Tropical enteropathy and tropical sprue

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A syndrome of unknown etiology, characterized by intestinal malabsorption, chronic diarrhea, and multiple nutritional disorders, was recognized in India a number of centuries B.C. by Caraka (1). Since that time, the syndrome has been documented by many investigators in different parts of the country in both endemic and epidemic forms. Many names have been given to this syndrome, but gradually the term “tropical sprue” was generally adopted for it. Much of the nineteenth and early twentieth century literature on sprue in India has been reviewed by O’Brien (2). Other more recent investigations have been carried out by workers in different parts of India such as Calcutta (3), Bombay (4), Delhi (5), Ludhiana (6), and Vellore (7, 8). It therefore appears probable that tropical sprue is prevalent throughout most of the Indian subcontinent.

In the past decade, with the introduction of newer techniques for the investigation of the gastrointestinal tract, there has also come a recognition that in the tropics, in addition to patients with classical tropical sprue, there are many asymptomatic subjects who have a milder form of small intestinal disorder. This may be manifested by minor histological abnormalities of the jejunal mucosa or abnormalities in absorption tests, or both. This disorder may be termed “tropical jejunitis,” or, more aptly, “tropical enteropathy.”

This communication compares and contrasts so-called “normal” subjects, many of whom have tropical enteropathy, with subjects suffering from tropical sprue.

Subjects and methods

The following three groups of subjects were studied:

1) Ward controls. This group consisted of 71 apparently healthy, asymptomatic, southern Indian adult volunteers who were mainly from the lower socioeconomic group and who were admitted to the hospital for periods of one to several weeks for detailed metabolic studies. Their ages ranged from 17 to 70 years with a mean of 32.1 years.

2) Village controls. In order to obtain a statistically valid population sample of a southern Indian village, a census was carried out in the village of Ma, and 94 families (29% of the population) were chosen for study by stratified random sampling. The health status of this group has been recorded over a 2-year period, and a subsample of this group had various absorption studies done—47 of which were fat excretion, 308 xylose absorption, and 205 vitamin B12 absorption tests in all.

3) Patients with tropical sprue. Epidemics of tropical sprue in two neighboring villages were studied. Epidemiologically these two epidemics appeared to be similar and, as there was no detectable difference between the clinical manifestations in patients from the two villages, they have been combined. A total of 90 patients were investigated in detail, all of whom had diarrhea and other symptoms such as vomiting, anorexia, abdominal distension, and loud borborygmi. One-third of the patients also had symptoms of deficiency states such as glossitis, hyperpigmentation, anemia, and edema, which had developed during the course of their illness. The symptoms were sufficiently severe so that the patients agreed to come to the hospital for investigation.

The ward controls and the sprue patients were studied in a metabolic ward where they received a standard diet containing 50 to 60 g fat. The village controls were brought into the metabolic ward for 1 day for xylose and vitamin B12 absorption tests, but stool collections for estimation of fecal fat excretion were done at home while the subjects were consuming a diet containing approximately 20 g fat/day.

The xylose absorption test was carried out using a 5-g dose D-xylose. Urine was collected for the 0 to 2- and 2 to 5-hr periods following administration of the dose. The xylose in the urine was measured by the method of Roe and Rice (9). The results were expressed both as total excretion in 5 hr and as the ratio of the 0 to 2/0 to 5-hr excretion (10). Stool fat was measured daily by the method of van de Kamer et al. (11), and the results expressed as a 3-day mean. An excretion of 6 or more per day was...
TABLE 1
Xylose excretion among different age groups of village controls

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>No.</th>
<th>Mean percent excretion</th>
<th>sd</th>
<th>Percent of group &lt; 25% excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4.9</td>
<td>25</td>
<td>13.2</td>
<td>9.4</td>
<td>92</td>
</tr>
<tr>
<td>5-11.9</td>
<td>95</td>
<td>22.1</td>
<td>11.4</td>
<td>54</td>
</tr>
<tr>
<td>12-17.9</td>
<td>57</td>
<td>25.0</td>
<td>11.9</td>
<td>46</td>
</tr>
<tr>
<td>Adults (18+)</td>
<td>131</td>
<td>24.9</td>
<td>12.6</td>
<td>31</td>
</tr>
</tbody>
</table>

taken as indicating steatorrhea. Vitamin B_{12} absorption was measured following a 1-μg dose of vitamin B_{12} labeled with 0.5 μCi of ^{57}Co. Absorption was estimated either by the fecal balance technique (12), an absorption of 0.3 μg or less being taken as abnormal; the urinary excretion method of Schilling (13), an excretion of 6% of the dose or less being taken as abnormal; or the rise in serum radioactivity (14), a level of 0.2% of the dose per liter of plasma or less being taken as abnormal.

Jejunal biopsies were performed with a Crosby capsule. Biopsies were graded into either "normal" or one of three groups of abnormality: grade I, the least abnormal, with shortening of the villi, some increase in the depth of the glandular layer, and an increase in the cellularity of the lamina propria and epithelial cells; grade II, showing further increase in the depth of the glandular layer up to one-half the total distance from crypt base to villus tip, and more cellular infiltration; and grade III being the most abnormal, with the glandular layer occupying more than one-half the crypt base to villus distance, together with flattening of the surface epithelial cells, disorganization of the brush border, and marked cellular infiltration of the lamina propria and epithelial cells. The completely flat mucosal surface, which occurs in some cases of celiac disease, was not encountered in this study.

Barium meal examinations were normal in all but six subjects, five of whom had grade I changes and one who had grade II changes.

**Results**

**Ward controls**

The mean daily fat excretion in the control subjects was 4.2 g (sd 1.1 g). Seven subjects (10%) had steatorrhea with an excretion between 6 and 8 g/day. The mean xylose excretion in the group was 30.1% (sd 8.3). Thirteen subjects (19%) had an excretion of less than 25% of the dose in 5 hr. The ratio of 0 to 2/0 to 5-hr excretion was 0.43 (sd 0.16). Vitamin B_{12} absorption in the control group was tested in one of three ways. Thirty-one subjects had a fecal balance study; the mean absorption was 0.66 μg (sd 0.17), and no subject absorbed less than 0.3 μg. Twenty-three subjects had a Schilling test; the mean excretion was 16% (sd 6.9) and all subjects excreted more than 6% of the dose. Seventeen subjects had their B_{12} absorption capacity tested by the serum method. The mean rise in plasma radioactivity was 0.79% of the dose per liter of plasma (sd 0.14). One subject had a rise below 0.2% and must be considered as having vitamin B_{12} malabsorption.

When all the above three tests were considered, no individual had abnormal results for all three substances, and only one subject had two abnormal tests, namely, fat and xylose.

Jejunal biopsies, viewed under the dissecting microscope, showed a convoluted pattern in 15 (21%) and the remainder exhibited a leaf-like pattern. On histological examination, 8% of biopsies were classified as "normal," 62% showed grade I changes, 26% grade II, and 4% grade III changes. There was no correlation between the biopsy findings and absorption tests. In the three subjects with the most abnormal biopsies, the results of all three absorption tests were normal.

Barium meal examination was normal in all but six subjects, five of whom had grade I changes and one who had grade II changes.

**Village controls**

Fecal fat excretion was measured in 45 adults; the mean excretion was 4.2 g/day (sd 1.6), and five (10.6%) had an excretion between 6 and 9 g/day. Three hundred eight individuals of all ages had a xylose absorption test; the results of which are summarized in Table 1. Xylose malabsorption was present in 92% of preschool children and in 51% of the adults, a difference significant at the 0.1% level. The 0 to 2-/0 to 5-hr ratio in the adults was 0.37 (sd 0.2). As in the ward controls, this low ratio was due to decreased excretion in the first 2 hr. Vitamin B_{12} absorption was tested in 205 subjects by the plasma radioactivity method. The mean rise in plasma radioactivity was 1.0% dose/liter plasma (sd 0.7). Seven subjects (3.4%) (five
adults and two schoolchildren) had abnormal absorption.

Of the 47 adults who had all three tests done, none had malabsorption of three test substances; two persons (4%) had malabsorption of two substances (one fat and xylose, one vitamin B12 and xylose); and 28 (56%) had malabsorption of one substance (2 fat, 25 xylose, and 1 vitamin B12). Two hundred five subjects had xylose and vitamin B12 absorption tests and only 6 (3%) had malabsorption of both substances. One person (0.5%) had malabsorption of vitamin B12 only and 108 (54%) of xylose only.

*Tropical sprue*

The age-specific attack rate in one of the two epidemics of tropical sprue is shown in Fig. 1. Children and adolescents are significantly less affected than adults \((P < 0.005)\). A similar pattern has been observed in all the other epidemics studied from this center.

The mean xylose excretion in the group of 90 patients with epidemic sprue was 12.0% (SD 10.0), and only two subjects excreted 25% or more of the dose. The mean stool fat excretion was 13.0 g/day (SD 7.5). Five subjects had no steatorrhea. Vitamin B12 absorption was determined by the fecal test in 30 patients; the mean absorption was 0.28 \(\mu\)g (SD 0.12). Eleven subjects (36%) absorbed 0.3 \(\mu\)g or more. In 60 patients the Schilling test was used and the mean excretion was 4.5% (SD 4.1); 15 subjects (25%) excreted more than 6% of the dose. The difference in the prevalence of B12 malabsorption employing the two tests is not significant.

The pattern of absorptive defects in these 90 patients is shown in Table 2. With three test substances there are seven possible combinations of abnormalities. The most common combination was malabsorption of all three test substances followed by malabsorption of fat and xylose without vitamin B12 malabsorption. The other combinations were much less common, and an isolated defect of vitamin B12 absorption was not seen in this group.

Dissecting microscope examination of the jejunal biopsy in these 90 patients showed a leaf-like pattern in 46 (51%) and a convoluted pattern in 44 (49%). On histological examination, 9 subjects (10%) had grade I, 44 (49%) grade II, and 37 (41%) grade III changes.

Barium meal examination was normal in 8 subjects, showed grade I changes in 37, grade II in 23, grade III in 16, and grade IV in 6 subjects.

**Discussion**

**Ward controls**

The mean 5-hr xylose excretion in the ward controls is in the lower range of normal values reported by others (16–19) for the 5-g dose (Table 3), and 19% of the subjects had values below the accepted limit of normal. The ratio of excretion in the 0 to 2/0 to 5 hr is considerably lower than the value of 0.62 (SD 0.10) reported by Sammons et al. (10), and 40% of all values fell outside the range of Sammons’s mean ± 2 SD. Examination of the xylose excretion in the different collection
TABLE 3
Results of 5-g D-xylene test in normal subjects reported by other investigators

<table>
<thead>
<tr>
<th>Studies</th>
<th>Mean percent excretion</th>
<th>sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santini et al. (16)</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Sammons et al. (10)</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Joske and Haagensen (17)</td>
<td>35</td>
<td>9</td>
</tr>
<tr>
<td>Butterworth et al. (18)</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Rinaldo and Gluckmann (19)</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Present study</td>
<td>30</td>
<td>8</td>
</tr>
</tbody>
</table>

periods shows that the reason for the lowered ratio is a considerable decrease in excretion in the first 2 hr. This lowered ratio occurred in many subjects, even in the presence of a 5-hr excretion of 25% or more, and suggests a widespread functional impairment of xylose absorption in the upper small intestine (20).

The mean fat excretion of this group (4.2 g) is higher than those reported by others, who give values of 2.5 g (sd 2.0) (21) and 2.6 g (sd 1.7) (22) for subjects on a 50 to 60 g fat intake. Seven subjects had an excretion of 6 g or more per day, even if these are arbitrarily excluded, the mean excretion (3.7 g) is still elevated, suggesting that in this group of patients fat absorption may not be as complete as in subjects living in temperate regions.

The grading of the degree of abnormality of intestinal biopsies is a subjective process, varying with different observers. Nevertheless, the jejunal biopsies in the majority of the control subjects were quite different from those reported from normal subjects in temperate regions (23-25).

It may be concluded that the majority of the ward control subjects had functional and structural abnormalities of the jejunum, or both, and must therefore be considered as having tropical enteropathy. On the other hand, ileal function as measured by the vitamin B₁₂ absorption test was normal in all but one subject, indicating a relative sparing of the ileum. A similar relative sparing of the ileum has been noticed in a postmortem morphological study of the intestine in subjects dying of non-gastrointestinal diseases (26).

Village controls

The prevalence of xylose malabsorption among the adults in the village controls was significantly higher than in the ward controls. The reasons for this are not clear, but this increase suggests that the prevalence of enteropathy may differ in different groups of subjects within the general population. Lindenbaum (27) has observed differences in the prevalence of xylose malabsorption between subjects living in urban and rural environments, and similar factors may be operating between these two control groups. Of considerable interest is the finding of a high prevalence of xylose malabsorption in the preschool children. Some of this increased prevalence may perhaps be accounted for by the fact that all subjects were given a 5-g dose irrespective of their weight. However, comparison of our data with those of Polonovski and Gombault (28) suggests that the majority of the children would still have had xylose malabsorption even if the dose had been adjusted for body weight or surface area.

The overall figure for steatorrhea in the adults in this group is similar to that in the ward control group, but the two are not strictly comparable because of the lower fat intake in the village controls. It is probable that a higher fat intake would have brought to light more subjects with increased fat excretion.

The low prevalence of vitamin B₁₂ malabsorption is in sharp contrast to the results of the xylose absorption test and, as in the ward controls, suggests a relative sparing of the distal small intestine.

Tropical sprue

The relatively lower incidence of tropical sprue among children compared with adults in the two epidemics has been a constant feature in all epidemics of sprue that have been studied. There are no data available on the incidence of endemic sprue in the community. Hospital statistics suggest it has a pattern of incidence similar to that of epidemic sprue, but such comparisons may be fallacious. Over the past year, studies have been conducted in a group of 25 villages covering 21,000 people. The incidence of chronic...
diarrhea (continuing for more than 1 month) clinically suggestive of tropical sprue, is shown in Fig. 2. Again, the lower incidence in children and adolescents is striking. Baker and Mathan (29) have shown that no clinical, biochemical, or pathological differences can be detected between epidemic and endemic sprue, except that patients from epidemics have a higher prevalence of vitamin B₁₂ malabsorption. It therefore seems probable that endemic and epidemic sprue are similar, if not identical, conditions.

The differences in severity and duration of illness and in the pattern of absorptive defects seen in different individuals raises the question of whether or not all these patients have the same illness. The epidemiological pattern in patients with an illness lasting less than a month was identical with that in patients with an illness of longer duration (30). Analyses of the patients in this study with malabsorption of fat, xylose, and vitamin B₁₂ and those with only fat and xylose malabsorption show no significant differences between them, either in the severity of their illness, the degree of fat or xylose malabsorption, or in biopsy or radiological findings. The other combinations of absorptive defects were found in such small numbers that it is not possible to analyze them meaningfully. However, all of them had similar symptoms and, inasmuch as they became ill at the same time as others in the village, they presumably had the same disease.

Comparison between controls and patients with tropical sprue

The pattern of xylose excretion in the sprue patients is compared with that of the ward and the village controls (Fig. 3). The sprue patients and the ward controls are two distinct populations \( P < 0.001 \), with only a small area of overlap between them. The village controls occupy an intermediate position with a much wider overlap; nevertheless, statistically they represent a population different from either the sprue group or the ward controls \( P < 0.001 \) and \( P < 0.005 \), respectively.

The fat excretion of the sprue patients and the ward controls is shown in Fig. 4. These form two different populations \( P < 0.001 \), although a few sprue patients had normal fat excretion and a few controls excreted 6 g or more of fat per day. The adults from the village Ma are not included in this chart because fat intakes differed, so the results are not strictly comparable with those of studies conducted in the ward. In another epidemic of sprue, similar estimations of fat excretion were made while the patients were living at home and consuming their ordinary diet; 72% were found to have steatorrhea (31).

Vitamin B₁₂ absorption in the patients with sprue and in the ward controls was measured...
4) and of histological appearances of the jejunal biopsies (Table 5) show significant differences between the sprue and ward control groups ($P < 0.001$ and $P < 0.0005$, respectively). The results of the barium meal examination are compared in Table 6. The two groups are significantly different ($P < 0.0005$).

It may be concluded that, in terms of xylose, fat, and vitamin $B_{12}$ absorption, jejunal biopsy, and radiological changes, the patients with epidemic sprue form a significantly different population from the ward control subjects. With respect to the two measurements made, namely, of xylose and vitamin $B_{12}$ absorption, sprue patients also

![Fig. 4. Pattern of fat excretion in ward controls and in patients with sprue. Symbols as in Fig. 3.](image)

![Fig. 5. a) Pattern of absorption of vitamin $B_{12}$ in the fecal test. Symbols as in Fig. 3. b) Pattern of urinary excretion of radioactive vitamin $B_{12}$ in the Schilling test. Symbols as in Fig. 3.](image)

TABLE 4

<table>
<thead>
<tr>
<th>Villus pattern</th>
<th>Percent of group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>Leaves</td>
<td>79</td>
</tr>
<tr>
<td>Convolutions</td>
<td>21</td>
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</table>

TABLE 5

<table>
<thead>
<tr>
<th>Histological group</th>
<th>Percent of group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>I</td>
<td>62</td>
</tr>
<tr>
<td>II</td>
<td>26</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
</tr>
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</table>

TABLE 6

<table>
<thead>
<tr>
<th>X-ray grade</th>
<th>Percent of group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
TROPICAL ENTEROPATHY AND TROPICAL SPRUE

represent a population different from the village controls.
However, it must be emphasized that the epidemic sprue patients studied in the ward were not a randomly selected group of affected individuals, because the willingness of an individual to be admitted to the hospital is directly related to the severity of his illness. It is possible that a random selection of affected individuals might have shown a greater degree of overlap between sprue patients and control subjects in absorption studies, biopsy, and X-ray changes.

Relationship between tropical enteropathy and sprue

On the one hand, if all other causes of malabsorption are excluded, an individual who has chronic diarrhea, multiple nutritional deficiencies, malabsorption of fat, xylose, and vitamin B₁₂, as well as severe biopsy and radiological findings, would be diagnosed as having tropical sprue. On the other hand, an apparently healthy, asymptomatic individual with normal fat and vitamin B₁₂ absorption, but with xylose malabsorption and mild histological changes in the jejunum, would be considered to have tropical jejunopathy. Patients who fall in between these two extremes may be more difficult to categorize. Because of their similarity to some of the cases seen in epidemics, those with or without symptoms and malabsorption of two or more substances would have to be arbitrarily classified as having tropical sprue. However, those with symptoms and malabsorption of only one test substance cannot be so readily classified.

Ignorance of the etiology of either tropical enteropathy or tropical sprue and the absence, in a given individual, of any definitive distinguishing feature between the two conditions makes it impossible to be sure whether they are differing expressions of the same syndrome or two unrelated conditions due to different etiological agents. Klipstein (32) has postulated that tropical sprue may be an "iceberg" disease. According to this concept, classical tropical sprue represents the tip of the iceberg above the water and tropical enteropathy represents the part below the surface; the whole representing different manifestations of the same disorder.

There is, however, epidemiological evidence that these are two unrelated conditions. First, the age distribution of the two conditions is quite different. The prevalence of xylose malabsorption in the village of Ma was highest in the preschool children, and as we have shown previously from this Unit, morphologic alterations of the jejunum occur maximally in the 1st year of life (26). On the other hand, the age distribution of both epidemic (Fig. 1) and endemic sprue (Fig. 2) is the reverse of this, being significantly higher in adults than in children.

Second, tropical jejunopathy appears to be widely prevalent in different parts of the tropics (33–37), yet frank tropical sprue does not occur in all these areas (38). Further, in the village Ma, although jejunopathy, as evidenced by xylose malabsorption, was present in 54% of subjects, no cases of tropical sprue were found.

Third, tropical jejunopathy tends to improve in subjects returning to temperate zones (38), whereas tropical sprue apparently may commence years after individuals leave the tropics (39, 40). For these reasons tropical sprue is probably an entity distinct from tropical enteropathy and of different etiology. Finally, it is possible, though unproved, that someone whose intestine is already damaged by tropical enteropathy may be predisposed to develop tropical sprue, even though the two are of differing etiology.

The etiology of tropical jejunopathy and tropical sprue

In the tropics there are potentially many agents, parasitic, bacterial, viral, toxic, or nutritional deficiency disorders, that may cause intestinal damage.

The southern Indian villager lives in a highly contaminated environment, in which sanitation is nonexistent. Analysis of well water shows most wells to be heavily contaminated with fecal organisms, and drinking water is never boiled. Bacterial cultures of stools from apparently healthy individuals grow recognizable enteric pathogens in 15% of random specimens from children and in 6% of specimens from adults (P. Bhat, personal communication). Viral isolates can be obtained from 58% of random
fecal specimens from children and 11% of specimens from adults (T. J. John, personal communication). As in most tropical countries, acute diarrheal attacks are common. In a study of the village Ma, these episodes were found to be of short duration (mean, 4.4 days) and occurred most commonly in the preschool children. There was, in fact, a striking parallel between the incidence of acute diarrheal episodes per hundred population and the prevalence of xylose malabsorption in the same community (41), suggesting that the two may be related. The studies of Lindenbaum et al. (27) and Sheehy et al. (38) also suggested that tropical enteropathy, as seen among expatriates, is related to exposure to a contaminated environment. The relative roles of all the potentially noxious agents in producing this enteropathy have yet to be elucidated.

The etiology of tropical sprue is still a mystery. The occurrence of epidemics, the pattern of spread in villages and in households, the occurrence of fever at the onset of illness in 25% of the patients, and an altered age-specific attack rate in a second epidemic, all suggest that it is caused by an as yet unidentified infectious agent or agents (30). When one or more causal agents are identified, it will then be possible to clarify further the relationship between tropical sprue and tropical enteropathy.

Summary

This study has confirmed the high prevalence of an enteropathy in apparently healthy, asymptomatic southern Indians. The enteropathy is manifested by jejunal biopsy changes and/or xylose, and to a lesser extent fat, malabsorption. There seems to be a relative sparing of the ileum, in that vitamin B\textsubscript{12} malabsorption is less prevalent.

With respect to absorption tests, biopsy, and radiological findings, the controls form populations distinct from patients with epidemic tropical sprue.

The evidence adduced suggests that tropical enteropathy and tropical sprue are two conditions of different etiology rather than different manifestations of the same disease.

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