The Epidemiology of Tropical Sprue

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Tropical sprue can occur in both endemic and epidemic forms. At present these two forms are clinically indistinguishable (Section 5) and can only be differentiated epidemiologically.

Very little is known about the incidence and prevalence of endemic tropical sprue in any community. Bahr (1915) carried out a field study in Ceylon and found 36 cases among 7592 Europeans, a prevalence of 4.7 per thousand.

Fig. 1. Map showing approximate location of reported epidemics of tropical sprue. (Reproduced with permission from the Proceedings of the Tropical Medical Conference, 1967; London: Pitman.)
He also found the disease in the indigenous population but did not study its prevalence. He could find no relationship between occupation, housing, source of water supply, diet, altitude or insect population and the incidence of the disease. A study in Cuba (Milanés, 1960) based on hospital statistics showed that the number of cases of sprue admitted to hospitals was decreasing. However such hospital-based studies are of doubtful significance.

In India, endemic tropical sprue in the indigenous population has been present for centuries (Caraka Samhita, 1949). Since 1955 it has been reported in detail from many different parts of the country (Baker, 1957; Jain and Sepaha, 1961; Jeejeebhoy, Desai, Noronha, Antia and Parekh, 1966; Tandon, Iyengar, Deo and Saraya, 1966; Misra, Krishnan, Ramalingaswami and Chuttani, 1967; Chuttani, Kasihuri and Misra, 1968; Cowen, Satija and Zacharia, 1968; Mehta, Mehta and Wadhwa, 1968) and it is probable that it occurs all over the subcontinent. There are, however, no data available regarding its prevalence.

Hillary (1759), in one of the earliest descriptions of tropical sprue, suggested that the disease assumed epidemic proportion in Barbados. All other reports of epidemics of sprue are from the Indian subcontinent. These epidemics were described under different names, and in many the diagnosis of tropical sprue was not made at the time they were studied. However, re-examination of the available clinical and laboratory data shows that the disease was most probably tropical sprue. These epidemics can be grouped geographically as occurring in northwest India, east India, East Pakistan and Burma, and south India (Fig. 1).

Northwest India

Grant (1853) gives a comprehensive clinical description of over 200 soldiers who became ill at a hill station. The patients included those who developed the illness at the hill station after a long stay and those who had been in the plains for varying periods of time and developed the disease, either in the plains or shortly after coming to the hill station. The clinical data suggest that many were cases of tropical sprue, but the epidemiological information is meagre.

Crombie (1880) described an epidemic of 'hill diarrhoea' in Simla which affected the local inhabitants, as well as Caucasians visiting the hill station. The clinical features of the disease were fairly typical of sprue. The patients with persistent diarrhoea were followed up for two months. The epidemiological observations suggested that the epidemic was probably not water-borne. Although Crombie thought that the disease was due to the effects of altitude on the liver, no definite conclusions as to the aetiology are possible.

The other epidemic described from this area was in the Yol-Kangra Valley in the Himalayan foot hills, in a group of Italian prisoners of war (Stefanini, 1948). The diagnosis was established in some of these cases by testing the absorption of fat and glucose. The epidemic curves for the years 1943 and
1944, for which complete data were available, showed the highest incidence in the months following the onset of the monsoon and only a few new cases in the hot dry summer. Although Stefanini postulated dietary deficiency as a possible aetiological factor, the prisoners in three other camps, receiving a similar diet, did not develop the disease. He also states that 'in our patients the onset of the deficiency symptoms did not precede the onset of diarrhoea'.

**East India, East Pakistan and Burma**

From 1942 to 1945 a number of epidemics were reported in this region (Leishman, 1945; Keele and Bound, 1946; Elder, 1947; Walters, 1947; Ayrey, 1948; Girdwood, 1948; Woodruff, 1949). Of all British troops repatriated for medical reasons 12 per cent had tropical sprue (Keele, 1946). The extent of the epidemics is difficult to assess and there is some overlap of cases between the various reports. Unfortunately, owing to war-time conditions, only very limited epidemiological investigations were possible.

Leishman (1945) mentions an epidemic in the Chittagong area where up to 50 per cent of some units developed sprue. In one unit 10 per cent had developed diarrhoea within three weeks of arriving in the area. Woodruff (1949) followed up some of these cases. He records that the peak incidence was in June and July and coincided with that of other dysentery-like disorders and suggested that the epidemic may have been of infective aetiology. The prognosis in 47 patients followed up in England was found to be good. 32-4 per cent were symptom-free when they arrived in England; 14-7 per cent of the patients had diarrhoea up to 18 months after return but no relapses after that. The rest had one or more short episodes of diarrhoea with glossitis or other symptoms after return but otherwise remained well. All the patients were able to carry out their work without 'specific therapy'.

Keele and Bound (1946) and Elder (1947) reported that in base hospitals in India the majority of cases of sprue were from Bengal, Assam and Burma. Fourteen per cent of the cases reported by the former authors occurred at Imphal on the Indo-Burma border. The months of peak incidence were reported as May, June and July in 1942, 1943 and 1944, but a small number of cases also occurred in the other months. It is of interest that these are the months during which the monsoon becomes active and 'flies were found in large numbers'.

The report by Walters (1947) describes an epidemic in a group of Indian soldiers, three-quarters of whom were strict vegetarians and others non-vegetarians. The troops developed diarrhoea while they were in the forward areas on the Assam-Burma border. The peak incidence of cases was in July. The incidence among the strict vegetarians was 13 times higher than in the non-vegetarians. The author postulates that the diet of the patients and their gross nutritional deficiency played a part in producing the disease.

Girdwood (1948) described the haematological features in British and Indian troops affected in an epidemic in Assam in 1943. Ayrey (1948) des-
cribed three outbreaks of sprue, one in the Bengal coastal area, one in the northern hills of Bengal and the third in Burma. The epidemics in Bengal had their peak incidence in May, June and July of 1943 and affected Indian and British troops. Apparently only Indian troops were affected in 1944 in Burma and in some units the incidence was as high as 60 per cent. On the basis of available epidemiological data, some diet analysis and the patient's response to treatment it was suggested that the disease was related to a deficient diet.

It is interesting that, in spite of the epidemics that occurred during the second world war, no further epidemics have been reported from this region in the last twenty years.

South India

In Tamilnadu (formerly Madras State) a disease which appears to be tropical sprue and which is characterized by chronic diarrhoea, a feeling of abdominal distension, and wasting has been known for a long time to the indigenous population as ‘Ubbumariyaiyee’, a Tamil name literally meaning ‘visitation of the Goddess of distension’. There are several descriptions of epidemics of ‘Ubbumariyaiyee’ in the Madras State Health Reports (Ranganathan, 1940). The first such recorded epidemic was in 1929 in the adjoining areas of Salem, Tiruchirappalli and South Arcot Districts which form the basin of the Vellar river (Fig. 2). The cases began to appear in October 1929 and the peak incidence was in November, the number of new cases decreasing rapidly after that. The occurrence of the disease in the various districts was recorded separately but it appears that they are all part of the same epidemic. The clinical description of the cases was as follows:

‘The clinical condition of several of them resembled sprue more closely than any other (disease). There was a chronic diarrhoea, with copious, foul, frothy, fermenting stools, progressive emaciation, severe anaemia with a colour index above unity and a raw, glazed or furrowed tongue’.

In 1934 another epidemic occurred in the same area. The epidemic curve was similar to that in 1929. Extensive bacteriological studies were carried out but no definitive causative agent was identified. In 1939 there was another epidemic in the Tiruchirappalli district. The epidemiological features were similar to the previous two epidemics. Surveys showed that the poorer areas of the village had an attack rate which was ‘probably less, certainly not more’ than in the richer areas. Stool cultures were done on several patients, about five months after the onset of symptoms, and a type of Shigella flexneri was isolated from the stools of a few. Five out of ten patients had low titres of an antibody to this organism in their blood. No further studies were carried out.

Since 1961 several epidemics of tropical sprue have been studied in detail in the North and South Arcot Districts of Tamilnadu (Fig. 2). A large epidemic that occurred in 1960-62 (Baker, Mathan and Joseph, 1963; Baker
and Mathan, 1968a, 1970; Mathan and Baker, 1970), an isolated household affected in 1961 (Mathan, Ignattius and Baker, 1966) and a village 'R' affected in 1967 (Mathan and Baker, 1968) have been reported.

The first of these epidemics in 1960-62 affected a large number of villages in an area roughly 100 miles north to south and fifty miles east to west (Fig. 2). Cases began to occur in September 1960 and continued till mid-1962.

Fig. 2. Map of Tamilnadu showing areas from which epidemics of tropical sprue have been reported.

The highest incidence was in the month of November, both in 1960 and again in 1961. Projecting the data obtained by sample field surveys (attack rate 45 per thousand, death to case ratio 33 per hundred) to the total area of the epidemic there must have been at least a hundred thousand cases with about thirty thousand deaths. Some cases have continued to be symptomatic till at least nine years after the onset.

The isolated household epidemic occurred in a family with 27 members, 16 of whom developed sprue over a three-month period in late 1961 and early 1962. The family lived near a village about 20 miles north-east of Vellore. At the
time of the epidemic there were no cases of diarrhoea in the village, but a year later 23 people were affected (Fig. 2, 1962).

The village ‘R’, 20 miles to the south of Vellore, was affected by an epidemic of sprue in 1967. The epidemic in this village started in August and, unlike the other epidemics studied, the peak incidence occurred in this month itself. The number of new cases gradually decreased from September 1967. In October 1967 another village, two miles to the south of village ‘R’, was affected by an epidemic of tropical sprue. Cases continued to occur in this village till the end of 1969 (Mathan, 1970, unpublished).

The epidemiological features of tropical sprue in southern India are well shown by an epidemic which occurred in the village of Ariyapadi, 18 miles to the south-east of Vellore (Fig. 2). This epidemic is compared with the incidence of diarrhoea in the population of a control village six miles from Ariyapadi.

**EPIDEMIC TROPICAL SPRUE IN ARIYAPADI 1964-1967**

Studies were begun in this village in January 1965 and continued till September 1968. A team of doctors and public health workers visited all the houses in the village at least twice a week and interviewed all the members of the household at least once a week.

For the purposes of the survey individuals were considered to have diarrhoea when they gave a history of increase in the number of stools per day and said that their stools had become ‘loose’. When such a history was obtained the exact date of first noticing diarrhoea was ascertained. Diarrhoea, as defined here, was taken as the major criterion for the identification and follow-up of cases. A record of the course of diarrhoea and other symptoms of the disease was kept for each patient. Thirty-four patients from the epidemic were studied in detail in a metabolic ward.

The Village

Ariyapadi is a typical south Indian agricultural village with a population of 2,180. The village is laid out in streets which are lined by houses, the majority of which are made of unbaked brick and have thatched roofs (Fig. 3). About 20% of the families live in houses with plastered walls and tiled roofs. The houses frequently share adjoining walls, are ill-ventilated and poorly drained. Flies, mosquitoes, bugs, cockroaches and rats infest all the houses.

There is no protected water supply. Drinking water is obtained from an open tank. A few semi-protected wells are present in the village, but the water in them is brackish and not used for drinking. The staple articles of diet are grown in the fields surrounding the village. These fields, and even the spaces surrounding the houses, are also used for defaecating and for disposal of garbage.
The village is 700 feet above mean sea level. The average maximum temperature is 105°F and minimum is 60°F. The year can be roughly divided into three seasons, the hot dry summer (March to July), the hot rainy monsoon (August to November), and the cool relatively dry winter (November to February). The diet, socioeconomic and other characteristics of a similar population have been documented (Rao and Rao, 1958a, b; Baker and Mathan, 1970).

The social structure of the village is still based on the ‘caste’ system and each street is inhabited by a more or less homogeneous group who are engaged in similar occupations. Caste Hindus, who are economically better off, occupy the main village. About half a mile away there is a hamlet of 70 Harijan or Scheduled caste families. These people are poorer and eat a more deficient diet.

The staple article of food is rice. Wheat was used very seldom by the villagers in 1964-65, although in 1968, owing to rice scarcity, wheat was used occasionally. The other grains which are used by the villagers are ragi (Eleusine coracana), cholam (Sorghum vulgare) and varagu (Paspalum scorbuticum). Almost all the vegetables in the diet are grown locally. Groundnut (Arachis hypogea) oil made locally is used most often for cooking. Occasionally the local supply is supplemented from commercial sources.

The Epidemic

The first cases in the epidemic occurred in the last week of November 1964 (Fig. 4). Further new cases appeared during December and a peak
incidence was reached in January 1965. From February to June there were only a few cases. However, in July 1965 there was an abrupt increase in the number of new cases giving rise to a secondary epidemic wave which was larger than the first. From August 1965 onward the number of new cases decreased gradually and there were only very few new cases in 1966. During early 1967 the epidemic appeared to have stopped, but from November onwards there were a small number of new cases.

Of the 437 families in the village, the index case occurred in the first wave in 156 and in the second wave in 197. Many of the families with index cases in the first wave of the epidemic had secondary cases only in the second wave. Index cases occurred in nine families in 1967. In January 1968 there were still 75 families in which no individual developed diarrhoea during the epidemic.

**Attack Rate**

The overall attack rate in the main village (918 cases in a population of 2,180) was 42.1 per hundred. The attack rate in the males was 42.9 per hundred and in the females 41.3 per hundred. This difference is not statistically significant.

The age-sex specific attack rate per hundred, in ten-year age groups, for the main village, is shown in Fig. 5. Women in the 30–39 age group had a significantly higher attack rate (51.9 per hundred) than the men (32.9 per hundred) ($P < 0.005$). The difference in the attack rates between women (47 per hundred) and men (57 per hundred) in the 40–49 age group is not statistically significant. The attack rates in adults (44.6 per hundred) was higher
than that in children (35.1 per hundred). This difference is statistically significant ($P < 0.005$).

There were 69 cases in the Harijan colony with an overall attack rate of 20.5 per hundred. This is significantly lower than the attack rate in the main village ($P < 0.005$).

![Figure 5. Ariyapadi: age specific attack rates, in ten year age groups, for males and females.](image)

**Family Incidence**

The average family size was 4.9 (range 1 to 15). There were 17 families with only one member and ten of these were affected in the epidemic. The attack rates per hundred population according to the family size did not show any statistically significant differences (Fig. 6). One hundred and three families with more than one member had only one case. In 28 of the 250 other affected families (average size 6.0, average number of cases 3.2) all the members had diarrhoea.

**Spread through the Families**

All the cases in a family did not usually start having symptoms on the same day. The mean interval between the index case and the second case, occurring within one year, was 10.7 weeks (Fig. 7). Of 238 such instances 92 cases occurred within two weeks. The mean interval in these 92 cases was 4.6 days. In 22 families the disease first occurred in two members on the same day.

The age and time of onset of all the cases in four families in which the index cases occurred during the first wave of the epidemic are shown in Fig. 8. It is clear that although occasionally more than one case started on the same
Fig. 8. *A. viscosa*: age of cases and temporal relationship of onset of symptoms in four families.

Fig. 9. *A. viscosa*: mean age of cases according to order of incidence (case rank) in families.
day, in general the interval between succeeding cases was days, weeks or months. It can also be seen from Fig. 8 that index cases were in general older than the subsequent cases. The mean ages of cases, ranked according to order of incidence (Fig. 9), showed a statistically significant downward trend ($P<0.001$). This trend was also found when the mean age of all cases in January 1965 (34.4 years) was compared to the mean age of all cases in July 1965 (29.0 years), the difference being significant at the one per cent level ($t = 2.935$). However, if only the mean ages of the index cases are compared between January and July 1965 (Jan 35.9, July 31.9) the differences are not significant ($t = 1.569$).

Spread within the Village

The spread of the epidemic through the village from December 1964 to December 1965 showed clustering in time and space (Fig. 10a, b). For purposes of description the village has been divided arbitrarily into 8 sections by grid lines. All these lines follow the streets in the village. In January 1965 there was clustering of cases in sections B and G (Fig. 10a). The other areas of the village were relatively less affected. Very few new cases occurred in the months February to June 1965 (Fig. 10a) and they were scattered over the village. New cases occurring in July 1965 were particularly concentrated in houses in area C with some cases in other areas (Fig. 10b). Area A still had relatively few cases and although some of the earliest cases in the village had occurred there, it was not until December 1965 that most cases occurred there (Fig. 10b). Cases occurring during 1966 were scattered all over the village.

No significant differences were found between the various areas of the village in the type of housing, occurrence of household pests or the socio-economic and dietary characteristics.

Symptomatology

The symptoms of patients in this village were similar to those described for the patients with tropical sprue in southern India in Section 8. In the majority of cases a feeling of abdominal distension and diarrhoea were the prominent early symptoms. Of the 34 patients admitted for detailed study, 13 had vomiting at the onset; in six blood and mucus were present in the stools for the first few days. Fifteen patients complained of fever at or prior to the onset of diarrhoea. At the time of admission 12 patients had glossitis and one cutaneous hyperpigmentation. Table I presents the age, duration of symptoms at the time of study, and the results of absorption studies, haematology, X-ray and biopsies on these 34 patients. Thirty-one patients had malabsorption of two or more substances, and three had malabsorption only of xylose.
Fig. 10a. Spread of epidemic through the village (November 1964—June 1965). Each small rectangle represents a household. The lines along the roads arbitrarily divide the village into eight areas (A-H) for purposes of description. Open circles represent unaffected individuals. Cases occurring in November and December 1964 are shown in blue; those in January 1965 in green and those in February to June 1965 in red.
Fig. 10b. Spread of epidemic through the village (July—December 1965). Cases occurring before July 1965 are shown in orange; those in July 1965 in blue; those in August to October 1965 in green and those in November and December 1965 in red.
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<th>R.B.12 absorption, µg</th>
<th>X-ray architecture</th>
<th>Histology</th>
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<td>88</td>
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</table>

X-ray Grading: as in Section 8

Villus architecture: L = leaves, C = convolutions

Histology: M = mild changes, PVA = partial villous atrophy, SPVA = severe partial villous atrophy

Bone marrow: N = normoblastic, M = megaloblastic
Fig. 11. *Arivopadi*: the presence of diarrhoea during the first 100 days after onset in five cases. The solid bar shows the days on which diarrhoea occurred.

Fig. 12. *Arivopadi*: percentage of cases symptomatic at the beginning of each month from the onset of disease. Graph obtained by correlation of data on all the patients, the time of onset in each patient being at 0.
The course of the diarrhoea was often remittant. The temporal pattern of occurrence of diarrhoea in five patients is shown in Fig. 11. Of all patients affected in the epidemic who had symptoms for longer than one month, 42 per cent had multiple remissions and relapses. During the diarrhoea-free periods these patients usually suffered from other symptoms such as a feeling of abdominal distension and anorexia. For the purposes of the study, all relapses of diarrhoea have been considered as a continuation of the same illness. Detailed case histories of two adults and a child affected in the epidemic are given in the Appendix, p. 184.

**Duration of Symptoms**

The duration of symptoms ranged from a few days to 42 months, the date of the last follow-up. Fifty-five per cent of patients had diarrhoea for longer than one month, and ten per cent for a year or more (Fig. 12). Eleven patients

![Graph](image_url)

Fig. 13. Arivapadi: epidemic curves for patients with duration of symptoms less than one week, two to four weeks, and more than four weeks.
were still ill in September 1968. The duration of symptoms of these eleven cases ranged from seven months to over three years.

The epidemic curves for patients with symptoms less than one week, two to four weeks and more than four weeks were plotted separately (Fig. 13). There is a striking similarity between these three different curves.

Deaths

Eighty-three patients died at different intervals of time from the onset of symptoms, 33 per cent of deaths occurring in the first month (Fig. 14). The early deaths appeared to be due mainly to fluid and electrolyte losses. The largest number of deaths occurred in children aged less than ten (Fig. 15).

Fig. 14. Ariysapadi: duration of symptoms prior to death.

Fig. 15. Ariysapadi: age distribution of patients who died.
The death to case ratio was high in the first and sixth to eighth decades and lower in the second to the fifth decades (Fig. 16).

![Graph showing age-specific case fatality rate](image)

**Fig. 16. Arjunapdi: age specific case fatality rate (death to case ratio).**

**Diet and Socioeconomic Aspects**

A detailed socioeconomic study was made of 122 households selected to give a statistically representative sample of affected and unaffected families (57 with cases, 65 without cases). The average annual per capita income of affected families in the main village was Rs.347 and of the unaffected families Rs.206. In the Harijan colony the income was lower, being Rs.186 in the families with cases of sprue and Rs.150 in the families without cases. Careful study of the social and cultural habits of the families, with and without cases, did not reveal any significant differences between them in either the main village or the Harijan colony.

A diet survey was done in which all food materials were weighed before cooking and the caloric and nutrient intake of the family was calculated using tables. A scoring system in which an adult male was given a score of 1 was used to calculate individual intake (Rao and Rao, 1958b). There was no detectable qualitative difference in the diet between affected and unaffected households or individuals.

**Bacteriology and virology**

Stool specimens from 55 patients were studied bacteriologically. Pathogenic bacteria were isolated from four (Shigella flexneri in one, *Salmonella* in two, and an enteropathogenic *E. coli* in one).
An attempt was made to isolate cytopathogenic viral agents in monkey kidney cell culture. No isolates were obtained from any of the 55 patients studied but nine isolates were obtained from 65 asymptomatic controls. These isolates were not identified further. Only one of these controls (a six-month-old child) subsequently developed a short episode of diarrhoea, nine months after the stool specimen was obtained.

**DIARRHOEAL ILLNESS IN A CONTROL VILLAGE**

Two hundred and twenty-eight individuals belonging to 39 families were selected by stratified random sampling in the control village. Public Health

Nurses visited every family three times a week and any individual having diarrhoea or other illness was seen by a doctor. The times of onset and subsidence of diarrhoea, as well as associated symptoms, were noted. The results of the first 12 months of survey from March 1967 to March 1968 showed that the cases were distributed more or less evenly over the whole year (Fig. 17).

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**Fig. 17.** The month-by-month distribution of cases of diarrhoea in the control village (July 1967 to June 1968) and in Ariyapadi (November 1964 to October 1965) as a percentage of total cases. For Ariyapadi all cases with diarrhoea, and cases with diarrhoea of less than a week’s duration, are plotted separately.
Fifty-four (23.7 per cent) (21 adults and 33 children) of the 228 individuals under surveillance had at least one episode of diarrhoea. The attack rate in the adults (17.6 per hundred) was significantly lower ($P < 0.005$) than that in the children (30.2 per hundred). Fifty per cent of all the cases occurred in children less than ten years of age (Fig. 18).

The duration of these diarrhoeal episodes was short, the mean of all cases being three days. In the adults, the longest duration was seven days in a 75-year-old woman and in the children 25 days in a one-year-old child.

![Graph showing percentage distribution of cases in different age groups.](image)

**Fig. 18.** Percentage distribution, in ten-year age groups, of cases of diarrhoea in the control village and in Ariyapadi. For Ariyapadi all cases with diarrhoea, and those in whom the symptoms lasted for less than one week, are plotted separately.

Multiple episodes of diarrhoea occurred in 14 children, one of whom, a six-month-old girl, had seven such episodes over a ten month period, the longest single episode lasting six days. The children were all completely symptom-free in the intervals between the episodes of diarrhoea. Three of the adults had multiple episodes of diarrhoea. The duration of all such episodes was three days. One of these patients, a 35-year-old woman, had four such attacks over a ten month period. This patient had no other symptom during the time she was not having diarrhoea.

There were no deaths due to diarrhoea in the village and none of the affected individuals required parenteral fluid therapy.

**DISCUSSION**

Relation between Sprue and other Diarrhoeas

The observations in the control village show a pattern of diarrhoeal disease in rural southern India which is similar to that seen in rural populations in other developing countries (Gordon, Gauzman, Ascoli and Scrimshaw, 1964; Moore, de la Cruz and Vargas-Mendez, 1965; van Zijl, 1966).
The distinctive features of all these reports are the high attack rates in children, especially pre-school children, and the short symptomatic course of the episodes of diarrhoea. In other countries there has been a seasonal pattern in the incidence of diarrhoea. A similar distinct seasonal pattern was not observed in the control village, although there was some variation in different months. A study of urban children in southern India (Kamath, Feldman, Rao and Webb, 1969) has also shown some variation in the incidence of childhood diarrhoea in different months, but unlike the findings in other countries these variations were not explicable on the basis of seasonal changes.

The pattern of diarrhoeal disease in Ariyapadi is different from that in the control village in that it shows the presence of distinct months of high incidence (Fig. 17), a high attack rate in adults (Fig. 18) and a longer duration of illness in the majority of patients (Fig. 12). In the control village nearly all the subjects with diarrhoea had symptoms for less than a week. The presence in the epidemic of some patients with symptoms lasting for less than a week raises the question of whether these cases are the same as the ones with symptoms of longer duration, or whether they are cases of diarrhoea which would in any case have occurred as part of the 'normal background' of diarrhoea in rural populations. The epidemic curve (Fig. 17) and the age distribution of the patients (Fig. 18) with symptoms for less than a week are identical with those of the patients with symptoms of longer duration and quite different from those in the control village. The similarity of the epidemiological pattern, irrespective of duration, and the distinct difference from the pattern in the control village, suggest that all these cases form an epidemiologically homogeneous group, which is quite different from the 'normal background' of diarrhoeal illness in the southern Indian rural population.

The Clinical Diagnosis of the Epidemic

It must be emphasized that at present the diagnosis of tropical sprue must be established by detailed investigation of individual patients before any epidemic of diarrhoea can be labelled with certainty as an epidemic of tropical sprue.

The majority of the patients studied in detail had malabsorption of at least two of the four substances tested (fat, xylose, vitamin B12 and glucose), abnormal intestinal biopsies and radiological changes in their intestine. It is of interest that malabsorption and quite marked changes in intestinal biopsy were present even in the first week of illness. None of the recognized causes of intestinal malabsorption were present in any of the patients. Since they were a representative selection of all the patients in the village with regard to their age, duration of symptoms and severity of the disease, the epidemic was one of tropical sprue. These patients were similar to patients studied from several other epidemics that have been investigated in detail in this
centre and they form part of the detailed report on clinical features that is presented in Section 8.

The Epidemic Curve

The course of the epidemic in Ariyapadi, spread out over 27 months, is similar to that of most of the other epidemics studied in this centre. In the 1960-62 epidemic, the peak incidence in different villages was in different months, but no particular pattern of spread of the epidemic from village to village could be detected. The build-up of cases in the individual villages was gradual. However, a distinct second wave of cases, as occurred in Ariyapadi, was not found in any village in this epidemic. The onset of the second wave in Ariyapadi was very abrupt and the epidemic reached its peak in the same month. This sharp peak is similar to the pattern of onset of the epidemic in village 'R'. The different months of onset and of peak incidence in different epidemics and in different villages in the same epidemic, does not appear to conform to any particular seasonal pattern.

Several villages near Ariyapadi were affected in an epidemic of sprue in November 1967 and the overall attack rates in these villages was about 40 per hundred. The new cases occurring in Ariyapadi in late 1967 were most probably a part of this epidemic. It is possible that these cases were so few because some degree of immunity had been given by the earlier epidemic, even though the majority of people affected in 1965 were asymptomatic by late 1967.

Attack Rate

A characteristic feature of all epidemics of sprue has been the higher attack rate in adults. This is in striking contrast to the pattern of diarrhoeal illness in the 'control' village and resembles the model, described by Burnet (1959), of the spread of a 'new' infectious disease in a community. However, the mortality in the epidemic does not fit this theoretical model which suggested higher case fatality rates in the 15-35 age group. Also, if sprue is an infectious disease, it is unlikely that there is total lack of immunity in a population where a chronic disease has been apparently endemic for over 2000 years!

The overall attack rate in males and females has been similar in all the epidemics of sprue. However, in general, the attack rate in women of childbearing age has been higher than that of men of the same age. These differences were not statistically significant in any of the earlier epidemics but in Ariyapadi in the 30-39 age group the attack rate is significantly higher in the women. The factors which make this section of the population more susceptible to the disease are not clear.

Children were affected by the disease in many of the epidemics studied in southern India and the clinical syndrome of sprue in children has been documented (Mathan, Joseph and Baker, 1969). The epidemiological data shows that the attack rate in children is lower and they are, in general,
affected later during the course of the illness. The reasons for this are not known. This lower attack rate in children may be one of the reasons why so few cases of endemic sprue have been described in this age group.

The Spread of the Epidemic in the Village and in Families

Clustering of cases in time and space as seen in Ariyapadi (Fig. 10a, b) is a characteristic though unexplained feature of all the epidemics of sprue studied so far. In the 1960-62 epidemic the Brahmin community were relatively unaffected (Baker and Mathan, 1970) but the reasons for this are not clear.

It was not possible to identify a pattern of spread among the children attending the village school in Ariyapadi, or among school-going children in any of the other epidemics so far studied. This and the pattern of spread of the epidemic over the village, does not support a person to person type of transmission.

In the 1960-62 epidemic two individuals, who visited villages affected by the disease for a single 24-hour period, developed the disease, one five days and the other six days after return to their homes outside the epidemic area. This suggests that the minimum "incubation period" of the disease may be of the order of a week. Nevertheless the interval between the index case and the second case was longer than a month in about 50 per cent of such instances (Fig. 7) and the spread of the epidemic through families was often over several months (Fig. 8). This suggests that this epidemic was probably not of the 'common source' type but was 'propagated'.

The Duration of Symptoms

Epidemic tropical sprue is a disease with a specific time of onset, in which some of the affected individuals recover rapidly, while in others the disease persists for months and in some cases for years (Fig. 12). The course of the disease is often characterized by periods of remission and relapse, which makes it difficult, without long periods of follow-up, to determine the exact duration of the disease (Fig. 11). In Ariyapadi and in the 1960-62 epidemic the percentage of cases with symptoms longer than one month was similar. In the epidemic in village 'R' (Mathan and Baker, 1968), only 20 per cent of cases had symptoms for longer than a month. This difference between epidemics could be due to differences in aetiology, differences in perpetuating factors or due to the shorter duration of follow-up in village 'R'.

Mortality in Epidemics of Sprue

The death to case ratio of nine per hundred in Ariyapadi is not as high as in the 1960-62 epidemic when it was 30 per hundred. Medical facilities were not available in a large number of the villages affected by the epidemic in 1960-62, while in Ariyapadi the study team treated all patients who came to
a twice-weekly field clinic. Another factor which contributes to the high mortality, is the traditional village custom of withholding all fluids from people having diarrhoea. In another epidemic in 1967, by using simple measures to control diarrhoea and educating the villagers to take adequate amounts of fluids, it has been possible to keep the case fatality rate to the order of 1 per hundred (Mathan, 1970, unpublished).

In 1961 the overall mortality rate for Tamilnadu was 13 per thousand. However, in six taluks of the state the mortality rate was from 26 to 33 per thousand (Census of India 1961, vol. 9, part 9, section 25). These six taluks were all affected by the 1960–62 epidemic of tropical sprue and the high case fatality rate in this large epidemic would appear to be the cause of the high mortality rate. Quite apart from the contribution to an overall high mortality the disease is also associated with considerable morbidity (see Chapter 8). Since the wage-earning age groups have higher attack rates the socioeconomic implications of these epidemics in the developing rural economy are considerable.

Epidemic Sprue and other Epidemics of Diarrhoea

Epidemics of acute diarrhoeal disease involving adults as well as children, occur from time to time in all parts of the world. Many of them are due to contamination of food material and the diarrhoea is usually of short duration (Costin, 1966; Gotoff, Boring and Lepper, 1966; Renteln and Himnana, 1967). Similar epidemics also occur in the tropics. One of the possibilities that has to be considered is that an acute diarrhoeal illness may unmask the underlying malabsorption in a population where tropical sprue is endemic. The extent of such malabsorption in the asymptomatic population is not known.

Two epidemics of acute diarrhoea have been studied in southern Indian villages (Mathan and Baker, 1968). These two epidemics, one of *Salmonella* enteritis and the other an acute gastroenteritis of unknown etiology, showed distinct clinical and epidemiological differences from the epidemics of sprue. The duration of these epidemics was short, fresh cases appearing in village ‘M’, with *Salmonella* enteritis, for a total of six weeks and in village ‘S’, with the diarrhoea of unknown aetiology, for only 18 days. The spread of the epidemic of *Salmonella* enteritis was mainly among the children, many of whom died. All age groups were affected in village ‘S’ but the attack rates in adults were higher than in children. A striking difference from the epidemics of tropical sprue was the fact that the diarrhoea cleared up in a matter of days in village ‘S’ and in about two weeks in village ‘M’, and no patient was symptomatic for longer than a month. None of the affected individuals developed the clinical features of tropical sprue and a few individuals, studied after cessation of diarrhoea, did not have malabsorption. It is clear that not every gastrointestinal ‘infection’ produces the syndrome of tropical sprue in this area, where sprue is both endemic and epidemic.
The Aetiology of Sprue

The aetiology of sprue is one of the enigmas of modern medicine. Study of patients during the presymptomatic and early symptomatic periods of the disease would appear to offer the best opportunity for determining the aetiology. The majority of endemic cases are seen when symptoms are chronic and, without keeping a large population under constant surveillance and studying every case of diarrhoea, it would be impossible to detect early cases. Epidemics of sprue offer a good opportunity of detecting cases early in the course of the disease. The social, dietary and other environmental factors can also be more easily studied in the epidemic situation.

Several authors studying epidemics during the second world war (Walters, 1947; Stefanini, 1948; Ayrey, 1948) postulated dietary deficiency as the cause of tropical sprue. In epidemic pellagra, the higher incidence in the economically poorer sections of the community and in women of child-bearing age who ate a very deficient diet were two of the factors that suggested a relation to deficiency states (Goldberger, Wheeler and Sydenstricker, 1920a, b, c). In Ariyapadi the average per capita income was lower in the unaffected families and in the poorer Harijan community the attack rate was significantly less than in the richer main village. Diet surveys (Rao and Rao, 1958a, b) in which the individual weight method was not used have suggested that the diet of women of child-bearing age is poorer. However, there are definite limitations in the interpretation of such data and preliminary results of diet surveys by the individual weight method have shown that, on a body weight basis, the intake of such women is comparable to that of the men (Mathan, 1970, unpublished).

The observation of a marked seasonal variation in the incidence of pellagra which correlated with seasonal variations in diet was another piece of evidence in support of pellagra being a deficiency rather than an infectious disease (Goldberger, Wheeler and Sydenstricker, 1920a). The seasonal variations in the diets of preschool children have been studied in southern India (Sundararaj, Begum, Jesudian and Pereira, 1969a, b). The only significant quantitative difference found was the increased intake of fat during the time of the groundnut harvest (October to December). However, the types of cereals used and the availability of greens and pulses showed considerable difference between different months. After weaning, the diet of all age groups in the village is similar and this data on the preschool children probably reflects the situation in the adults. The lack of any seasonal pattern of incidence in the epidemics of sprue would therefore suggest that they may not be related to dietary deficiency, or consumption of dietary items that have a distinct seasonal pattern.

It is possible that the disease may be due to a food toxin. In the 1960-62 epidemic careful comparison of the diets in the areas affected by the epidemic, and nearby unaffected areas, did not reveal any significant differences between
the sources of the various dietary items. At the time of the epidemic in Ariyapadi none of the surrounding villages were affected although the source of food material to all the villages was common. However, more detailed information is needed with regard to the diet prior to and during epidemics.

Galloway, in 1905, was possibly the first person to suggest an infectious aetiology of sprue. Bahr (1915) extended these observations further on the basis of his epidemiological field studies, and cited six instances in which the disease had developed in close household contacts. On the basis of these observations he tried unsuccessfully to transmit the disease to animals. Some of the studies of the epidemics during the second world war (Keele and Bound, 1946; Elder, 1947; Girdwood, 1948) showed a relationship to the monsoon and an association with large numbers of cases of infective dysentery. On this basis it was suggested that the disease may be infectious in nature.

Malabsorption of short duration has been reported following acute gastro-enteritis (King and Joske, 1960), cholera (Lindenbaum, 1962) and R.E.O virus infections (Sabin, 1956). The widespread nature of the epidemics in southern India, their slow spread within individual villages, the clustering of cases in time and space in villages and in families, and the initial occurrence of fever in 25 per cent of the cases, suggests an infective aetiology. However, no viral or bacterial pathogen which could be causally associated with the disease has yet been isolated in any epidemic. More detailed longitudinal virological and bacteriological studies of controls and patients during the course of epidemics are needed.

CONTINUED SURVEILLANCE OF ARIYAPADI

From September 1968 there were no new cases of diarrhoea similar to those in the epidemic till October 1969, although an occasional child had an acute diarrhoeal episode of short duration. At the beginning of October 1969 there were 1,205 people in the village who had not had any episodes of diarrhoea in the epidemic and of these 195 were under the age of five. From October 1969 till January 1970 there were 75 new cases of diarrhoea the largest number (55) being in November. In January there were only three new cases.

The attack rate (among those not previously symptomatic) was higher in the children under five years (13.3 per hundred) than in the older age groups (4.5 per hundred). This difference is significant at the 0.1 per cent level. Four of these adults were studied in the hospital and found to have tropical sprue.

The peak incidence of new cases in November, in this outbreak, emphasizes the lack of a clear cut seasonal pattern. It is possible that the children affected in 1969 were not suffering from tropical sprue, but since they were clinically similar to the adults, who did have sprue, it is reasonable to conclude that the children were also suffering from the same disease. The significantly higher attack rate in these children, previously unexposed to the epidemic, suggests that the other age groups were relatively immune and is in striking
contrast to the findings in 1964–65 (Fig. 5). This relative immunity is best explained if the disease has an infectious aetiology (Burnet, 1959).

EPIDEMIOLOGICAL CONCLUSIONS

Although large numbers of cases with endemic sprue are seen in southern India, and in many other parts of the world, very little is known about the epidemiology of this form of the disease.

The epidemics of tropical sprue occurring during the second world war were all in military populations and war-time conditions prevented detailed epidemiological and aetiological studies.

The study of epidemics of tropical sprue in southern India has revealed characteristic features which distinguish them from other epidemics of diarrhoea and from the 'background' of diarrhoeal disease in the indigenous population. These studies have suggested that epidemics of tropical sprue have the features of a propagated epidemic and that they are unlikely to be due to a common source contamination.

The epidemiological pattern, with a lack of seasonal incidence and the changing age incidence during the course of the epidemic, strongly suggest an infective aetiology although this still awaits proof.

At the present time, epidemics of sprue appear to offer the best opportunity for further study which must include more detailed dietary and sociological investigations and the application of the latest techniques in bacteriology and virology.

APPENDIX—CASE STUDIES

Case No. 1

First Admission

This fifty-year-old male farmer from Ariyapadi was well until July 26th 1965, when after his noon meal, he felt slightly feverish and that night started to have diarrhoea. He passed about twenty watery stools and by next morning was prostrate. He was brought to hospital dehydrated and in shock, and parenteral fluid replacement therapy was started. A hanging drop examination was negative for Vibrio cholera. Physical examination after resuscitation did not reveal any abnormal findings.

No other member of his family was affected at this time.

The investigations (Table A), after correction of fluid balance, showed that the patient had a mild iron deficiency anaemia. In the first week of admission he had malabsorption of fat and xylose but vitamin B12 absorption was normal. Three weeks later he had defective absorption of vitamin B12 (0.13 μg). Changes were also present in jejunum biopsy, gastric biopsy and the barium meal. Stool culture did not show any pathogenic organism.

The diarrhoea was controlled with a mixture containing kaolin and tincture opium and he felt better. He was not given folinic acid or antibiotics. His steatorrhoea persisted up to the time of discharge 30 days after admission.
### Table A

**RESULTS OF INVESTIGATIONS ON CASE 1**

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</table>

**Jejunal biopsy:**
- Villous architecture: C = convolutions, L = leaves; Villous structure: PVA = partial villous atrophy, M = mild changes; gastric biopsy: MA = moderate atrophic gastritis.

**Bone marrow:**
- N = normoblastic; Villous architecture: C = convolutions, L = leaves; Villous structure: PVA = partial villous atrophy, M = mild changes; gastric biopsy: MA = moderate atrophic gastritis.

### Second Admission

Since discharge from hospital the patient had been sporadically attending the field clinic. He continued to have diarrhoea and was losing weight and was readmitted on January 12th 1966. Physical examination did not reveal any abnormal finding.

The results of investigations (Table A) showed that he was still slightly anaemic, and had mild steatorrhoea, an abnormal xylose excretion and defective vitamin B12 absorption. Jejunal biopsy still showed marked changes but the barium meal was less abnormal.

The patient's diarrhoea was again controlled by kaolin mixture. On the 18th hospital day he was started on sulphasemethazine 1 g four times a day for five days followed by tetracycline 250 mg four times a day for five days and then chloramphenicol 250 mg four times a day for five days. Vitamin B12 absorption tested on the 24th day (six days after start of antimicrobials) and on the 28th day in hospital was normal. The xylose absorption had become normal prior to starting antimicrobials but the mild steatorrhoea persisted. After completion of the antimicrobials the patient was discharged. He was symptom-free at that time.

### Third Admission

The patient was keeping well but still having two semi-formed stools daily. There was occasional blood streaking of the stools. He was readmitted on April 6th, 1966 for evaluation. Physical examination did not show any abnormality other than the presence of haemorrhoids.

The investigations (Table A) showed that he was more anaemic at this time but still had normal levels of serum vitamin B12 and folate. There was still a mild malabsorption of fat and xylose but vitamin B12 absorption was normal. The jejunal
biopsy also showed some improvement. He was in hospital for 14 days and at the
time of discharge did not need any medicine for control of diarrhoea. He was
given 360 mg of ferrous sulphate daily.

Follow-up at Home
The patient continued to feel well, although he was still having two or three
seminated stools daily, till July 1967, when he started to have more diarrhoea
and became markedly anaemic. He lost weight in spite of being given kaolin
mixture in the village clinic to control the diarrhoea.

Fourth Admission
The patient was admitted on February 16th 1968. He was having three to six
seminated stools daily with mucus. On examination he had a moderate degree
of glossitis. Apart from this and the presence of haemorrhoids there were no
abnormal physical findings.
The patient had mild steatorrhoea (Table A). All other tests of absorption were
normal at this time. Jejunal biopsy showed mild abnormalities.
The diarrhoea was controlled with kaolin mixture and after the first week the
dose given was gradually decreased. By the end of the third week in hospital he was
not taking any medicine for control of diarrhoea. The steatorrhoea also decreased
gradually and in the last week in hospital he was passing less than 5 g of fat daily
in the stool.

Fifth Admission
He was readmitted on February 6th 1969. He had been keeping well at home for
about nine months since the last admission. Three months prior to this admission
he again started having diarrhoea and had lost some weight. On examination there
were no abnormal physical signs.
The patient had defective absorption of xylose at this time (Table A) but other
absorption tests were normal. The jejunal biopsy showed marked abnormalities.
He was again given kaolin mixture for control of diarrhoea. The xylose absorp-
tion had become normal at the time of discharge but he had slight diarrhoea,
passing two to three semiformed stools and mild steatorrhoea (6 g per day).

Comment
This patient had a more acute onset than the majority of patients affected in the
epidemic. He had intestinal malabsorption from the first few days of illness and the
course of the disease was characterized by symptomatic remissions and relapses.
In spite of the mild degree of malabsorption the patient had marked histological
changes. He did not develop overt deficiency of vitamin B₁₂ or folic acid. It is
interesting that his vitamin B₁₂ absorption became normal five days after starting
antimicrobials and remained normal for three years. Apart from this, treatment
with antimicrobials did not appear to influence the course of the disease signifi-
cantly.

Case No. 11
This patient was a six-year-old boy from Ariyapani, who started having diarrhoea
on July 17th 1965. He had had no fever prior to the onset of diarrhoea. During
the first week of illness he passed several large semiformed stools daily, was markedly
anaemic, had a feeling of abdominal distension and noticed loud berborym. He
attended the field clinic where he was given kaolin mixture which reduced the sever-
ity of the diarrhoea. On August 13th 1965 he was admitted for further evaluation.
The patient was the second case in the family, his elder brother having developed
diarrhoea in January 1965.
On examination he was thin and under-nourished. Bitot's spots were present in both eyes but there were no other abnormal physical signs. The haemoglobin was 13 g per 100 ml and packed cell volume 39 per cent. The peripheral blood picture showed anisocytosis and hypochromia and the bone marrow showed megaloblastic erythropoiesis with signs of iron deficiency. Serum vitamin B12 was 120 μg per ml and the serum folate was 8 ng per ml. The serum iron was 45 μg per 100 ml, with a total iron binding capacity of 345 μg per 100 ml. The serum albumin was 3.2 g per 100 ml.

The stool fat (mean of first week in hospital) was 9 g per day. The five-hour urinary excretion of xylose was 20 per cent. The maximum rise in blood glucose after 50 g of glucose orally was 8.6 mg per 100 ml. The patient absorbed 0.22 μg of a 1-μg dose of vitamin B12. Folic acid absorption was 76 per cent. Jejunal biopsy showed fat leaves under the dissecting microscope. Section showed partial villous atrophy with moderate cellular infiltration. Barium meal examination showed some increase in calibre and coarsening of the mucosal pattern of the jejunal loops.

The patient's diarrhoea was controlled with bowel binding mixtures. The steatorrhoea and the defective absorption of vitamin B12 and xylose persisted. On the 30th day in hospital he was started on tetracycline 250 mg thrice daily for five days, followed by chloramphenicol 250 mg thrice daily for five days and then sulphamethazine 1 g thrice daily for five days. By the fifth day of tetracycline therapy the absorption of vitamin B12 had become normal. Xylose absorption did not become normal and the steatorrhoea persisted. His diarrhoea had decreased in frequency and he felt much better. He was discharged home after 50 days in hospital.

The patient was followed up for three years at home and he remained clinically well. Three months after discharge all medicine for control of diarrhoea was stopped.

Comment

This boy had malabsorption of fat, xylose, glucose and vitamin B12 as well as changes in jejunal biopsy and radiology. He is typical of the many children affected in the epidemic. The course of antimicrobials produced a rapid return of the vitamin B12 absorption to normal, but at the time of discharge the other absorptive defects persisted. It is not clear to what extent the antimicrobials influenced the course of the disease.

Case No. 30

A 55-year-old male farmer from Ariyapadi was admitted on April 22nd 1965. His complaints began in early December 1964, when he started having watery diarrhoea, passing about 10–12 large watery stools each day. He became anorectic and had loud borborygmi. He took some herbal treatment at that time. After three weeks his diarrhoea became less but he continued to feel weak, lethargic and anorectic. A week prior to admission he started having diarrhoea again, passing about three semiformal stools daily. Physical examination revealed a man with moderate glossitis and patchy areas of hyperpigmentation of the palms.

The haemoglobin was 7 g per 100 ml and the packed cell volume 20 per cent. The peripheral blood film showed anisocytosis, hypochromia, polychromasia and macrocytosis. Hypersegmented polymorphs were present. Total w.b.c. count was 5800 per mm^3 with normal differential count. Platelet count was 185,000 per mm^3. The bone marrow showed megaloblastic erythropoiesis and stainable iron was present. The serum vitamin B12 was 192 μg per ml, and the folate 1.8 ng per ml. The serum iron was 24 μg per 100 ml, and the total iron binding capacity was 402 μg per 100 ml. The serum albumin was 2.9 g per 100 ml.
The stool fat was 20 g per day (mean of first week in hospital). The five-hour urinary excretion of xylose was 12 per cent. The maximum rise in blood glucose after 50 g of glucose orally was 50 mg per 100 ml. A 0.04 μg of a 10 μg dose of vitamin B₁₂ was absorbed. Folic acid absorption was 75-5 per cent. Jejunal biopsy showed convolutions and on section severe partial villous atrophy with moderate cellular infiltration. Barium meal showed that peristalsis was slow and abnormal. The duodenal and jejunal loops were markedly dilated with coarse mucosal pattern.

The patient was given kaolin mixture but the high stool weight and the steatorrhoea persisted. On the 16th day in hospital he was started on 16 g of yeast by mouth to study the haematological response to food folic. There was a prompt reduction in the weight of stool and the fat excretion (Fig. 31, p. 228). After he had been given yeast for three days it was stopped and he was given 200 μg of folic acid orally daily, as he was not able to stay in hospital for a sufficiently long period for the haematological responses to yeast to be studied in detail. With this treatment there was a prompt reticulocyte response and the bone marrow gradually became normoblastic. At the time of discharge steatorrhoea and xylose malabsorption were still present but the patient was symptomatically much better.

Comment

This patient is typical of chronic, untreated cases from the epidemic, with severe malabsorption, biopsy and radiological changes. He had developed folic acid deficiency and megaloblastic anaemia. The decrease of steatorrhoea and stool weight coincided with the introduction of yeast and may have been causally related, but similar responses have not been observed in other patients.