

Title: Studies on the Nonspecific Jejunal Abnormality of Thai People

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Introduction: It has been implied that tropical sprue is widespread as a subclinical entity in hot climates (1), Jejunal biopsy of asymptomatic adults in India (2), Pakistan (3, 4), and Thailand (5) has shown a histologic lesion of varying severity, consisting of focal villous thickening and fusion with cellular infiltration of the lamina propria. Under the dissecting microscope this abnormality is associated with leaf-shaped or ridged villi, and in more extreme cases, convolutions. Abnormalities of xylose absorption have been noted in a significant percentage of such asymptomatic individuals (1-4). Recently, Klipstein et al. (6) were able to diagnose tropical sprue in Haiti, although it was previously unknown there, by selecting patients with sympt suggestive of the disease. In addition, the ease with which the same anatomic and biochemical abnormalities were found in a group of asymptomatic Haitians led these workers to speculate that sprue was a disease with a wide range of expression, with clinical cases representing but a fraction of the total number affected.

Because a jejunal lesion has been found commonly in asymptomatic subjects in Thailand (5), we undertook to study its functional expression with a wider variety of tests than previously employed, to assess the lesion as a possible precursor of tropical sprue.

#### Methods:

Forty volunteer subjects, primarily from two villages on the outskirts of Bangkok, gave informed consent and were hospitalized for the studies to be described. There were 22 females, age 16-72 years and 18 males, age 13-45 years. History and physical examination were within normal limits in those accepted for the study. The following were also performed in every subject: WBC, Total serum protein and electrophoresis, serum phosphorus, calcium, iron, B-carotene, hemoglobin, and hematocrit. Urinalysis, blood urea nitrogen and serum creatinine were carried out in all subjects and found to be normal by North American standards. Chest X-rays, performed in all subjects, were also normal.

Five hour urinary d-xylose excretion and 2 hour serum xylose levels were measured in fasting subjects. All subjects received 25 g. of xylose except for three who received 0.5 mg/kg (13.7, 22.0, and 22.6 g.).

Urine and serum specimens were kept frozen after collection. The xylose determination (7) was performed within 24-48 hours after completion of the test.

Vitamin B<sub>12</sub> absorption was measured by the Schilling technique (8) using Co<sup>57</sup> Vitamin B<sub>12</sub>\* with Intrinsic Factor. Vitamin A absorption was tested in fasting subjects by the oral administration of a dose of 260,000 international units mixed in corn oil. Serum levels were measured before and five hours after ingestion of Vitamin A (9).

Lactose tolerance tests were performed using a dose of 1.5 g/kg body weight. Blood glucose was measured (10) fasting and at 30 and 60 minutes in all subjects, and generally at 15, 45, 90, and 120 minutes as well.

Glucose absorption was tested using an oral dose of 0.75 g/kg body weight, equivalent to the glucose content of lactose used above. A standard oral glucose tolerance test (100 g. dose) was also done in 4 subjects. Blood was taken for sugar determinations at the same time intervals as for the lactose tolerance test.

Stool fat analysis by the method of van de Kamer (11) was carried out on 3-to 6-day collections. Because fat intake in the average Thai diet is low (12), a daily supplement of 7.5 g. of butter was given during the collection period. Carmine red was used to make the beginning and end of the collection periods.

Fluoroscopic examination of the upper gastrointestinal tract with small bowel follow-through studies were also performed+.

Small bowel biopsy specimens were taken from the jejunum with either a Crosby (13) or a Carey (14) biopsy capsule after x-ray verification of its position.

### Results:

Laboratory data are shown in Table 1. Urinary excretion of d-xylose following a 25 g. dose was  $5.84 \pm 1.54$  g. (S.D.) of the administered dose in 36 subjects. The mean two hour serum level was  $39.8 \pm 7.5$  mg/100 ml. (S.D.). The percentage of xylose excreted by the 3 subjects given the smaller dose (0.5 g/kg body weight) was comparable to that following a 25 g. dose. Mild diarrhea consisting of 2-4 watery stools occurred after ingestion of the 25 g. dose in 3 subjects. Five hour urine volumes were above 225 ml in all subjects tested.

Little or no increase in blood glucose occurred following oral lactose in any of the 39 subjects tested (Fig. 1), the mean rise being  $2.97 \pm 3.07$  mg/100 ml. Diarrhea, consisting of up to 10 loose stools, and/or abdominal cramps, occurred in 28 of the 39 subjects.

In contrast to the flat lactose tolerance test, glucose absorption was normal. The mean maximum rise in blood sugar after ingestion of 0.75 g/kg body weight glucose was  $42.5 \pm 20.5$  mg% in 33 subjects (Fig. 1). Only four subjects showed a rise of less than 20 mg% (7, 15, 16, and 19 mg%). In 4 other subjects given 100 g. of glucose the mean maximum rise in blood sugar was 61.5 mg%.

Vitamin B<sub>12</sub> absorption was normal in 33 of 34 subjects tested (Fig. 2). Only one subject, with a hemoglobin of 12.4 g. was abnormal (4% excretion).

Stool fat excretion averaged  $2.3 \pm 1.4$  g/day in twenty-nine subjects tested. The values were below 5 gms. in all except two in whom the fat excretion was 6.3 and 6.8 g/day (Fig. 2).

Vitamin A tolerance in twenty-four or twenty-seven subjects showed a rise of more than 125 mg% above baseline (15).

The mean serum total cholesterol was  $177.5 \pm 31$  mg/100 ml. There was no correlation between xylose excretion and serum cholesterol (16).

\*Racobalamin, Abbot Laboratories.

+ We are indebted to Dr. Chitti Palavatana, Maj., RTA, for performing the x-ray studies.

The following mean serum levels ( $\pm$ S.D.) were obtained (the number of subjects tested is in parenthesis): Calcium,  $9.31 \pm 0.49$  mg/ml (29), cholesterol,  $177.5 \pm 31$  mg/100 ml (25), beta carotene,  $133.1 \pm 65.0$  ug/100 (34), albumin,  $4.18 \pm 0.56$  g/100 ml (32). Hematologic findings were as follows: males, hemoglobin  $13.8 \pm 1.9$  g/100 ml (18), females, hemoglobin  $12.1 \pm 1.2$  g/100 ml (22).

Fifteen subjects were found to harbor the following small intestine parasites: Ascaris alone in eleven, Ascaris and Hookworm in one, Hookworm alone in one, Hookworm and Strongyloides in one, and Giardia in one. No difference in absorption tests were noted between these subjects and the twenty-four whose stools were negative for parasites, although it was interesting to note that the one Giardia-positive stool was found in subject No. 8, whose xylose excretion 2.99 g, was the lowest recorded. The small-bowel biopsy did not show the protozoa in this subject, and unfortunately, duodenal aspiration was not performed.

No abnormality was seen in the x-ray of the small bowel in the 29 subjects studied except for mild mucosal irregularity in the ileum of one. In six subjects, worm-like objects, probably ascarids, were seen in the mid-ileum.

One duodenal and thirty-nine jejunal biopsy specimens were obtained from the forty subjects. The biopsies showed the same mild abnormalities including focal fusion or blunting of villi and increased cellularity of the lamina propria as previously reported from Thailand (5). Under the dissecting microscope the villi were broad and leaf-shaped, with occasional biopsies showing ridges or convolutions. In no specimen did finger-like villi predominate, and none of the biopsies were flat. The single duodenal biopsy was very similar in appearance to the specimens from jejunum except for the presence of Brunner's glands. No correlation was noted between the degree of microscopic or gross appearance of the biopsies and any of the above absorption tests, x-rays, or the presence or absence of parasites.

## Discussion

In this population of asymptomatic Thai subjects, absorption of fat, vitamin B<sub>12</sub>, vitamin A, and glucose was normal in comparison to North American subjects (17). Xylose and lactose absorption and the histologic appearance of the jejunal mucosa were different. Since changes of similar degree have been found by others in healthy subjects and interpreted as indicators of subtle intestinal disease (2-6), it is important to ask whether these findings, in the absence of malabsorption of nutritionally important substances, actually represents a disease.

Urinary xylose excretion following a 25 gm dose in this population ( $5.84 \pm 1.54$  g) was the same as Gardner and Perez-Santiago ( $5.60 \pm 0.60$  g) and Butterworth, et al. (18) ( $5.70 \pm 1.40$  g) have reported from Puerto Rico, and Lindenbaum et al. (4) from East Pakistan ( $5.38 \pm 1.75$  g) with the exception of one study (19), these results are definitely lower than other series of Americans, whether studied in the United States (20, 21), Thailand (22), or the "protected" Westerners referred to by Lindenbaum et al. (4) in Pakistan, where the lower limit of normal xylose excretion is 5 g.

The xylose excretion in the present study and in a group of Pakistanis reported recently in another study by Lindenbaum et al. (23) appear normally distributed. When this occurs, indicating a homogeneous population, it is not valid to impose a criterion of normality (e.g. greater than 5 g excretion) derived from a different group (North Americans) which arbitrarily splits the population into two nearly equal segments. While the reasons for this mild reduction in xylose excretion is not clear, it is important to point out that these are clearly different than values found in classical sprue (17). The absence of steatorrhea or vitamin B<sub>12</sub> malabsorption in the Thai population supports the concept that this is not tropical sprue. In addition there was no correlation between xylose excretion and serum cholesterol, as recently found in Puerto Rico (16).

The lactose tolerance test was abnormal in all subjects. Although it has been observed in tropical sprue (24), lactose malabsorption has also been described in a variety of other gastrointestinal diseases (25), as a possible genetically controlled enzyme defect (26), and in a surprisingly high percentage of normal adults (27). In view of the apparent universal occurrence of lactose malabsorption in Thais, the test is of no value as a screening test for tropical sprue.

The interpretation of the non-specific jejunal abnormality is difficult because other factors must be considered in its pathogenesis. Similar histologic changes have been reported in kwashiorkor (28), hookworm disease (29), some viral illnesses (30), rosacea (31), in acute diarrhea (32), and after MER-29 (Triparand) Administration (33). None of these conditions were operative in our subjects, although it does emphasize that the intestine has limited ability to respond to injury. What, then, is the relationship between this non-specific histologic abnormality and tropical sprue? It has been suggested that there is a spectrum of small bowel disease in the tropics which ranges from mild and asymptomatic malabsorption to overt sprue (6). Furthermore, this coexistence of tropical sprue and milder forms of jejunal abnormality in the same tropical population has been cited as evidence supporting an association between the two processes. However, intestinal function in Thai subjects in the present study with non-specific jejunal abnormality is different than that in overt tropical sprue, and further, clinical tropical sprue appears to be rare in Thailand. Thus, we have no evidence that there is any relationship between these two conditions. A recent study of Pakistanis (23) with similar histologic changes failed to show improvement in absorption tests after treatment with tetracycline or folic acid, which further indicates that the mild non-specific jejunal biopsy changes, so common in tropical areas, are not necessarily of tropical sprue.

Note Bibliography available upon request

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