A household epidemic of tropical sprue

V. I. MATHAN, M. IGNATIUS, AND S. J. BAKER

From the Wellcome Research Unit, Christian Medical College Hospital, Vellore, S. India

EDITORIAL COMMENT   This study focuses on an Indian family unit in which 16 out of 27 members developed a malabsorption syndrome: seven were studied in detail and the possible epidemiological factors are analysed. The possibility of a virus infection is discussed.

Tropical sprue has been described as occurring in both endemic and epidemic forms (Walters, 1947; Ayrey, 1948; Stefanini, 1948; Baker, 1957; Baker, Mathan, and Joseph, 1962). Bahr (1915) mentions 'sprue houses' where successive tenants were attacked with sprue, and records several cases occurring among members of one family.

This paper presents epidemiological, clinical and laboratory data on a relatively isolated household of 27 people, of whom more than half developed tropical sprue over a period of three months.

METHODS

Haematological investigations were carried out by the methods described by Dacie (1956). Serum vitamin B_{12} levels were estimated microbiologically using *Euglena gracilis* Z strain (Ross, Hutner, and Bach, 1957). The Figlu test was carried out by the method of Kohn, Mollin, and Rosenbach (1961). Faecal fat estimations were determined by the method of van de Kamer, ten Huinink, and Weyers (1949). Xylose absorption was studied by giving a 5 g. dose of d-xylose and measuring the urinary excretion of xylose in the subsequent five hours. Vitamin B_{12} absorption studies were carried out using a 1 μg. dose of labelled B_{12} and measuring the faecal excretion (Heinle, Welch, Scharf, Meacham, and Prusoff, 1952); when abnormal it was repeated using 40 mg. of a known active intrinsic factor preparation.

Barium meal examinations were carried out using non-flocculable barium as described previously (Paterson and Baker, 1958). Jejunal biopsies were performed using the multiple retrieving biopsy tube (Baker and Hughes, 1960).

THE HOUSE AND THE ENVIRONMENT

The house (Fig. 1), with three acres of farm land, is situated in a fertile valley at the foot of some low hills. It is built in two identical sections, each arranged around a central courtyard. On one side is a windowless room used for cooking and storage. The other three sides of the courtyard are open ver-

andahs, of which one part is used for sleeping, and the rest to shelter the cattle. The roof is made of thatch, and the walls and floor are of dried earth. There are no latrines, the surrounding fields serving for this purpose. Household waste, cow dung, and other refuse are collected in a pit in front of the house, and periodically transferred to the fields.

Immediately surrounding the house is a small grove of coconut palms and mango trees, and beyond are fields where rice, ground-nuts, sugar-cane, plantains, some vegetables, and a little ragi (*Elusine coracana*) are grown. Two unprotected wells about a hundred yards from the house provide water for drinking and irrigation.

The average yearly rainfall in this area is about 30 in., occurring mainly in the months July to December. In 1961 the rainfall was 34·6 in. The average day time temperature is about 35 to 40°C. in the shade in the summer, and 16 to 25°C. in the winter.
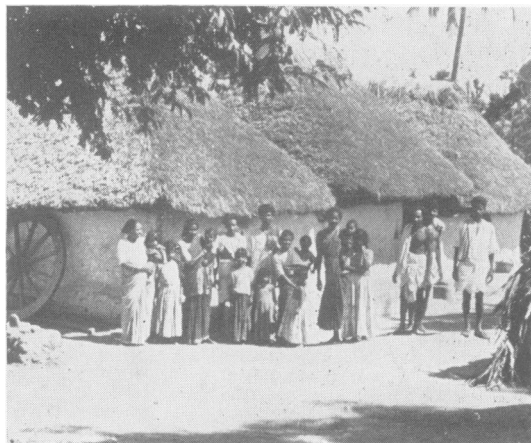

FIG. 1.   *The house and some of the family.*

THE FAMILY

This is a Hindu joint family, consisting of 13 females and 14 males belonging to four generations, 12 being children under the age of 12 (Fig. 2). Four of the younger children attend primary school in the nearest village half a mile away. All the adults and the older children work in the fields, but have frequent contacts with the village.

The family own the house and the land, and also possess two pairs of bullocks used for ploughing and two cows. The crops grown provide the chief source of income, which for the whole family in cash and kind is estimated to be in the region of Rs. 100 to 150 (£8 to £12) per month.

The family are not strict vegetarians, but meat, fish, or eggs are rarely used because they are expensive. The chief sources of protein are dhal and similar pulses, while calories are supplied mainly by rice and ragi. The two major meals are at noon and at night, when rice and preparations of dhal, with occasionally a few vegetables and sometimes curds or buttermilk, are eaten. In the morning, the cold rice left over from the night before, or a preparation of ragi called 'kulu', is eaten. Most of the family's food is grown in their own fields, but some commodities such as oil and pulses are obtained from shops in the neighbouring village. Although the family keeps two cows, the milk yield is poor, and what little milk there is, is used for the very small children or for preparation of curds. No extra milk is bought.

The estimated daily food intake per adult male is in the region of 1,800 calories with 50 g. of protein, 20 g. of fat, 20 to 30 mg. of ascorbic acid, 1,000 i.u. of vitamin A, and 80 to 100 μg. of folic acid. These figures are similar to those found by analysis of food as eaten by similar people in a neighbouring area (Rao and Rao, 1958). The vitamin B_{12} and iron intake were measured by microbiological assay and chemical analysis of the food as eaten. The mean daily intake of vitamin B_{12} was 0·38 μg. and iron 26 mg. The diet is thus deficient in animal protein,
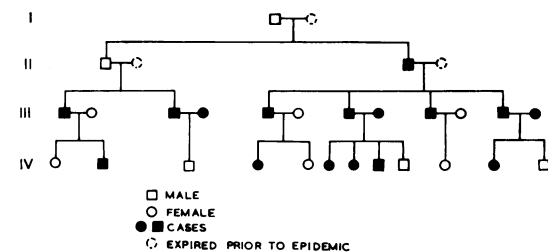
calories, and vitamins. Unboiled water from the wells is used for drinking.

ONSET OF THE EPIDEMIC

The family had an uneventful medical history until 15 November 1961, when a man, Ks. aged 59, developed diarrhoea. Three weeks later, M., a man aged 35, developed fever and two days later diarrhoea. Five days later K., a man aged 30, developed diarrhoea. Over the next two weeks a further 13 individuals became ill (Fig. 3). In all, 16 people (nine males and seven females) ranging in age from 2 years to 59 years were affected. Six of those affected were under 12 years of age.
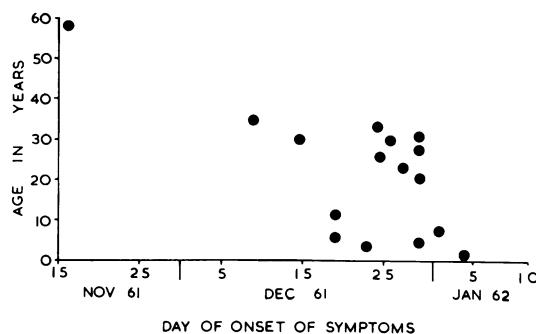

FIG. 3. *Time of onset and age of the 16 cases.*

Detailed questioning did not reveal any change in the diet, source of food or water before the onset of the disease. No history of contact of any member of the family with other known cases of diarrhoea could be elicited. A survey of the neighbouring village was made, including the local school, and no other cases of diarrhoea were detected.

CLINICAL FEATURES

The onset of the disease was usually gradual over a period of two or three days. At the onset four subjects noticed fever, all noticed general malaise, anorexia, a feeling of fullness or distension of the abdomen, loud gurgling borborygmi, and the passage of several watery or loose stools. In three, small amounts of blood and mucus were present in the stools for the first few days.

The diarrhoea usually persisted thoughout the course of the disease, but in five subjects intermissions of one to several days occurred at varying intervals. Frequently the stools were pale, bulky, and mushy in consistency.

FIG. 2. *Family tree.*

Clinical examination of the affected individuals, when first seen in January 1962, showed no specific physical signs which could be attributed to the diarrhoea. Six subjects showed some evidence of recent loss of weight. There were no clinically detectable signs of avitaminosis.

INVESTIGATIONS

Seven of the affected individuals were admitted to hospital for study in a metabolic ward. Cases P. and Ch. were asymptomatic at the time of study.

STOOLS Examination of the stools showed no evidence of parasites such as hookworm, amoebae, or giardia lamblia. In three cases, admitted within two weeks of the onset of symptoms, no bacterial pathogen, including pathogenic *E. coli*, could be isolated from the stools on repeated cultures.

BLOOD The haematological data at the time of admission are shown in Table I. Ka., who had been delivered one month previously, was suffering from an iron-deficiency anaemia. Three subjects had a megaloblastic bone marrow and five out of six had a serum B_{12} level below 100 $\mu\mu$g./ml. Patient M. had a positive Figlu test. Serum folic acid levels could not be determined.

INTESTINAL FUNCTION Steatorrhoea was present in five of the six adults, the faecal fat exceeding 6 g. per day. In one adult (P.), who was asymptomatic at the time of study, there was no steatorrhoea. The child (Ch.), aged 2, also had steatorrhoea, excreting 10% of the daily fat intake.
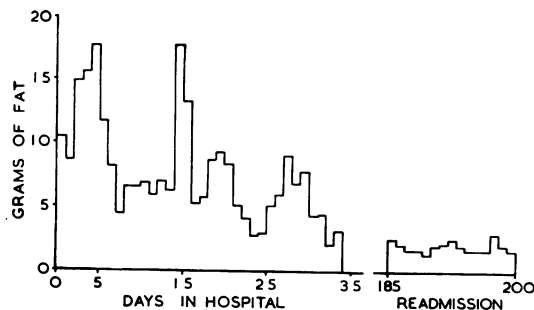

FIG. 4. *Faecal fat excretion of M., shown as a three-day running mean during original admission and readmission.*

The xylose excretion was abnormal in all seven patients and the glucose tolerance test was abnormal in three out of six patients. One patient (M.) showed a defect in vitamin B_{12} absorption not corrected by intrinsic factor but the other five patients had normal vitamin B_{12} absorption. The results of the studies are shown in Table II, and the daily faecal fat excretion of patient M. is shown in Figure 4.

RADIOLOGY A barium meal study of the gastrointestinal tract was carried out in five cases. The typical pattern of malabsorption with dilated loops, increased transverse barring, and a coarse mucosal pattern were found in all five (Fig. 5). There was no evidence of strictures or other organic lesions in any of them.

JEJUNAL BIOPSY Jejunal biopsies were performed in five

TABLE I

HAEMATOLOGICAL DATA

Initials	Age	Sex	Hb (g./100 ml.)	P.C.V.	Serum Vitamin B_{12} ($\mu\mu$g./ml.)	Figlu Test	Bone Marrow
M	35	M	16	43	70	Positive	Megaloblastic
K	30	M	13	40	75	Negative	Normoblastic
Ar	33	M	14	41	75	Negative	Megaloblastic
Ka	25	F	9	29	140	Negative	Normoblastic
R	28	M	14	41	97	Negative	Megaloblastic
P	30	M	15	46	88	Negative	Normoblastic
Ch	2	M	12	36	—	—	Normoblastic

TABLE II

ABSORPTION STUDIES[1]

Initials	Mean Stool Fat (g./day) during First Week of Study (Intake 50 g/day)	Xylose Excretion in Urine (% of dose)	Glucose Tolerance Test (maximum rise in blood sugar mg./100 ml.)	B_{12} Absorption (μg.)	
				Without Intrinsic Factor	With Intrinsic Factor
M	12·5	11	8	0·09	0·12
K	12	13	80	0·60	—
Ar	9	7	50	0·43	—
Ka	10	6	17	0·61	—
R	7	12	19	0·60	—
P	3	3	60	0·67	—
Ch	2[2]	5	—	—	—

[1]Case P. and Ch. were asymptomatic at the time of study. All the other patients had symptoms.
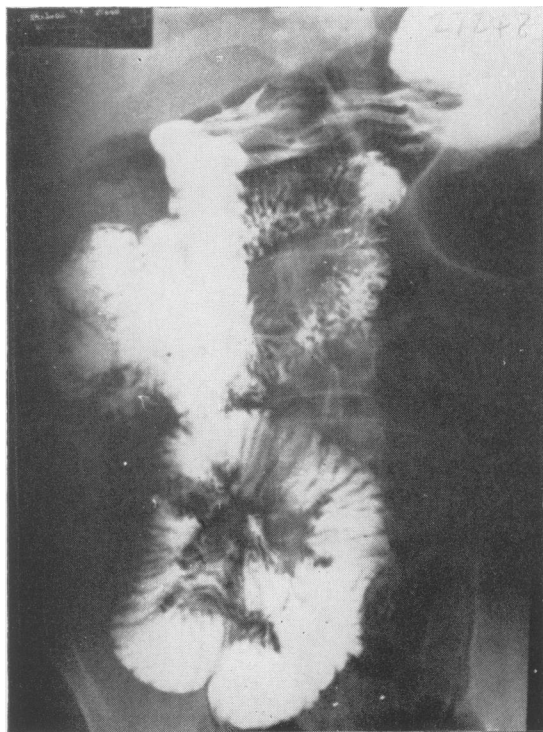[2]Intake 20 grams/day.

FIG. 5. *Barium meal picture of M. showing dilatation and transverse barring.*

FIG. 6. *Dissecting microscopic appearance of M.'s jejunal biopsy in 1962 (× 30).*

out of the seven patients in hospital. In each case changes in villus architecture ranging from leaves to convolutions were found, together with various histological abnormalities (Table III). The most abnormal biopsy was that of patient M. who showed a convoluted pattern (Fig. 6) and a histological picture of 'partial villous atrophy' (Fig. 7).

COURSE

Ks., the first individual affected, developed oedema and died 45 days after the onset of the diarrhoea, the day before the family were first seen. The others were treated symptomatically with antidiarrhoeal agents such as belladonna, bismuth, and opium.

They became symptom free in periods varying from a few weeks to 12 months after the onset of symptoms. Patient M. was readmitted to hospital one month after cessation of symptoms and nine months after the onset and found to have no steatorrhoea (Fig. 4), normal vitamin B_{12} absorption, and no other evidence of malabsorption. He was reinvestigated again in June 1964. At this time he was found to have no steatorrhoea, normal vitamin B_{12} absorption (0·82 μg.), and normal xylose excretion (27%). The barium meal, however, still showed dilatation of the jejunum and sluggish peristalsis. A jejunal biopsy still showed a convoluted pattern, although histo-

TABLE III

JEJUNAL BIOPSY FINDINGS

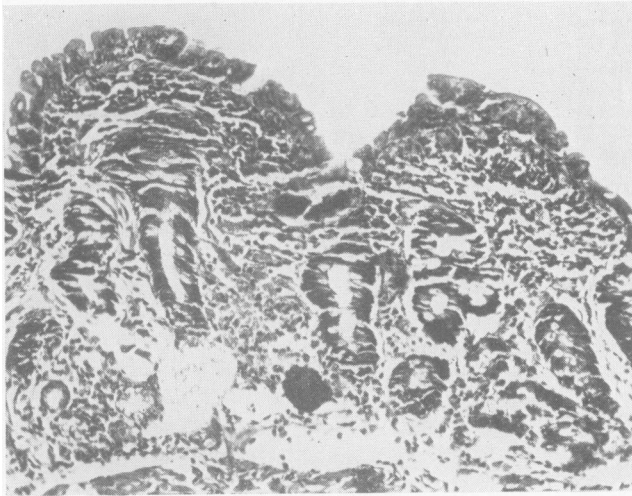|	Dissection Microscopic Appearance	Villi	Epithelial Cells		Lamina Propria Cell Infiltration
			Shape	Cell Infiltration	
M(1962)	Convoluted	Partial villous atrophy	Flattened	+ +	+ + +
M (1964)	Convoluted	Short	Columnar	+	+ +
K	Broad leaves	Shortened	Columnar	+ +	+ +
Ar	Ridges	Shortened	Slightly flattened	+	+ +
KA	Leaves	Slightly shortened	Columnar	+ + +	+ +
R	Leaves	Shortened	Columnar	+	+ + +

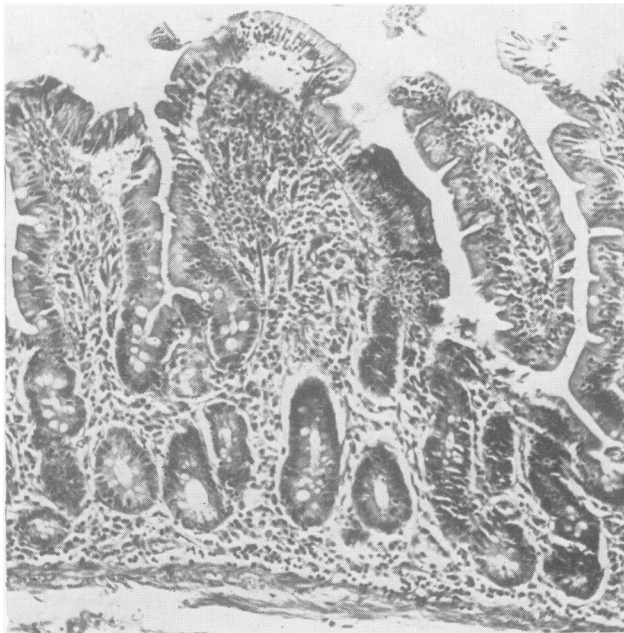FIG. 7. *Jejunal biopsy from M. in 1962 showing partial villous atrophy (haematoxylin and eosin × 110).*

FIG. 8. *Jejunal biopsy from M. in 1964 showing considerable improvement (haematoxylin and eosin × 110).*

logically there was considerable improvement (Fig. 8).

NEIGHBOURING VILLAGE

A survey of the adjacent village at the time of the family epidemic showed no cases of diarrhoea. Another survey a year later, however, showed that 26 people in the village had developed symptoms suggestive of sprue during the months of September and October 1962, nine months after the onset of the last case in the family.

DISCUSSION

Tropical sprue may be defined as a 'primary' malabsorption syndrome (characterized by steatorrhoea and other evidence of small intestinal disfunction) occurring among people resident in the tropics.

Until more is known about the cause, or causes, of

this syndrome the diagnosis of tropical sprue must rest on the finding of clinical and biochemical evidence of malabsorption and the exclusion of lesions known to produce similar defects such as intestinal strictures (Baker, 1957).

Patient M., who had steatorrhoea, defective B_{12}, xylose, and glucose absorption, marked radiological changes in the intestine, and a convoluted biopsy with partial villus atrophy, was a typical case of severe tropical sprue. The other affected patients studied showed a somewhat milder form of malabsorption with steatorrhoea, defective xylose absorption, and radiological changes, but with less severe histological changes and normal vitamin B_{12} absorption.

Since the other nine members of the household who were taken ill had symptoms similar to the members studied in detail, it is probable that they all had a similar disease. Tropical sprue has been thought to be very rare in children (Manson-Bahr, 1960). Miller (1933) and Bahr (1915) described one case each, and Mathew, Ignatius, Meenakshiammal, and Baker (1964) have described a typical case of sprue in a 5-year-old boy. Unfortunately it was not possible to study any of these children in detail during the active stage of the disease. One child, Ch. aged 2, was studied one month after the subsidence of symptoms and still had mild steatorrhoea and defective xylose absorption. The history and clinical features in all the children were similar to those in the adults, and there can be little doubt that they also suffered from the same disease.

The demonstrated low serum B_{12} levels in five out of six subjects studied is probably largely due to the defective dietary intake of vitamin B_{12}. In M. this was presumably aggravated by the B_{12} absorptive defect. It is possible that the other affected subjects may also have had temporary B_{12} absorptive defects which had cleared by the time they were studied. Unfortunately serum folate levels could not be measured in these people, but since most people with tropical sprue have subsequently been found by us to have low serum folate levels this may have also contributed to the low serum B_{12} levels and the megaloblastosis.

Numerous theories have been advanced as to the cause or causes of tropical sprue. It appears to be the result of damage to the intestine. Possible damaging agents are dietary deficiency, food toxins, *e.g.*, rancid fats (French, 1955), or some infective agent (or agents), or a combination of these. The diet of this family did not differ from that of families in the adjacent village, and their source of cooking oil was the same. There is therefore no evidence to support the suggestion of dietary deficiency or food toxin as an aetiological agent.

Bahr (1915) felt that the association of sprue with certain houses might be related to the presence of dry-rot and of general unhygenic conditions. This house had been built for only two years and contained no detectable dry-rot, and it was considerably cleaner than many of the houses in the adjacent village.

The presence of fever at the onset in four cases, and other features, such as the age-time distribution of the onset, are suggestive of an infective aetiology. However, failure in this and in other studies (Baker *et al.*, 1962) to isolate any bacterial pathogen (including pathogenic *E. coli*) suggests that it may be viral in nature. In this connexion it is of interest that Sabin (1956) reported a 'steatorrhoeic enteritis' occurring in a family associated with a reovirus infection, and it is possible that a similar type of virus infection may have been responsible for this epidemic.

SUMMARY

A family outbreak of tropical sprue is described in which 16 out of 27 members developed the disease. Epidemiological and clinical features are described. Seven of the affected subjects were studied in detail, and were shown to have evidence of malabsorption. The possible aetiology of the disease is discussed.

REFERENCES

Ayrey, F. (1948). Outbreaks of sprue during the Burma campaign. *Trans. troy. Soc. trop. Med. Hyg.*, 41, 377-406.
Bahr, P. H. M. (1915). *A Report on Researches on Sprue in Ceylon 1912-1914.* University Press, Cambridge.
Baker, S. J. (1957). Idiopathic tropical steatorrhoea. *Indian J. med. Sci.*, 11, 687-703.
——, and Hughes, A. (1960). Multiple-retrieving small-intestinal biopsy tube. *Lancet*, 2, 686-687.
——, Mathan, V. I., and Joseph, I. (1962). The epidemiology of tropical sprue. *Malabsorption Syndrome*, Symposium, 2nd World Congress of Gastroenterology, Munich 1962, pp. 4-7. Karger, Basle, and New York.
Dacie, J. V. (1956). *Practical Haematology*, 2nd ed. Churchill, London.
French, J. M. (1955). Disorders of alimentary tract and their nutritional effects: disorders of fat absorption. *Proc. Nutr. Soc.*, 14, 33-41.
Heinle, R. W., Welch, A. D., Scharf, V., Meacham, G. C., and Prusoff, W. H. (1952). Studies of excretion (and adsorption) of Co^{60} labeled vitamin B12 in pernicious anemia. *Trans. Ass. Amer. Phycns*, 65, 214-222.

Kamer, J. H. van de., Huinink, H. ten B., and Weyers, H. A. (1949). Rapid method for the determination of fat in feces. *J. biol. Chem.*, 177, 347-355.

Kohn, J., Mollin, D. L., and Rosenbach, L. M. (1961). Conventional voltage electrophoresis for formininoglutamic-acid determination in folic acid deficiency. *J. clin. Path.*, 14, 345-350.

Manson-Bahr, P. H. (1960). *Manson's Tropical Diseases*, 15th ed., p. 505. Cassell, London.

Mathew, K., Ignatius, M., Meenakshiammal, and Baker, S. J. (1964). Tropical sprue in children. *Ind. Paed.*, 1, 271-274.

Miller, R. (1933). Sprue commencing at eleven and a half years of age. *Proc. roy. Soc. Med.*, 27, 113-114.

Paterson, D. E., and Baker, S. J. (1958). Radiological investigation of the small intestine in tropical idiopathic malabsorption. *J. Fac. Radiol.* (*Lond.*), 9, 183-194.

Rao, B. R. H., and Rao, P. S. S. (1958). General health and nutrition survey of the rural population in Pennathur Part III. The quantitative dietary survey. *Indian J. med. Sci.*, 12, 726-730.

Ross, G. I. M., Hutner, S. M., and Bach, M. J. (1957). An improved Euglena method of vitamin B12 assay. In *Vitamine B12 and Intrinsic factor: 1st European Symposium*, pp. 305-310, ed. by H. C. Heinrich, Enke, Stuttgart.

Sabin, A. N. (1956). The significance of viruses recovered from the intestinal tracts of healthy infants and children. *Ann. N.Y. Acad. Sci.*, 66, 226-230.

Stefanini, M. (1948). Clinical features and pathogenesis of tropical sprue. *Medicine* (*Baltimore*), 27, 379-427.

Walters, J. H. (1947). Diatetic deficiency syndromes in Indian soldiers. *Lancet*, 1, 861-865.