

Tropical Sprue: implications of Manson's concept

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The term sprue was first used in the English language by Sir Patrick Manson in 1880 while working in Amoy, China. He adopted the Dutch word *spruw*, which had long been applied to oral aphthous ulceration in children and was then in use in Java. He described a chronic diarrhoeal syndrome associated with aphthous ulcers, which he regarded as a specific entity. Oral changes and diarrhoea were periodic, and the 'great wasting was altogether out of proportion to the amount of diarrhoea'; patients with the disease could seldom say when it began, it was 'exceedingly insidious in onset, and very slow in its progress' (Table 1). However, he cited a case (1880) which began shortly after acute dysentery. He was also aware that in Manila and the Straits 'the course of the disease was more rapid and steady than in Amoy'. Manson's description served to emphasise the potential gravity of the disease, which had a substantial mortality when untreated, but whether he was justified in considering it to be a single entity must be seriously questioned. By 1898, Manson's experience of the disease had increased and he was of the opinion that it had been 'more or less recognised' for many years. Although *Strongyloides stercoralis* and *Entamoeba histolytica* were sometimes present in the stool, he did not regard them as aetiologically important. The disease usually started slowly, but on a basis of months or years of bowel irregularity that began soon after arrival in the tropics; however, he was by then quite clear that it could start with an attack of dysentery (with bloody stools) or acute enterocolitis. He recognised a great variability in the rate of progress of the disease; the course varied between a year or two, and ten or fifteen years.

REPORTS OF TROPICAL MALABSORPTION (TM) BEFORE MANSON

Owing to the difficulties of clinical observation and investigation in tropical countries, many early descriptions of tropical malabsorption (TM) were made in England of people who had returned from India and the Far East (Martin, 1856; Fayrer, 1881).

Table 2 summarises descriptions of TM by four physicians from 1766 to 1866. Hillary (1766) saw one case in Barbados between 1747 and 1751, then three more in the next three years and some scores of cases in the following four years. Most

Table 1. Clinical and pathological features of sprue according to Sir Patrick Manson

Date of report	Name of disease	Geographical distribution	Ethnic group affected	Mode of onset	Predisposing factors:					Pathological features				
					climate	dysentery	scurvy	malaria	anaemia	tongue	mouth	intestine		liver
												small	large	
1880	<i>Sprue</i>	China (Amoy), India, Java	European adults only	Exceedingly insidious; (acute dysentery in one case)	+	+	-	-	+	Swollen, with red shallow ulcers	Swollen, tender, bleeding gums	Inflammation	Inflammation	General atrophy
1898	<i>Sprue</i> (psilosis)	South China, Manila, Cochin China, Java, Straits Settlements, Ceylon, India, tropical Africa, West Indies	European adults only	Usually slow but also acute or subacute	+	+	-	-	+	Inflamed, bare, eroded mucous membrane	Same as tongue	Atrophy of mucosa. Thinning and ulceration of ileum	Ulceration of colon	-



Fig. 1. Sir Patric Manson, 1844-1922

Table 2. Some early descriptions of TM

Authors	Date of report	Name of disease	Geographical location of investigation	Ethnic group affected	Mode of onset
Hillary	1766	Aphthoides chronica; Impetigo primarum viarum	Barbados, West Indies	Inhabitants of Barbados & other West Indian islands	'Comes on so slowly, and increases gradually and almost imperceptibly'
Twining	1835	Chronic diarrhoea of Europeans	Bengal, India	Europeans	'Comes on slowly'; sometimes suddenly (e.g. case 37 at Simla)
Grant	1854	Hill diarrhoea & dysentery	Indian hill-stations	Europeans	Frequently acute (Simla trots)
Goodeve	1866	White flux; cachetic diarrhoea	India	Europeans & natives of India	Usually insidious

reporters stressed the insidious or slow onset of the disease. Pringle had recognised in 1764, however, that dysentery could proceed to chronic diarrhoea and the 'white flux', in which 'the aliment will pass through the intestines with little alteration'; he also recognised that aphthae could be associated features. Twining (1835), too, was aware that the onset could be acute – with dysentery and bloody stools. Grant (1854) gave a clear description of a disease with an acute onset – hill-diarrhoea. Goodeve (1866) drew a sharp distinction between the 'white flux' of the plains of India and hill-diarrhoea, which itself could progress to a fatal diarrhoea alba. He was aware of an associated arthropathy, scorbutic patches, corneal ulceration (especially in the natives of India) and terminal fluid retention. Unlike most of his contemporaries, he did not feel that liver involvement was important in the pathogenesis of the disease. He stressed the risk of relapse.

Predisposing factors:					Pathological features				
climate	dysentery	scurvy	malaria	anaemia	tongue	mouth	intestine		liver
							small	large	
+	-	-	-	-	Red, inflamed raw & tender	Small pustulae or pimples	Excoriation	-	-
+	+	-	-	-	Clean & smooth	Swollen & glossy gums	Thin coat; superficial ulceration of ileum	Thin coat; superficial ulceration of caecum & sigmoid colon	Small & greyish; enlarged hepatic ducts
+	+	+	+	+	Aphthous and congested	Gums congested and bled freely	Coats strikingly atrophied; ileum sometimes affected	Extensive ulceration	Small, pale and friable
+	-	+	+	+	Sore, smooth, shining with aphthous ulcers	Aphthous ulcers of lips	Great thinning of all coats	Ulceration and sloughing	-

In describing the oral changes associated with TM, which dominated most early accounts, Hillary (1766) wrote of 'little small pustules, or pimples, filled with a clear acrid lymph' at the 'end and sides of the tongue, which gradually increase in number and which slowly spread to other parts of the mouth'. 'Soon the thin skin slips off and the tongue looks red and a little inflamed, and is almost raw like a piece of raw flesh and is tender and sore'. Of the white flux, Martin (1856) described 'the anaemic ulcerations (chronic aphthae) of the mucous digestive surface'.

The use of the term insidious to describe the onset of the disease is probably a source of confusion in interpretation of the early literature. Insidious is defined (*Concise Oxford Dictionary*) as 'treacherous, crafty; proceeding secretly or subtly'. That does not necessarily imply the opposite of acute in describing the onset of a disease, as it often does today. During the nineteenth century the

notion of treachery or low cunning was probably dominant; since then the word has increasingly conveyed the idea of slow concealed working or gradual operation.

REPORTS OF TM SOON AFTER MANSON'S DESCRIPTION

Tables 3 and 4 summarise some descriptions of TM after 1880. Most stressed the oral changes, and Rogers (1913) considered that they were dependent on the length of the history of disease. Of 150 cases reported in London by Low (1928) 100 had tongue lesions when first seen; 44 also had other oral symptoms. In 19 per cent of 200 cases reported by Manson-Bahr and Willoughby (1930) buccal changes preceded the onset of diarrhoea. Bahr (1915) felt that exactly similar aphthae to those seen in 'tropical sprue' occurred in normal Europeans in otherwise perfect health. It seems possible that aphthous ulceration was sometimes associated with secondary infection, possibly monilial (Bahr, 1915), which was superimposed on a progressive nutritional deficit. Brown (1908) emphasised that the oral lesions were similar to thrush. It is now clear that aphthous ulceration can occur after long-standing malabsorption of other causes; a high incidence has been reported in coeliac disease (Ferguson *et al.*, 1975).

The clinical picture of TM was usually dominated by diarrhoea with grey-white stools at some stage or other, but that was not always severe. A feature of most early reports was of diarrhoea in the early hours, which had subsided about mid-day (Chevers, 1886; Thin, 1897; Brown, 1908; Rogers, 1913; Low, 1928). Brown (1908) differentiated the severe initial diarrhoea from the chronic diarrhoea of advanced disease. According to Bahr (1915) 24-hour stool weight in 'chronic sprue' was 259, 303 and 605 g respectively in contrast to 174 and 135 g in two normal healthy subjects. Dyspepsia was frequently reported (Brown, 1908). Oesophageal pain was also emphasised by many writers (Manson-Bahr and Willoughby, 1930) and morphological changes similar to those in the tongue and mouth described by Thin (1890), Begg (1912), Rogers (1913), and Brown (1908). Hillary (1766) stressed 'burning heat about the cardia, or upper mouth of the stomach'. Rogers (1913) and Brown (1908) mentioned shallow ulcers and congestive patches in the stomach. Anaemia was emphasised by most workers (Tables 1 to 4); it latterly became clear that it was macrocytic (Thin, 1897; Bahr, 1915; Low, 1928; Brown, 1908). Rogers (1913) was of the opinion that the severity of anaemia was dependent on the length of history and was always marked in fatal cases; 15 of 28 cases had anaemia (severe in 2) in under one year.

Most observers were aware of changes in the small intestine, although most expressed caution in that they might be due to postmortem change (Brown, 1908) (Table 4). Cantlie (1905), Brown (1908), Rogers (1913) and others described thinning of the mucous membrane with extensive atrophy of villi and the tube glands, together with small-celled inflammatory infiltration; in chronic cases, there were fibrotic changes in the mucous coat and, sometimes, superficial ulcers.

Marked changes in the ileum were stressed by Thin (1890, 1897), Manson (1898) and Begg (1912). Begg (1912) demonstrated many bacteria in the ileal region, and was convinced that infection was the basis of the disease. Thin (1897) also considered that high faecal bacterial counts were of aetiological importance. Rogers (1913) felt that the disease had a bacterial or protozoal basis. Enlarged and hardened mesenteric glands were mentioned by Fayrer (1881), Goodeve (1866) and Manson (1898).

Colonic pathology, including ulceration, was described by several writers. Brown (1908) and Rogers (1913) considered that the large intestine exhibited changes similar to but less severe than those in the small intestine. Ulceration and sloughing at a late stage in the disease were recorded, but the appearances were unlike those of dysentery (Brown, 1908). Sigmoidoscopy showed an atrophic colonic mucous membrane in chronic cases studied by Manson-Bahr and Willoughby (1930).

Most early reports stressed hepatic changes (Tables 1 to 4). Atrophy was associated with a small, pale, constricted capsule. Rogers (1913) considered that the liver was often slightly large during the early stages of the disease, but atrophied later. Postmortem evidence was felt to confirm clinical impressions of hepatic atrophy (MacLean, 1886; Fayrer, 1881). Liver weight was reduced to 1.0, 0.8 or even 0.7 kg compared with a mean normal weight of 1.4 kg (Brown, 1908) which was regarded as being due to simple atrophy superimposed on a general subacute hepatitis. Most writers (Brown, 1908) considered the changes to be of nutritional origin. Jaundice did not occur (Begg, 1912), and histology (Brown, 1908) and liver function tests were normal (Low, 1928).

The majority of cases reported by Rogers (1913) were admitted between 6 and 12 months after onset; in a quarter, the disease had lasted for longer (up to eight years). Most of those reported by Low (1928) had had symptoms for 4 to 8 months. Rogers (1913) considered that prognosis regarding complete recovery was very unfavourable; of 45 cases only 2 (one was in hospital for 383 days) were discharged cured and one of them returned with sprue several months later. Twenty-six of 45 showed no improvement after hospital treatment, and six died while under observation. Most deaths, usually due to intercurrent infection, occurred during the first six to twelve months. Early cases did no better than late ones. Of 150 cases described by Low (1928) in London, 10 ultimately died; most were more than 50 years old. Seven of 200 cases seen by Manson-Bahr and Willoughby (1930) in London died.

HILL-DIARRHOEA AND MANSON'S SPRUE

Most workers since Grant (1854) considered 'sprue' and hill-diarrhoea to be separate entities (Chevers, 1886; Bahr, 1915). However, some (Crombie, 1880; Fayrer, 1881; Begg, 1912) felt that they were mere modifications of a single disease. Rogers (1913) considered that only neglected cases of hill-diarrhoea

Table 3. Reports of TM between Manson's adoption of the term sprue and 1900

Author	Date of report	Name of disease	Geographical location of investigation	Ethnic group affected	Mode of onset
Fayrer	1881	White flux	India and China	Europeans (in hills)	Often insidious; sometimes sudden (e.g. case 7)
Chevers	1886	Chronic tropical diarrhoea (diarrhoea alba)	Bengal, India	Europeans (in hills)	Insidious
MacLean	1886	White flux; scorbutic diarrhoea	Plains and hills of India, Ceylon	Europeans	Insidious
Moore	1886	Diarrhoea alba; hill-diarrhoea	India: Himalayan hill-stations and plains	Europeans	Usually acute
Thin	1890	Psilosis (linguae et mucosae intestini)	Straits, Batavia, China, Ceylon & India	Europeans	Insidious
Thin	1897	Psilosis (linguae et mucosae intestini)	Ceylon; Straits Settlements; coast of China and Manila	Europeans	Insidious; sometimes acute (e.g. cases 3, 5, 13, 17, 19, 22, & 25)

developed into 'sprue', and Manson-Bahr and Willoughby (1930) seemed to be in no doubt of that association.

DYSENTERY PROCEEDING TO CHRONIC TM

Progression of acute dysentery, with bloody stools, to the 'white flux' was

Predisposing factors:					Pathological features				
climate	dysentery	scurvy	malaria	anaemia	tongue	mouth	intestine		liver
							small	large	
+	+	+	+	+	Dry, smooth, red and glazed	Aphthous ulcers	Atrophied; ulceration of ileum	Ulceration; mesenteric glands enlarged	Shrunken pale and contracted
-	-	-	-	+	-	Aphthous condition (mucous membranes)	Pale, blanched and anaemic; atrophied	Leadens spots; mesenteric glands enlarged	-
-	+	+	+	+	Red, smooth and glazed	Gums: red, soft & spongy. Aphthous sores	Thinning of all coats; esp. ileum	Congestion of mucous membrane	Atrophy (?peri-hepatitis)
+	-	+	-	-	-	-	Pale, atrophied	(Mesenteric glands enlarged)	Pale
-	-	-	-	+	Smooth, cracked, tender, white patches	Pale and anaemic	Thin and translucent (ileum most affected)	Abrasions of coat, with mucous material	Shrunken
-	-	-	-	+	Swollen, red; denuded of epithelium	Erythema of palate; herpetic eruptions	Walls thin with very marked ileal changes	Few small superficial ulcers	-

recognised long before Manson's time. Pringle (1764) was well aware of that complication of dysentery. Twining (1835) wrote that dysentery could proceed to a condition in which the 'stools are sometimes a copious, paste-like, brown mass, in a state of fermentation; occasionally they are frothy, with a subalbid, or pale-grey sediment, like a mixture of chalk and beer'. Fayrer (1881), Thin (1897)

Table 4. Reports of TM between 1900 and the era of laboratory investigation

Author	Date of report	Name of disease	Geographical location of investigation	Ethnic group affected	Mode of onset
Brown	1908	Sprue	Eastern tropics	Chiefly Europeans	Insidious and chronic, but initial severe diarrhoea
Begg	1912	Sprue	China (Hankow); England (London)	Europeans	Gradual but sometimes acute (several case reports)
Rogers	1913	Hill-diarrhoea; diarrhoea	Calcutta, India	Europeans (rare in natives)	Hill-diarrhoea (acute); Diarrhoea alba (subacute)
Bahr	1915	Sprue	Ceylon	Europeans & natives	Acute (explosive) in some; chronic in others
Low	1928	Sprue	England (London)	Europeans; rare in natives	Variable (sometimes acute)
Manson-Bahr & Willoughby	1930	Sprue	England (London)	Europeans & native Indians	Usually gradual; sometimes acute

and Rogers (1913) were among others to recognise the progression of dysentery to chronic TM. Fever and repeated dysentery were striking factors in several case histories (e.g. case 7) of TM reported by Fayer (1881). Thin (1897) recognised

Predisposing factors:					Pathological features				
climate	dysentery	scurvy	malaria	anaemia	tongue	mouth	intestine		liver
							small	large	
-	+	-	-	+	Red, smooth dry, aphthous plaques	Desquamation of epithelium	Pale, atrophied & collapsed. Thin mucosa, with loss of villi.	Ulceration and atrophy (mesenteric glands swollen & atrophied)	Subacute hepatitis. Atrophic contraction
-	+	-	-	+	Raw, red irritable	Denudation of epithelium	Disintegration of epithelium especially in ileum	-	Contracted
+	+	-	-	+	Raw with thin epithelial coat. Aphthous ulcers.	Aphthous ulcers	Atrophy & thinning of mucous membrane	Atrophy & thinning of mucous membrane	Atrophy
-	-	-	-	+	Raw; atrophy of papillae. Aphthous ulcers.	Same as tongue	Shrunken villi with round cell infiltration; transparent distended ileum	Ulcers sometimes	Atrophy
-	+	-	+	+	Red, congested, inflamed with vesicles or ulcers	Superficial ulcers	-	-	Shrunken
-	+	-	+	+	Aphthous ulceration	Same as tongue	-	Atrophic mucous membrane	Shrinkage

that patients who had suffered from severe attacks of dysentery were liable, even after return to temperate climates, to a form of diarrhoea and dyspepsia, but they did not get 'the very specific eruption (in the mouth) which characterises psilosis'.

He also recognised cases of 'psilosis' in which the disease set in 'by severe diarrhoea from the first'. Brown (1908) had often seen dysentery give way to TM but was not convinced that that was a causative relationship. Rogers (1913) concluded that five of his 50 cases of 'sprue' had followed dysentery. In view of the fact that 91 of 150 cases had a history of debilitating disease (most had dysentery, diarrhoea or malaria) Low (1928) concluded that 'prolonged residence in the endemic area, diseases of the alimentary canal such as hill-diarrhoea and dysentery; in short any debilitating disease may bring it out'. MacLean (1866) considered that progression was dependent upon whether the lesions were bounded by the ileo-caecal valve or passed into the small intestine. *The Lancet* (1944) considered that fatty stools had long been known to occur after dysentery, and Howat (1944) reported such a case. Two further patients were reported by King and Joske (1960).

ACUTE TROPICAL DIARRHOEA PROCEEDING TO CHRONIC TM
Grant (1854) was responsible for the first detailed report of hill-diarrhoea, although it had apparently been well recognised long before that. The disease started with fluid stools (from 4 to 12 daily) which usually did not contain blood, excessive flatulence, and air bubbles in the stools. The condition frequently started soon after reaching a hill station, was often epidemic and sometimes proceeded to chronic diarrhoea alba. Hill-diarrhoea often started with headache, nausea and vomiting as well as severe diarrhoea; in addition, fever (up to 102° F) and rigors were frequent accompaniments (Brown, 1908). There was much speculation on the cause of hill-diarrhoea. A water-borne infection was favoured by some (Grant, 1854; Dickson, 1871; Fayer, 1881; MacLean, 1886) but not all (Morehead, 1860; Crombie, 1880; Moore, 1886; Rogers, 1913) observers. The possible role of mica in the water supply was raised (Moore, 1886; Duncan, 1905) but never proved. Galloway (1905a, b) concluded that both hill-diarrhoea and 'sprue' were caused by a specific micro-organism. Begg (1912) was convinced that TM was caused by a micro-organism that was probably water-borne; his use of santonin in its treatment was given in support of that view. Yeasts were also suggested (Nicholls, 1918). Most of the cases of TM reported by Low (1928) from London seemed to be post-infective, and he felt that a gastrointestinal toxin would 'best explain the real cause of the disease'. That view accords with recent demonstrations of increased enterobacterial counts in the small intestine in tropical malabsorption (Banwell and Gorbach, 1973; Klipstein *et al.*, 1973; Tomkins *et al.*, 1975). Furthermore, Lindenbaum (1965) demonstrated progressive TM in otherwise healthy subjects in Bangladesh, following acute intestinal infections; there was evidence of malabsorption of xylose (at 378 days) and B₁₂ (at 196 days) after the diarrhoea had stopped. Further examples of acute diarrhoea proceeding to TM have been given by Montgomery *et al.* (1973) and Haeney *et al.* (1974). Young adults who have made overland journeys across

central Asia, and have had acute diarrhoea in Afghanistan and/or Nepal, frequently have persisting TM (Tomkins *et al.*, 1974). Although some of those patients have a *Giardia lamblia* infection, some doubtless started as travellers' diarrhoea (Rowe *et al.*, 1970).

THE BEGINNINGS OF LABORATORY INVESTIGATION

The early phase of clinical investigation of TM was dominated by the work of Fairley and his colleagues who published numerous papers in the 1920s and 1930s. The disease was thought to be infective although the causative organism was unknown. In Bombay TM was common, but often in a minor form (Fairley and Mackie, 1926), and was rare in Indians (Megaw and Gupta, 1927). Long residence in Bombay and preceding malaria and dysentery were considered to be outstanding predisposing factors. An adverse climate and malaria were thought to undermine the constitution of the individual, and preceding disease to damage the alimentary tract. Several hospital admissions with debility and enteritis often preceded the classical picture of TM with sore tongue and white, gaseous, bulky stools. Anaemia dominated the clinical picture in other cases. However, some cases had a clearly defined acute onset with fever for two to three days (Fairley, 1936). Gross intestinal ulceration and involvement of the terminal ileum were described. Mackie and Fairley (1929) concluded that 'the changes in the intestine are most marked in the ileum but are present to some degree throughout the whole tract'. Later, however, Fairley (1936) considered, on limited evidence, that those appearances were largely a result of postmortem change. The changes described were degeneration and aplasia of the small intestinal mucosa, and there was ultimately 'almost complete disappearance of the absorptive and secretory epithelium'. They also felt that there was ante-mortem invasion of the gut wall by bacteria as 'in conditions of malnutrition due to vitamin deficiency'. Duodenal contents were found to be rich in bacteria. Searches for specific bacteria continued to be unrewarding (Mackie *et al.*, 1928), and protozoa — including amoebae and flagellates — were excessively rare, 'possibly because of the high faecal acidity'. Manson-Bahr and Willoughby (1930) considered that despite the large amount of work expended upon the aetiology of the disease from a bacteriological standpoint, the bulk of the evidence was negative.

Working in Puerto Rico, Castle *et al.* (1935) and Suarez (1938) concluded that the primary defect in 'sprue' was haematological rather than small-intestinal and was produced by a nutritional factor.

THE SECOND WORLD WAR AND AFTER

Several detailed reports on large numbers of cases of TM were published during the Second World War. In the vast majority the disease started with an acute

attack of diarrhoea, but there were inconsistencies regarding its being a sequel to dysentery. It seems likely that the disease often started as travellers' diarrhoea or hill-diarrhoea (Green, 1854) and differed from Manson's concept of sprue.

Leishman (1945) described his experience of sprue in many hundreds of soldiers. It occurred in the fly season when dysentery was common. Seventy-five per cent of patients were affected in the first two years of service and sometimes very soon after arrival in the tropics. The onset was usually acute; 9 per cent gave a history of frank dysentery (4 per cent amoebic and 3.5 per cent bacillary). In more than 50 per cent the disease was fully developed two months after the onset of diarrhoea. It was uncommon in West Africans. Leishman referred also to a 'marasmic syndrome' in Indians. That seems to resemble Manson's chronic sprue. He attributed TM to a disturbance of bacteriological equilibrium in the small intestine, possibly due to stagnation within the small intestine. A recent observation showing diminished small intestinal transit in TM (Cook, 1978) accords with that hypothesis. Keele and Bound (1946) reported their experience of TM in India between 1942 and 1944. Forty-five per cent of cases occurred after one of the two years in India; after that the incidence declined with increasing residence. Peak incidence in both plains and hills was in May and June, when the hills are cool and the plains hot. Although epidemiological evidence suggested that the peak occurred earlier in the year than for dysentery and diarrhoea, in some individuals amoebic and bacillary dysentery preceded an acute onset of steatorrhoea. Many had an acute onset related to dysentery (usually amoebic); there was some evidence of colonic involvement. Malaria was thought to be an aetiological agent and recovery occurred after treatment. Giardiasis and tabes mesenterica were excluded. Diarrhoea preceded a sore tongue by about six weeks in 80 per cent of cases; the reverse association was rare. Stefanini (1948) reported 1,069 cases of TM in 12,500 Italian prisoners-of-war in the Himalayan foothills. The disease followed the rainy season, and in 73 per cent began with a sudden onset of explosive diarrhoea (5 to 15 stools daily); bacillary dysentery was rife, and there was also much amoebic dysentery and malaria. Previous illnesses seemed to favour onset of the disease. A mild continuous fever was noted in 12 per cent of cases. Associated symptoms, including deficiency signs and macrocytic anaemia, followed two to four weeks after the onset of diarrhoea. Ninety per cent developed glossitis; the edges and tip of the tongue were first reddened, to be followed after a few days by small aphthae. Gastric mucosa showed patches of atrophy, purpuric spots and signs of inflammation and oedema; most had hypochlorhydria. Sigmoidoscopy showed a reddened and congested mucosa which progressed to greyish, atrophic mucosa in the chronic case. In five who died, the intestinal mucosa was pallid and atrophic. Elder (1947) described 400 cases of sprue in British soldiers in Bengal, Assam and Burma. The disease also occurred in Indians. In many, illness began after a short stay in the tropics and was sometimes of sudden onset, although insidious in most cases. Up to 20 to 30 stools were

passed daily. The disease started with a definite attack of dysentery in 15 per cent of cases. Glossitis was present in 393 cases and many also had angular stomatitis and cheilosis. Macrocytic anaemia was found in 22 per cent. Walters (1947) reported 42 cases of TM in Indian soldiers. Three-quarters of a battalion under investigation were Jats, who were vegetarians, and one-quarter were Rajputana Musselmans, who were meat eaters. Thirty-nine Jats and three Musselmans developed severe TM. They had had diarrhoea (in 6), frank dysentery (bacillary in 16 and amoebic in 5) or malaria (in 10) in the preceding two to three months and had an acute onset of disease. Skin changes were common. Steatorrhoea was demonstrated in 28 cases and macrocytic anaemia in 37. Peripheral neuropathy was present in 64 per cent. In 6 of 14, sigmoidoscopy showed a thin mucosa with a granular surface. There were 2 deaths. TM developed therefore after an acute infection, usually bacillary dysentery, in vegetarians. Ayrey (1948) also considered, from experience in Burma, that sprue was basically a disease of malnutrition although diarrhoea could precipitate it. In a retrospective study comparing previous histories of 47 patients with sprue with 100 suffering from diseases other than sprue or dysentery, Woodruff (1949) concluded that 'organisms producing frank dysentery and enteritis apparently do not predispose to the development of sprue'. However, most cases occurred when amoebic dysentery was prevalent, and other intestinal infections were common.

Both Stannus (1942) and Leishman (1945) suggested that the condition was caused by an infection that upset the intestinal bacterial flora and led to the impaired biosynthesis of B vitamins. That theme was the subject of an hypothesis by Manson-Bahr (1953).

If diminished small intestinal peristalsis predisposes to the bacterial colonisation leading to TM (Drew *et al.*, 1947; O'Brien, 1967; Cook, 1978), an observation that large intestinal disease can be associated with decreased small intestinal motility (Cook, 1978) is of interest; a predominantly large intestinal disease preceded many of the wartime cases.

RECENT DESCRIPTIONS OF TM

Baker (1967) and O'Brien (1967) described cases of TM with an acute onset. Those reported by Baker from Madras State, in poorly nourished Indians had a very acute onset and occurred in epidemics (Baker and Mathan, 1968; Mathan and Baker, 1968); the incubation period was five to six days. Diarrhoea (96 per cent), vomiting (50 per cent) and fever (at least 30 per cent) were common symptoms; adults were affected more often than children. O'Brien (1967) described 64 English servicemen with TM during a five year period; in most, the disease had started in Borneo. Watery diarrhoea and colic started suddenly; it was worst at night in 11 patients. Six presented with glossitis and megaloblastic anaemia but did not have diarrhoea. Most had lived on tinned food, and developed symptoms as soon as they returned to fresh rations.

Fifty per cent of Baker's cases had glossitis associated with folate deficiency. Anaemia, hypoproteinaemia and vitamin A deficiency were common; the severely anaemic patients had splenomegaly. Sigmoidoscopy showed a hyperaemic mucosa in some. Two-thirds of O'Brien's cases had a sore tongue, with a raw and inflamed mouth in some. The anaemia was due to folate deficiency, and responded to folic acid; after two months all marrows showed megaloblastic change. In both series, fat, xylose and vitamin B₁₂ were usually malabsorbed. In Baker's series 50 per cent also had a low serum B₁₂ concentration which was not associated with intrinsic factor deficiency. Although most had a low serum folate concentration and 68 per cent had megaloblastic anaemia, folate malabsorption was thought to be uncommon. O'Brien, however, considered that folate deficiency was progressive and associated with malabsorption of folate; after one month serum folate was usually < 3 µg/litre and at four months most had megaloblastic anaemia. Vitamin B₁₂ malabsorption was not dependent on an ileal lesion and was rapidly corrected by oral broad spectrum antibiotics. Jejunal biopsies in both series showed various grades of abnormality, the severest change being 'convolutions', which O'Brien considered occurred after three months of disease; a submucosal infiltration with lymphocytes and plasma cells was usually present. In O'Brien's experience, ileal changes were less severe than those in the jejunum. Changes in stomach (gastritis and gastric atrophy) and colon (increased cellularity in the lamina propria) were reported by Baker. Concerning aetiology, Baker considered that folate deficiency was common but played little or no part in the production of steatorrhoea. In some, bacterial colonisation of the ileum was probably related to B₁₂ malabsorption and steatorrhoea, and was followed by improvement after antibiotics; in those who did not respond, invasion of the ileum was thought to be by tetracycline-insensitive bacteria. In about half, there was spontaneous improvement in B₁₂ absorption. O'Brien considered that B₁₂ malabsorption was similar to that in the blind-loop syndrome; 8 of 10 cases had a raised urinary indican, probably due to abnormal ileal flora. One-third of Baker's cases died but most of the survivors recovered spontaneously; untreated, some 15 per cent went on for a year or more.

Most of the cases described by Klipstein (1971) seem to have suffered from a disease of acute onset. Mollin (1967) described 13 Europeans and Anglo-Indians with TM which started in India or South-east Asia and some of whom had a very chronic condition (up to 22 years). They had gastrointestinal symptoms and folate deficiency anaemia which sometimes started after they had left the tropics. Folic acid, fat, xylose and B₁₂ were malabsorbed. Jejunal morphological changes were usually mild but ileal changes were often more severe, especially in those who did not respond to folic acid. Therapeutic response was obtained after folic acid, vitamin B₁₂ or broad-spectrum antibiotics. Recovery after antibiotics suggested that the intestinal defect was related to the presence of bacteria, but the slow response suggested that it was not a simple direct relationship.

With the exception of the reports of Mollin (1967) and Mollin and Booth (1971), the vast majority of recent reports of TM describe an illness with an acute onset.

GIARDIA LAMBLIA IN HILL-DIARRHOEA AND TM

Giardia lamblia is today frequently identified in the stool, duodenal aspirate or jejunal biopsy of patients with TM (Wright *et al.*, 1977). Many cases begin with an acute episode and are epidemic. It is possible that the cases described by Hillary (1766) in Barbados, and some nineteenth century epidemics of hill-diarrhoea were associated with that protozoan. The descriptions of an acute onset of diarrhoea and excessive flatulence starting in the early hours of the morning in many reports of hill-diarrhoea are consistent with epidemic giardiasis. Very similar is the acute onset of diarrhoea with excessive flatulence and abdominal distention reported in giardiasis in Colorado (Moore *et al.*, 1969) and Leningrad (Brodsky *et al.*, 1974; Jokiph and Jokiph, 1977); significant malabsorption occurred in many. Microscopy was well developed in the latter decades of the nineteenth century and it seems unlikely that the parasite would have been missed. However, awareness of its pathogenicity was not apparent until the early twentieth century. Castellani (1905), working in Ceylon, was of the opinion that flagellates were important in producing diarrhoea, if present in great enough numbers. He added that they also occurred in normal people, especially natives. *G. lamblia* was associated with diarrhoea in soldiers during the First World War, in both the Middle-East and Indo-China (Porter, 1916; Fantham, 1916).

The mechanism of diarrhoea and steatorrhoea in giardiasis is not clear. There is now evidence that the organism invades the duodenal and jejunal mucosa (Brandborg *et al.*, 1967; Morecki and Parker, 1967; Saha and Ghosh, 1977) but it is difficult to understand how a flagellated protozoan can invade. It is not clear how many giardia are present in the ileal region; attempts to isolate the organism are usually directed to finding trophozoites in the upper jejunum, and cysts in the stool. Some patients with giardiasis have a significant overgrowth of enterobacteria in the small intestinal lumen and free bile acids in duodenal aspirate (Tandon *et al.*, 1977). *Giardia* and/or enterobacteria living in association with it might cause bile salt deconjugation, and subsequent malabsorption.

STRONGYLOIDES STERCORALIS IN THE AETIOLOGY OF TM

Strongyloides stercoralis is now known to be associated with chronic malabsorption (O'Brien, 1975). It was very common in chronic TM, particularly in Cochin China, and was at one time thought to be the cause of 'sprue' (Manson, 1898). Brown (1908) claimed that about 30 per cent of cases of sprue in Cochin China, Siam and Malaya had intestinal parasites in the stool, one of the commonest being *S. stercoralis*. That agent was, he said, considered by Normand in 1876 to be the

aetiological agent in epidemic diarrhoea in Cochin China, 'but its presence is now known to be merely adventitious, and to have no essential significance in the causation of the disease'. It now seems highly probable that *S. stercoralis* was responsible for a significant number of cases of TM in Cochin China. Manson (1898) considered that sprue there was more chronic than in India, and that observation is consistent with a *S. stercoralis* infection which, due to auto-infection, is known to be associated with very chronic malabsorption. A large series of patients with chronic strongyloidiasis has been reported many years after residence in the Far East (Gill *et al.*, 1977).

The role of coccidiosis (isospora), which has an extensive world distribution, in the aetiology of some cases of TM is unknown. It is an intra-cellular parasite and is difficult to detect in stool specimens.

DIFFERENCES BETWEEN THE DISEASE DESCRIBED BY MANSON AND THE TM SEEN TODAY

Today most cases have an acute onset; although the start of the disease is not always clearly demarcated, most patients can trace the disease to a bout of severe diarrhoea. Buccal changes, which often used to precede intestinal changes (Hillary, 1766; Rogers, 1913), are today most unusual, except in very severe cases; aphthous ulceration is never seen. Severe anaemia is also unusual, although folate deficient megaloblastic anaemia is present in severe cases of long duration.

CONCLUSIONS

Chronic TM was well recognised before 1880. Most early authors considered that it could have an insidious or an acute onset, beginning with either dysentery or non-dysenteric gastroenteritis. Other aetiologies, especially tuberculous ileitis, were undoubtedly responsible for some early cases. In 1880, Manson gathered all cases of TM under one heading – sprue – and that, with hindsight, was probably unfortunate (Cook, 1977). If the term tropical malabsorption (TM) had been used throughout, recognition of several entities – hill-diarrhoea and the 'white flux' or 'diarrhoea alba' – would have continued, and much subsequent confusion would have been avoided. Most TM seen today has an acute onset with diarrhoea (Lindenbaum, 1973) that is occasionally associated with bloody stools. Some are probably cases of travellers' diarrhoea (Rowe *et al.*, 1970). In some cases *G. lamblia* is present in the small intestine but its role in TM is unclear. High concentrations of enterobacteria are present in the small intestinal lumen (Gorbach *et al.*, 1969, 1973; Klipstein *et al.*, 1973; Tomkins *et al.*, 1975). The cause of continuing overgrowth after recovery from an acute gastrointestinal infection in some subjects is unknown. Small intestinal stasis, which sometimes follows such an infection (Drew *et al.*, 1947; O'Brien, 1967; Cook, 1978) might be important. A major problem is why only some cases of acute dysentery and

non-dysenteric disease progress to TM. Use of diphenoxylate, by depressing small intestinal motility, might be important in some cases. A disease with a slow or insidious onset now seems much less common than envisaged by Manson (1880). Of recent reports, those from London by Mollin (1967) and Mollin and Booth (1971) seem to be most closely related on clinical grounds to Manson's sprue. *S. stercoralis* has been clearly implicated in chronic TM and it seems likely that much disease described by Manson and others in China and the Far East was associated with that parasite, which, although common, was not then regarded as a pathogen.

General factors — chronic infections (including malaria) and vitamin deficiencies — were widely thought to be important factors in the 'diarrhoea alba' of the plains of India. The role of chronic malnutrition is still difficult to understand. People who have repeated infections, both intestinal and systemic, frequently find it difficult to associate a specific attack with the onset of an illness. Some patients with an 'insidious' onset of diarrhoea might fall into that group. Recent investigations have shown an impairment of glucose (Cook, 1971, 1973) and folic acid (Cook, 1974) absorption in patients with systemic infections; these observations might be important in the pathogenesis of chronic TM. None of the early workers incriminated intestinal parasites, including fungi (Low, 1928), in the aetiology of TM, despite their occasional presence (Manson, 1898; Begg, 1912; Low, 1928). The problem of the onset of TM long after removal from a tropical country is unsolved (Martin, 1856; Thin, 1897; Manson, 1898; Brown, 1908; Mollin, 1967), but because post-infective malabsorption can follow acute intestinal infections in non-tropical countries (Bahr, 1915) such cases must be viewed with scepticism. Why is the disease relatively unusual in Africa (Begg, 1912; Low, 1928; Cook, 1974)? It seems to be related to a lower incidence of acute diarrhoeal disease in Africa (Cook, 1974). Incidence of the disease in children (Grant, 1854; Crombie, 1880; Rogers, 1913) has always been low; this might be associated with their high rate of small intestinal transit.

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