secondary to nutrient malabsorption, resulted in better understanding of the linkages between the gut and systemic illness and changes in nutrient metabolism. The importance of the intestinal microbiota in health and disease was indirectly inferred from studies on tropical sprue, including changes in microbial metabolism of drugs that altered their bioavailability. A distinction was made between tropical sprue, in which there was clinical illness, and tropical enteropathy in which minor reductions in the mucosal surface area of the intestine, accompanied by increased mucosal permeability led to subclinical malabsoption[19]. To this day, the issue of whether tropical enteropathy was part of a spectrum that encompassed tropical sprue has never been answered with certainty.

The aetiology of tropical sprue continues to remain a mystery. Some investigators found an overgrowth of bacteria in the small intestine of patients with tropical sprue[20], while other investigators demonstrated that both apparently normal healthy adults and those with tropical sprue had significant contamination of the small bowel with bacteria[21]. While the Western norm for bacterial presence in the jejunum was 10^3 colonies/ml[22], in Indians it would not be unusual to find 10^5 colonies/ml. Primary overgrowth of the small intestine with bacteria could explain some cases of tropical sprue occurring sporadically. However, it is unlikely that epidemic forms of tropical sprue were due to non-specific colonization of the small bowel with bacteria. Epidemic tropical sprue afflicted large numbers of soldiers and prisoners-of-war in the Indian subcontinent, in addition to causing severe disease associated with a high mortality in southern India[8,11]. The epidemiology of these outbreaks of sprue were consistent with the possibility that tropical sprue was an infective disease. However, despite intensive search for a variety of pathogens, no single causative agent was identified. Studies of tropical sprue in the Caribbean found an association with periodic feasting and consumption of fatty foods leading to the theory that tropical sprue was caused by toxigenic bacteria (*Klebsiella* and *Escherichia coli*) that colonized the small intestine and that long chain fat was somehow responsible for this colonization[23]. Intriguingly, these

bacteria produced toxins that could be detected only by perfusion in intestinal loops in small animals, and these toxins were never definitively characterized[24]. The theory that viruses were responsible for the small bowel pathology of tropical sprue found some credence in early studies[25], but again these were never substantiated in definitive studies.

In this issue, Ghoshal and colleagues[26] identified small intestinal bacterial overgrowth in some patients with tropical sprue and showed that this overgrowth was associated with an exaggerated "ileal brake" causing stasis in the proximal small bowel. They showed that fat entering the ileum in some patients with tropical sprue led to increased secretion of the gut hormones peptide YY and neurotensin, thus slowing motility in the proximal small intestine. Dietary fat is predominantly composed of neutral fat or triglycerides. The process of fat digestion begins in the gastric antrum where these are emulsified and continues in the small intestine with the action of bile salts and lipase, and the liberated free fatty acids and monoglycerides are rapidly absorbed in the jejunum. The ileum contributes little to fat absorption and the study of patients in whom the ileum has been surgically resected shows that approximately 100 cm of ileum need to be removed for steatorrhoea (fat loss in faeces) to occur[27]. In patients with malabsorption such as tropical sprue, the stool normally contains free fatty acids and not neutral fat[16], in contrast to patients with fat maldigestion such as occurs in pancreatic insufficiency where lipase is not available to digest fat. Thus, it would appear that the ileal mucosa of some patients with tropical sprue may be hypersensitive to fatty acids leading to a vicious cycle in which the ileal brake causes slowing of the upper small intestine motility followed by further malabsorption. Even if their hypothesis regarding this sequence of events is correct, we would still need to identify why only some patients with sprue have this exaggerated ileal hormone response to fat. Many questions in this important area continue to remain unanswered including the relative response of ileal receptors to fatty acids and triglycerides. If these receptor respond only to fatty acids and not to triglycerides, it may be presumed that a similar mechanism may operate in other patients with fat malabsorption due to mucosal disease (*e.g.* celiac disease, strongyloidiasis) but not in pancreatic insufficiency. It is also not clear why only some patients with tropical sprue (those with the greater degree of malnutrition in this study[26]) show an exaggerated ileal hormone response to luminal fat, and whether this is genetically determined or only a part of the spectrum of disease of tropical sprue indicating more extensive mucosal damage. In the current era of molecular tools and invasive endoscopy, it may not be difficult to obtain ileal mucosa from patients with sprue and from individuals without malabsorption undergoing colonoscopy, to obtain the answers to some of these questions.

The significance of the work reported by Ghoshal and colleagues[26] is the documentation that tropical sprue continues to be a significant cause of adult malabsorption in India, and that study on the pathophysiology of the disease continues to fascinate medical researchers and provide insights into gastrointestinal physiology.

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