Papers and Originals

Military Tropical Sprue from South-east Asia

W. O'BRIEN,* M.D., M.R.C.P.; M. W. J. ENGLAND,† M.B., B.Sc., M.R.C.P.ED., M.C.PATH.

Brit. med. J., 1966, 2, 1157-1162

Baker *et al.* (1962) defined tropical sprue as a "primary" malabsorption syndrome occurring in people resident in or previously resident in the tropics, usually associated with defective absorption of fat, carbohydrates, vitamins, and other nutrients and with radiological changes in the small intestine. The clinical and pathological features of sprue are modified by the age of the patient (Carmichael-Low, 1928; Stefanini, 1948), by the climate (Manson, 1879-80; Bahr, 1915), by previous nutritional deficiency, and by the duration of the illness (Gardner, 1958).

British Servicemen and their families in South-east Asia form a relatively homogeneous group in whom tropical sprue is seen with some frequency. Such a population is comparatively young, lives under constant medical care, and is unlikely to be malnourished. In such patients tropical sprue would be seen at an early and uncomplicated stage, and these form an ideal group for studying the pathogenesis of the disorder. Detailed studies have been made in a series of 42 patients who contracted sprue in South-east Asia or after their return to the United Kingdom from South-east Asia. The patients treated in London had severe sprue and showed no improvement during a control period of observation; indeed, they all showed further deterioration.

These patients were Servicemen or their wives, and were seen at the British Military Hospital, Singapore, or at the Queen Alexandra Military Hospital, London. We describe below our findings in this tropical sprue series and compare the results obtained with similar observations made on 12 patients having other forms of the malabsorption syndrome studied at the same time. This work was undertaken as part of the Wellcome Trust study into tropical megaloblastic anaemia.

Methods

Faecal fat excretion was estimated by the method of van de Kamer *et al.* (1949). Patients received a diet containing 50-100 g. of fat daily. Stools were collected, at first over periods of three to five days and later throughout the patients' stay in hospital. A mean daily fat excretion over 6 g. was regarded as abnormal.

D-Xylose absorption was measured by the D-xylose excretion test, with an oral dose of 5 g., by the method described by Santini *et al.* (1961). The lower limit of normal was taken as 25% excretion of the oral dose within five hours. Control subjects in our laboratory all excreted more than 30%.

Vitamin-B₁₂ absorption was determined by means of ⁵⁸Co-labelled vitamin B₁₂ and the modified faecal excretion technique described by Mollin *et al.* (1957). Hog intrinsic factor concentrate was given with 0.5 µg. of radioactive B₁₂. With this technique control subjects absorb more than 50% of the oral

dose. The results were checked by a scintillation count over the liver after a week (Glass *et al.*, 1954).

Barium-meal intestinal radiographs were obtained with the use of Micropaque as the barium preparation.

Jejunal biopsies were taken from the first 2 feet (30 cm.) of the jejunum with a Crosby capsule (Crosby and Kugler, 1957). The position of the capsule was determined radiologically after injection of sodium iodide down the tube. The biopsy specimens were examined under a dissecting microscope immediately after removal from the patient, as suggested by Holmes *et al.* (1961). Later they were sectioned and examined under high-power light microscopy and detailed measurements of the villi were made. In control subjects the villous height ranged from 345 to 616 µ (mean 446 µ) and the villous width from 98 to 135 µ (mean 124 µ). The height of the columnar cells ranged from 26 to 34 µ (mean 30 µ) (England and O'Brien, 1966). The term "partial villous atrophy" was used for villi which were under 300 µ in height and over 135 µ in width. Ileal biopsy specimens were taken by the same method.

Augmented histamine gastric test meal examinations were made by the method of Kay (1953).

Haematological methods were those described by Dacie (1956). A male was regarded as anaemic if his haemoglobin concentration was less than 13.6 g./100 ml., and a female if her haemoglobin concentration was less than 11.6 g./100 ml. (Wallensten, 1954).

Serum folate activity was measured by microbiological assay by means of *Lactobacillus casei*, as described by Waters and Mollin (1961). Serum samples were dispatched by air from Singapore to Dr. Mollin's laboratory after the addition of ascorbic acid and a bacteriostatic agent. The normal range by this method is 5.9 to 21 µg./ml. The serum folate levels of 50 soldiers serving in Singapore were found to be 3.0 to 13.8 µg./ml. (mean 6.7 µg.).

Serum vitamin-B₁₂ concentrations were also measured in Dr. Mollin's laboratory by microbiological assay, using *Euglena gracilis* according to the method described by Hutner *et al.* (1956). With this method the serum concentrations in healthy subjects range from 140 to 900 µg./ml. The serum vitamin-B₁₂ concentrations of 100 soldiers in Singapore ranged from 160 to 920 µg./ml. (mean 370 µg.).

Treatment.—Patients were treated either with folic acid or with an antibacterial course designed to reduce the bacteria of the intestine. Folic acid was given by intramuscular injection in doses of 0.2 mg. daily for two to eight weeks followed by larger oral doses. The other patients were given a mixed antibacterial course lasting 15 days, as recommended by French *et al.* (1956). The details were as follows: Succinylsulphathiazole 10 g. daily for five days, chlortetracycline 2 g. daily for five days, and chloramphenicol 2 g. daily for five days. The drugs were given consecutively.

Thirty-five of the forty-two patients appeared to be suffering from uncomplicated tropical sprue. In the remaining seven

* Consulting Physician, Queen Alexandra Military Hospital, London.

† Consulting Pathologist, Queen Alexandra Military Hospital, London.

the disorder was complicated by pregnancy or by a severe nutritional defect.

Uncomplicated Tropical Sprue

The natural progression of the syndrome is best described by dividing the 35 patients with uncomplicated sprue into three groups according to the duration of symptoms. Thus group 1 consists of eight patients in whom the duration of symptoms was under two months (mean 1.4 months). Group 2 consists of nine patients in whom the duration of symptoms was from two to three and a half months (mean 2.8 months). Group 3 consists of 18 patients in whom the duration of symptoms was from 4 to 12 months (mean 5.8 months).

Clinical Features

There was a preponderance of men among the patients presenting early; thus the ratio of men to women in the three groups was 7:1, 6:3, and 9:9 respectively. Approximately half the patients in all three groups had been living on an unsatisfactory diet for some weeks or months before the onset of symptoms.

Many of the female patients had eaten badly for some weeks or months before the onset of other symptoms. They were often reduced to taking snacks such as tea and toast, while they cooked full meals for their husbands. They usually blamed the heat for this loss of appetite. It was possible that this symptom was due to early sprue, but there was no evidence on this point. So far as the men were concerned the dietary deficiency was usually associated with the pack ration. The following history is typical: "Went to Borneo in February 1965 and was engaged on jungle patrols and lived on pack rations. After three weeks his appetite went off; he found the food too monotonous and he became unable to eat more than a part of the ration. At first he discarded the large and heavy meat tins, and then discarded more and more until he was living on two packets of biscuits and one packet of cheese daily. Diarrhoea did not start until he returned to base and fresh rations in July." This type of story was repeated again and again.

The presenting symptom was diarrhoea in all except two patients in the first two groups but in only just over half of those in group 3. One patient in group 1 presented with severe

glossitis and denied having diarrhoea. The presenting symptom in the remaining patients was increasing asthenia, loss of appetite, and reduction in weight.

Symptoms.—By the time these patients were admitted to hospital all but one patient in group 1 and three patients in group 3 complained of diarrhoea. Diarrhoea was precipitated by a return to fresh rations in five patients, by dietary indiscretions in three, and after what appeared to be an attack of acute febrile gastroenteritis in two. In another patient diarrhoea was precipitated by an emotional upset, and in three patients it occurred after short visits to other territories in the East. All the patients complained of loss of appetite, asthenia, and loss of weight. Loss of weight was proportional to the duration of symptoms; thus the mean loss in the three groups was 1.3, 1.8, and 2.9 stone (8.3, 11.4, and 18.4 kg.) respectively. Dyspepsia was limited to the patients in groups 2 and 3, two-thirds of whom suffered from this complaint, while vomiting was common only in the group 3 patients.

Physical examination revealed no abnormal signs apart from glossitis in the first two groups. Glossitis was present in a quarter of the patients in group 1 and in two-thirds of the other patients. The patients in groups 1 and 2 did not appear ill, but 10 patients in group 3 were obviously ill, pale, and showed hyperpigmentation; seven of these displayed a depressed mental state.

Laboratory Investigations (see Table)

Intestinal absorption tests showed malabsorption of fat, xylose, and radioactive vitamin B₁₂ in all patients. The degree of intestinal malabsorption was relatively mild in group 1 and more severe in the other groups, with daily faecal fat excretion rising to 34.9 g. Though, in general, malabsorption of vitamin B₁₂ was less severe in group 1, in some of these patients it was severe.

Barium-meal intestinal radiographs were normal in half the patients in group 1 but were abnormal in all other patients. The abnormal radiological findings were of "thickened transverse mucosal folds with or without dilatation of the jejunum."

Jejunal biopsies taken from the patients in group 1 showed villi and leaves when viewed under the dissecting microscope. The histological changes were mild, with some loss of height and increase in width of villi and with increased cellular infiltration. The dissecting microscopical appearance of the

Results of Laboratory Investigation of 42 Patients with Sprue and 12 Patients with other Forms of Intestinal Malabsorption

	Uncomplicated Sprue			Complicated Sprue		Other Causes of Malabsorption	
	Group 1 (0-2 months)	Group 2 (2-4 months)	Group 3 (over 4 months)	Sprue after Pregnancy	Sprue with Malnutrition	Idiopathic Steatorrhoea	Intestinal Helminths
No. of patients:	8	9	18	4	3	6	6
Faecal fat excretion (g./day)	9.9-22.0 (14.4)	13.0-34.9 (20.5)	6.6-34.8 (21.2)	12.0-21.8 (15.8)	11.2-17.5 (14.3)	8.5-21.0 (11.3)	6.6-42.6 (20.9)
D-Xylose excretion (%)	8.0-24.1 (14.5)	6.2-16.0 (9.5)	3.6-17.9 (8.3)	3.2 (2 pt)	12.8 (1 pt)	4.4-32.1 (20.0)	18.0-35.5 (29.0)
Absorption ⁵⁸ CoB ₁₂ (%)	0.9-41.0 (22.3)	0.0-29.5 (13.1)	0.0-23.0 (10.0)	10.0 (1 pt)	30 (1 pt), (0.9) (Schilling) (2 pt)	36.1-82.6 (58.5)	5.0-25.0 (11.0)
Barium meal	Normal 4, Abnormal 4	Abnormal 8	Abnormal 17	Abnormal 4	Abnormal 3	Abnormal 6	Normal 5, Abnormal 1
Jejunal mucosa dissecting microscope	Villi or leaves in 8	Leaves in 3, Convulsated in 6	Leaves in 6, Convulsated in 12	Leaves in 3, Convulsated in 1	Villi or leaves in 3	Flat in 6	Villi or leaves in 6
Histology:							
Mean villous height (μ)	375	271	249	198	352	S.V.A. 6	Normal 3, M.A.C. 2. P.V.A. 1
Mean villous width (μ)	125	131	151	139	135		
Mean columnar-cell height (μ)	26.1	24.1	23.3	20	27.1		
Hb in men (g./100 ml.)	12.3-15.0 (13.8)	11.8-15.0 (13.6)	4.6-12.8 (9.3)		5.2-9.5 (7.3)	10.0-13.8 (12.0)	11.8-14.8 (13.2)
Hb in women (g./100 ml.)	11.7	10.1-12.7 (11.6)	4.1-11.8 (7.3)	5.3-10.7 (7.3)	4.1	10.0-10.1	
Sternal marrow biopsy	Normoblastic 2, Mildly meg. 6	Mildly meg. 8, Frankly meg. 1	Mildly meg. 5, Frankly meg. 13	Frankly meg. 4	Frankly meg. 3	Mildly meg. 5, Frankly meg. 1	Normoblastic 5, Mildly meg. 1
Serum folate activity (mμg./ml.)	1.7-3.8 (2.7)	0.6-2.7 (1.6)	0.4-3.2 (1.4)	1.0-1.6 (1.3)	1.7-2.6 (2.0)	0.8-4.3 (2.6)	1.0-3.6 (2.4)
Serum vitamin B ₁₂ (μμg./ml.)	170-480 (320)	145-300 (225)	50-175 (120)	155-300 (220)	25-200 (100)	295-395 (360)	80-460 (230)

Figures in parentheses = Mean values.

M.A.C. = Minor histological abnormality. P.V.A. = Partial villous atrophy. S.V.A. = Subtotal villous atrophy. meg. = Megaloblastic.

biopsy specimens taken from the other groups was of thickened leaves or, more often, convolutions. The histological abnormality was more severe (see Table).

Ileal biopsies were taken from one patient in group 2 and from two patients in group 3, the jejunal biopsies of all three having shown convolutions with partial villous atrophy. The ileal biopsy from the patient in group 2 was normal and the biopsies from the other two patients showed a leaf pattern with partial villous atrophy, though of a less severe degree than that seen in the jejunum.

Haematological Findings.—There was no anaemia among the patients in group 1, but the sternal marrow showed mild megaloblastic change in six patients and was normoblastic in two. In group 2 patients four out of nine were mildly anaemic, and the sternal marrow showed mild megaloblastic change in eight and frank megaloblastic change in one. All but one of the patients in group 3 were anaemic; the sternal marrow showed frank megaloblastic change in 13 and mild megaloblastic change in five.

Serum folate activity was low in all patients, the mean levels for the three groups being 2.7, 1.6, and 1.4 $\mu\text{g.}/\text{ml.}$ respectively.

Serum vitamin-B₁₂ concentrations showed a progressive fall with increasing duration of symptoms; thus the mean concentrations for the three groups were 320, 225, and 120 $\mu\text{g.}/\text{ml.}$ respectively.

Tropical Sprue after Pregnancy

Clinical features.—Four patients developed sprue within three months of childbirth. In each patient the duration of symptoms was approximately one month, and the presenting symptom was asthenia, followed shortly by diarrhoea. Three of the patients were severely ill and all had severe glossitis.

Laboratory Investigation (see Table).—There was intestinal malabsorption of fat, carbohydrate, and vitamin B₁₂. Jejunal biopsies showed the appearance of partial villous atrophy associated with a swollen leaf pattern in three patients and convolutions in the other. (The mean villous height was 198 μ , width 139 μ , and mean columnar cell height 20 μ). All four patients were anaemic and bone-marrow biopsies showed frank megaloblastic change. Levels for serum folate activity were low and the serum vitamin-B₁₂ concentrations were similar to those found in group 2 patients.

Tropical Sprue Complicated by Previous Nutritional Deficiency

Clinical Features.—Three patients—two soldiers and the wife of a soldier—had for a variety of reasons been unable to eat more than small snacks for periods of 6 to 10 months before their admission. Some of the patients with uncomplicated sprue had also eaten badly before they developed diarrhoea, but in these three patients the dietary defect was outstanding. In two patients diarrhoea started two months and two weeks respectively before admission, while the other patient denied having diarrhoea. Physical examination revealed pallor, hyperpigmentation, and severe glossitis in all three.

Laboratory Investigation (see Table).—Steatorrhoea was mild or moderate. Xylose excretion was moderately depressed in one patient and flat glucose-tolerance curves were obtained in the other two. There was severe malabsorption of radioactive vitamin B₁₂ in two patients and mild malabsorption in the other. Barium-meal intestinal radiographs were abnormal. Jejunal biopsies showed a normal villous or leaf pattern and there was only mild histological abnormality. (The mean villous height was 352 μ , width was 135 μ , and the columnar cell height was 27.1 μ). All three patients were anaemic, with frank megaloblastic marrow change. The serum folate activity was low and the serum vitamin-B₁₂ concentration was below

80 $\mu\text{g.}/\text{ml.}$ in two patients. In one patient, in whom there was a very low serum vitamin-B₁₂ concentration and severe intestinal malabsorption of vitamin B₁₂ when given with intrinsic factor, there was also gastric achlorhydria after maximal histamine stimulation. In this patient normal acid secretion and normal absorption of vitamin B₁₂ did not return until after 18 months.

Intestinal Malabsorption due to Idiopathic Steatorrhoea

In six patients intestinal malabsorption was thought to be due to gluten enteropathy for the following reasons. In five there was a long history of intestinal trouble pre-dating their arrival in the tropics, while the other patient, who presented with an iron-deficiency anaemia, had a sister suffering from coeliac disease. In addition, jejunal biopsies showed the classical pattern associated with coeliac disease. Two patients were treated with folic acid, and though both showed a haematological response there was no improvement in intestinal absorption or in the jejunal mucosal pattern. Two patients were treated with a gluten-free diet and improved.

Laboratory Investigation (see Table).—There was variable steatorrhoea and malabsorption of xylose. Absorption of radioactive vitamin B₁₂ was mildly subnormal in two patients and normal in three. Barium-meal intestinal radiographs were abnormal, and jejunal biopsies showed a flat or pavement pattern with subtotal villous atrophy in all. Anaemia if present was mild and the sternal marrow showed mild megaloblastic change in five patients and frank megaloblastic change in one, who had become anaemic towards the end of pregnancy. There was folate deficiency, but the serum vitamin-B₁₂ concentrations were normal.

Intestinal Malabsorption with Early Intestinal Helminth Infestation

Six soldiers from Borneo were admitted with a history of diarrhoea indistinguishable from that suffered by patients with tropical sprue but they differed from the latter in the following respects. There was evidence of recent helminth infestation in the form of irritating rashes and pulmonary episodes, a high blood eosinophilia, and in three the ova of hookworms or the larvae of *Strongyloides stercoralis* were found. In addition, the absorption of xylose was normal in five out of six patients, and the symptoms and steatorrhoea subsided after anthelmintic treatment in five patients.

Laboratory Investigation (see Table).—All these patients showed steatorrhoea and malabsorption of radioactive vitamin B₁₂, but xylose excretion was normal in five. Barium-meal intestinal radiographs were normal and jejunal biopsies were normal apart from heavy eosinophilic infiltration in five patients. There was mild anaemia in three patients and the sternal marrow was normoblastic in five. Serum folate activity was low in all, and the serum vitamin-B₁₂ concentration was subnormal in two. In one of these latter patients malabsorption of vitamin B₁₂ persisted following anthelmintic treatment and was associated with a serum vitamin-B₁₂ concentration of 115 $\mu\text{g.}/\text{ml.}$ An ileal biopsy at this time was normal. This malabsorption defect was rapidly corrected after a short course of chlortetracycline. One patient showed malabsorption of xylose, partial villous atrophy, and mild megaloblastic marrow change and required folic acid to complete his cure.

Treatment

The response to treatment with either folic acid or antibiotics in the patients of group 1 was uniformly satisfactory and intestinal malabsorption cleared within a month. Considerable improvement often occurred after patients' admission to hospital and before any specific treatment was started, so it is doubtful

whether such treatment did more than hasten recovery. On the other hand, there was little evidence of spontaneous improvement in the patients of the other groups, though several were observed for four to five weeks before specific treatment began. There was little difference between the response of the group 2 and group 3 patients, though the former tended to improve more quickly.

Folic Acid Treatment in Groups 2 and 3

Symptomatic Response.—Fifteen patients were treated with folic acid alone, with remarkable symptomatic improvement. Those who were ill with diarrhoea, sore mouth, complete anorexia, severe asthenia, and deep mental depression would within 48 hours be difficult to keep in bed. The sore mouth rapidly cleared, diarrhoea ceased, energy returned, and the appetite became insatiable. A steady gain in weight ensued.

Intestinal Response.—Nine of these patients were followed until eventually they were cured. Absorption of fat, xylose, and radioactive B_{12} returned to normal within a month in one patient, within three months in three patients, and within a year in five. The jejunal mucosa returned to normal in five within a year and in another within 18 months. In three patients the repeat biopsy was taken after only three months' treatment, the only abnormality found being minor histological change. The fate of the remaining six patients was as follows. Two were given antibiotics after treatment with folic acid for one and two months respectively; they had only mild residual malabsorption at this time, which later subsided and the jejunal mucosa returned to normal. Three patients who still had intestinal malabsorption after less than two months' treatment had to return to the United Kingdom for reasons unconnected with their health. They thus left our care, but we have heard since that all three are well. Finally, one patient in whom intestinal malabsorption of fat and carbohydrate had cleared still had malabsorption of vitamin B_{12} and an abnormal jejunal biopsy after three months. He continued to remain well but was unable to return for further follow-up.

Haematological Response.—The haematological response of these patients to folic acid in doses of 0.2 mg. intramuscularly daily was satisfactory and has already been described (O'Brien and England, 1964).

Folic Acid Treatment in Complicated Tropical Sprue

Three of the four patients who developed sprue following pregnancy showed a dramatic symptomatic improvement after folic acid, and steatorrhoea rapidly subsided. In one patient 0.2 mg. of folic acid daily was insufficient to raise the serum folate level above 2 $\mu\text{g./ml.}$ after a month; there was little symptomatic improvement and steatorrhoea continued unabated. The three patients in whom sprue was complicated by previous nutritional deficiency also showed a striking improvement after folic acid, and steatorrhoea rapidly subsided. However, in two of them malabsorption of vitamin B_{12} persisted.

Antibiotic Treatment in Groups 2 and 3

Symptomatic Response.—Eleven patients were treated with the antibacterial course. Four of those more severely affected also received small oral doses of folic acid at some period. There was no symptomatic improvement for two to three weeks, and thereafter improvement was slow. Diarrhoea was often aggravated during treatment with chlortetracycline, and glossitis persisted.

Intestinal Response.—The longest follow-up period in these patients was three months, and by that time intestinal absorption of fat, xylose, and vitamin B_{12} had returned to normal in nine of them. In two patients absorption of vitamin B_{12} was

still grossly abnormal, and one of these patients also had mild residual steatorrhoea. Jejunal biopsies were repeated after three months in nine patients, and in six the mucosal pattern had returned to normal, while in three there was only mild abnormality. An ileal biopsy was taken from one of the patients in whom malabsorption of vitamin B_{12} had persisted and it was normal. In this patient a further short course of chlortetracycline was followed by a return to normal absorption of vitamin B_{12} .

Haematological Response.—The haematological response to antibiotics differed from that seen to follow intramuscular folic acid. In two patients with moderate and severe megaloblastic anaemia respectively there was a delayed response. After 14 and 25 days respectively a low reticulocytosis developed, rising to a peak of 12.8 and 12.0% on the twenty-sixth and fiftieth days. This was followed by a satisfactory rise in haemoglobin and a slow rise in serum folate activity. The effect of small oral doses of folic acid in relation to antibiotics was also studied. Two anaemic patients received small oral doses of folic acid, the haematological responses being illustrated in Figs. 1 and 2. One patient was given 0.1 mg. of folic acid daily, and after two weeks there was no haematological response whatsoever. The same dose of folic acid was then continued while she received the antibacterial course, when a satisfactory haematological response followed. The other patient was given 0.2 mg.

FIG. 1.—Haematological response to 0.1 mg. of folic acid orally before and with antibiotics in tropical sprue.

FIG. 2.—Haematological response to 0.2 mg. of folic acid orally after a course of antibiotics in tropical sprue.

of folic acid daily by mouth after the antibiotic course, and a haematological response ensued.

Discussion

Course of Tropical Sprue

Stefanini (1948) described three consecutive stages in the sprue syndrome. The first stage was characterized by diarrhoea and extreme asthenia, the second stage by the addition of glossitis, while in the third stage, which supervened after five weeks, there was megaloblastic anaemia. Gardner (1958) adopted this classification and thought that sprue as seen in American soldiers in Puerto Rico did not progress beyond the first stage, that the majority of the British military patients reported by Keele and Bound (1946) and by Elder (1947) were in the second stage, while most civilians with sprue in Puerto Rico were first seen in the third stage. Gardner thought that the incidence of anaemia merely reflected the duration of the illness and the previous nutritional state of the patients. A further stage in sprue was described by Booth and Mollin (1964) in which there was severe vitamin-B₁₂ deficiency and in which indiscriminate treatment with folic acid might precipitate subacute combined degeneration of the cord.

In the present series of patients with "military sprue" there was a regular pattern of development of the syndrome which was very similar to that seen in Stefanini's patients, except that the progress was slower. In patients presenting within two months of the onset of symptoms there was malabsorption of fat, xylose, and vitamin B₁₂ associated with mild abnormality of the intestinal mucosa. At this early stage there was always folate deficiency and usually mild megaloblastic marrow change. In patients seen between two and four months of the onset of symptoms malabsorption and intestinal mucosal changes were more severe. The folate deficiency was more severe and the serum vitamin-B₁₂ concentration had begun to fall. Megaloblastic marrow change was universal, though there was little anaemia. In patients in whom the disorder had been present for four months or more intestinal malabsorption had not significantly worsened, but the jejunal mucosa now showed the classical pattern of partial villous atrophy. Ileal biopsy specimens taken from two patients also showed partial villous atrophy, though of a less severe degree than seen in the jejunum. This was in contrast to the normal finding in the ileal biopsy from a patient in group 2. Megaloblastic anaemia had now become more evident and in some patients it was severe. Folate deficiency was more severe and the serum vitamin-B₁₂ concentration showed a considerable fall, though not to the very low levels seen in pernicious anaemia.

The progress of the clinical course of sprue was altered by pregnancy and by previous nutritional deficiency. Four patients who contracted sprue within three months of childbirth showed severe intestinal malabsorption, severe jejunal mucosal change, and frank megaloblastic anaemia in spite of a short history of illness. It may be that the symptoms of sprue were suppressed during pregnancy, or, perhaps more likely, that severe folate deficiency hastened the progress of the condition. There were also three patients who appeared to suffer primarily from nutritional megaloblastic anaemia with mild sprue, and it seems possible that folate deficiency under certain circumstances may be associated with intestinal malabsorption in the tropics. It may be relevant that ten Thije *et al.* (1964) found megaloblastic change in the jejunal crypt epithelium associated with folate deficiency, the cells reverting to normal after treatment with folic acid.

The uniform pattern of tropical sprue seen in our patients was a considerable aid to diagnosis. Admittedly the patients with idiopathic steatorrhoea formed a small and selective group, but the association of normal or near-normal absorption of vitamin B₁₂ with the more severe jejunal mucosal change was in contrast to the findings in patients with tropical sprue. This

finding had previously been noted by Mollin and Ross (1957). Similarly the normal absorption of xylose distinguished the patients with malabsorption associated with early intestinal helminth infestation.

Effects of Treatment of Tropical Sprue

In these patients folic acid was effective in the treatment of sprue of up to a year's duration. It is not suggested that the small doses of folic acid used were optimal for the purposes of correcting the intestinal defect. In three patients with severe folate deficiency 0.2 mg. of folic acid given intramuscularly daily for four to eight weeks was insufficient to raise the serum folate level to above 3 $\mu\text{g./ml.}$, and it is of interest that there was no intestinal response in these patients while the serum folate level remained low. The results of treatment of 11 patients with the antibacterial course given with or without small oral doses of folic acid were, if anything, better than the results obtained with folic acid. The persistence of intestinal malabsorption of vitamin B₁₂ in two patients after this short course of treatment was disturbing. Mollin *et al.* (1957) had a similar experience, and it may be that antibiotics should be given for a longer period.

The two main differences in the response to treatment with folic acid and antibiotics were in the symptomatic and haematological responses. Symptomatic improvement after antibiotics was slow and contrasted with the dramatic improvement after folic acid. The haematological response to 0.2 mg. of folic acid given intramuscularly daily was rapid and full, and has already been reported (O'Brien and England, 1964). After antibiotics the haematological response in two anaemic patients was delayed. This was contrary to the experience of Klipstein (1964), who obtained a satisfactory haematological response when antibiotics were given with a full hospital diet. Antibiotics appeared to improve the intestinal absorption of folic acid, for with small oral doses of folic acid a haematological response did not occur until antibiotics were given.

Aetiology of Tropical Sprue

In some patients diarrhoea was precipitated by non-specific gastrointestinal insults or by infective gastroenteritis. Lindenbaum (1965) showed that short-lived intestinal malabsorption was common with various infections of the small intestine in India. It is, however, the persistence of intestinal malabsorption which distinguishes tropical sprue. In other patients the onset of symptoms was related to a change from a limited to a full diet. This, with the disparity between the degree of malabsorption and the mild intestinal mucosal change in early sprue, is suggestive of a primary functional disorder. The constancy of folate deficiency and malabsorption of vitamin B₁₂ at this early stage and the satisfactory therapeutic response to both folic acid and antibiotics suggest that this disorder of function may be related to folate deficiency and bacterial colonization of the small intestine.

In studies of "military tropical sprue" in Puerto Rico, Sheehy *et al.* (1963) also found that the jejunal lesion might be mild, but their patients differed from ours in that megaloblastic anaemia did not occur in spite of a relatively long duration of symptoms. These patients also differed in that folic acid did not improve intestinal malabsorption if the duration of symptoms was over four months (Sheehy *et al.*, 1965). It seems likely that folate deficiency was less severe in the American patients. In this context the previous diet of our patients may have been of importance. Ayrey (1948) found a high incidence of sprue among soldiers living on pack rations that contained no fresh food. We compared the serum folate levels of 50 soldiers living on fresh rations in Singapore with the levels in 50 soldiers living on pack rations in Borneo. The mean serum folate level for the former group was 6.7 $\mu\text{g./}$

ml. compared with a mean level of 4.3 $\mu\text{g.}$ for the latter group. In a population in the tropics where folate deficiency was common sprue might also be expected to be common.

Summary

The clinical and pathological findings in 42 patients with "military tropical sprue" from South-east Asia are described.

In the early stages intestinal malabsorption of fat, xylose, and vitamin B₁₂, mild jejunal change, and folate deficiency were found. In patients seen after two months these abnormalities were more severe. After four months the intestinal mucosa, both jejunal and ileal, had the appearance of partial villous atrophy, megaloblastic anaemia due to folate deficiency occurred, and there was a considerable fall in the serum vitamin-B₁₂ concentration. The regular clinical and pathological pattern was found helpful in diagnosis.

Both folic acid and a mixed antibacterial course were effective in causing a remission of intestinal malabsorption and a return of the intestinal mucosa to normal. The symptomatic and haematological responses to antibiotics were slow. Antibiotics appear to improve intestinal absorption of folic acid.

These findings are in accord with the hypothesis that temporary intestinal malabsorption arising from non-specific causes may be maintained by secondary folate deficiency and bacterial proliferation in the small bowel. In a population in the tropics where folate deficiency is common sprue might also be expected to be common.

We thank Lieutenant-General Sir Robert Drew for his active interest and the Wellcome Trust for generous financial support. We are particularly indebted to Professor D. L. Mollin for constant help and advice throughout this work. We also thank Dr. Leon

Ellenbogen, of the Lederle Laboratories, Pearl River, N.Y., for the supply of intrinsic factor.

REFERENCES

- Ayrey, F. (1948). *Trans. roy. Soc. trop. Med. Hyg.*, **41**, 377.
 Bahr, P. H. (1915). *A Report on Researches on Sprue in Ceylon*. University Press, Cambridge.
 Baker, S. J., Ignatius, M., Mathan, V. I., Vaish, S. K., and Chacko, C. C. (1962). In *Ciba Foundation Study Group Report*, No. 14, p. 84.
 Booth, C. C., and Mollin, D. L. (1964). *Amer. J. dig. Dis.*, **9**, 770.
 Carmichael-Low, G. (1928). *Quart. J. Med.*, **21**, 523.
 Crosby, W. H., and Kugler, H. W. (1957). *Amer. J. dig. Dis.*, **2**, 236.
 Dacie, J. V. (1956). *Practical Haematology*, 2nd ed. Churchill, London.
 Elder, H. H. A. (1947). *J. trop. Med. Hyg.*, **50**, 212.
 England, N. W. J., and O'Brien, W. (1966). *Gut*, **7**, 128.
 French, J. M., Gaddie, R., and Smith, N. M. (1956). *Quart. J. Med.*, **25**, 333.
 Gardner, F. H. (1958). *New Engl. J. Med.*, **258**, 791, 835.
 Glass, G. B. J., Boyd, L. J., Gellin, G. A., and Stephanson, L. (1954). *Arch. Biochem.*, **51**, 251.
 Holmes, R., Hourihane, D. O'B., and Booth, C. C. (1961). *Lancet*, **1**, 81.
 Hutner, S. H., Bach, M. K., and Ross, G. I. M. (1956). *J. Protozool.*, **3**, 101.
 Kay, A. W. (1953). *Brit. med. J.*, **2**, 77.
 Keele, K. D., and Bound, J. P. (1946). *Ibid.*, **1**, 79.
 Klipstein, F. A. (1964). *Amer. J. dig. Dis.*, **9**, 778.
 Lindenbaum, J. (1965). *Brit. med. J.*, **2**, 326.
 Manson, P. (1879-80). *China imp. Customs med. Rep. Shanghai*, **19**, 33.
 Mollin, D. L., Booth, C. C., and Baker, S. J. (1957). *Brit. J. Haemat.*, **3**, 412.
 — and Ross, G. I. M. (1957). *Vitamin-B₁₂ and Intrinsic Factor*, 1st Europ. Symp. Hamburg, 1956, p. 413. Enke, Stuttgart.
 O'Brien, W., and England, N. W. J. (1964). *Brit. med. J.*, **2**, 1573.
 Santini, R., Sheehy, T. W., and Martinez-de Jesus, J. (1961). *Gastroenterology*, **40**, 772.
 Sheehy, T. W., Cohen, W. H., and Brodsky, J. P. (1963). *Amer. J. dig. Dis.*, **8**, 826.
 —, Wallace, D. K., and Legters, L. J. (1965). *J. Amer. med. Ass.*, **194**, 1069.
 Stefanini, M. (1948). *Medicine (Baltimore)*, **27**, 379.
 ten Thije, O. J., Veeger, W., Braams, W. G., and Nieweg, H. O. (1964). *Amer. J. dig. Dis.*, **9**, 774.
 van de Kamer, J. H., Huinick, H. ten B., and Weyers, H. A. (1949). *J. biol. Chem.*, **177**, 347.
 Wallensten, S. (1954). *Acta chir. scand.*, Suppl. No. 191.
 Waters, A. H., and Mollin, D. L. (1961). *J. clin. Path.*, **14**, 335.

Tropical Sprue in Hong Kong

J. F. WEBB,* M.C., M.D., M.R.C.P.ED.; B. SIMPSON,† M.R.C.P.ED.

Brit. med. J., 1966, **2**, 1162-1166

Many descriptions of tropical sprue have been published, but several aspects of the disease are inadequately documented or the subject of dispute, and four of these form the subject of this paper. First, the fully developed clinical picture is easily recognized, but the diagnosis may be missed in the early stages because the significance of certain initial symptoms is not appreciated. Secondly, while antibacterial therapy produced an excellent response in British patients treated in England by French *et al.* (1956), it is not known whether similar subjects respond so well when treated in the tropics. Thirdly, folic-acid therapy usually corrects the anaemia which is a common feature of tropical sprue, but its effect on the intestinal lesion is less certain: Gardner (1956) obtained a reasonably good response in United States Service men in Puerto Rico, but Sheehy and Floch (1964) concluded from experience in the same area that folic acid rapidly alleviated the haematopoietic but not the intestinal lesion, and although previous reports from Hong Kong on the effects of folic acid in sprue (Rosenthal, 1952; Webb, 1956) have been favourable, more detailed data are desirable. Finally, remarkably little is known about the fate of expatriate patients who remain in the tropics after treatment.

Material and Methods

Our series comprises 21 men aged 18 to 38 and nine women aged 18 to 50; they belonged to a closely knit community and rarely left Hong Kong. Parasitic infestation and bacterial infection of the gastrointestinal tract were excluded by stool examination.

Haematological methods were as described by Dacie (1956). Serum folate levels were estimated by the method of Waters and Mollin (1961), the normal range being 6 to 21 $\mu\text{g.}/\text{ml.}$, and serum vitamin-B₁₂ levels by the method of Hutner *et al.* (1956), the lower limit of normal being 140 $\mu\text{g.}/\text{ml.}$; these tests were performed in the laboratory of Dr. D. L. Mollin at the Hammersmith Hospital.

Gastric Function.—In anaemic patients the fasting aspirate was tested for free acid, and if none was present an augmented histamine test meal examination was made (Kay, 1953).

Faecal fat excretion was measured in at least three consecutive 24-hour specimens of stool by the wet method of van de Kamer *et al.* (1949), 6 g./day being taken as the upper limit of normal.

Glucose absorption was assessed by using an oral dose of 50 g. of glucose, capillary blood specimens being taken and the total reducing substances present being estimated. A rise in

* Colonel, late R.A.M.C.

† Major, R.A.M.C.