Subclinical malabsorption in Thailand.
I. Intestinal absorption in Thai children

Gerald T. Keusch, M.D.

The interpretation of subclinical malabsorption in tropical populations has been a subject of considerable interest since its high prevalence was first appreciated. A controversy has centered over whether asymptomatic jejunal morphologic and functional lesions are adaptations to the tropical environment or a subclinical form of the tropical sprue syndrome. While the etiologic agent of sprue continues to elude discovery, thus precluding specific diagnosis except by exclusion, the debate has suffered this limitation. Some workers (1) have stressed the functional and morphologic continuum between sprue and asymptomatic malabsorption in the same population, whereas our group working in Thailand chose to emphasize that laboratory and clinical data separated overt and asymptomatic sprue into two populations (2). Both points of view are, however, usually qualified by a rejoinder that the question remains an open one. And so it might remain, a classic academic riddle, were it not for the therapeutic implication inherent in a concept of overt tropical sprue existing side by side with the treatable, overt form of the disease, an enormous implication considering the vast numbers of people who may have overt sprue.

Our initial efforts to find tropical sprue in Thailand, centering at the Thai Army Hospital in Bangkok, were rewarded by one patient whose disease was well documented (3). This experience led us to suggest that overt sprue might be uncommon in Thailand, although the natural history of a similar hypothesis in Haiti (4) made us cautious that more extensive field studies might reverse this conclusion. Further field studies of an adult population in rural northeast Thailand with extensive smooth muscle deposition of ceroid pigment (5), and a more limited survey (6) in the province that yielded our single case of overt sprue, did not, however, augment the total.

To provide additional perspective, studies were extended to the pediatric age group. Because of the potential pathogenetic significance of bacterial contamination of the proximal small bowel, quantitative microbiological studies of jejunal fluids from a group of Thai adults will also be reported.

Subjects and methods

Pediatric group

Forty-five children, 2.5 to 9 years old (mean age 4 years), were studied. Nearly all were 25% or more deficient in weight-for-age, as classified by the standards of INCAP. Thirty were residents of a Bangkok orphanage where, in addition to the usual rice-based Thai diet, they received two glasses of milk daily. The remaining 15 were from a lower socioeconomic district (Huay Kwang village) in Bangkok. All 45 appeared free of chronic illness by history and physical examination, including chest X-ray. Stool examination revealed Ascaris ova in all children. Entamoeba coli or nana cysts were present in 16 from the orphanage, whereas three village children were infested with Trichuris. Giardia lamblia cysts were identified in four orphanage children but not in any of the village children.

Laboratory studies included a complete blood count, urinalysis, BUN, serum vitamin A, carotene, cholesterol, iron, total protein, and A/G ratio. Gastrointestinal function was assessed by absorption and tolerance tests for xylose (0.5 g/kg), lactose, sucrose, and glucose (2 g/kg with the exception of 1 g/kg glucose in the orphanage children), and fecal fat. Urine and stool collections and timed blood samples were closely supervised by specially trained nurses from the metabolic ward.

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Xylose was determined in a 5-hr urine collection by the method of Roe and Rice (7). Total blood reducing substances (hereafter called blood sugar) were determined by a ferricyanide method adapted to the AutoAnalyzer (8). Three-day stool collections, marked by pathogen-free carmine red dye, were begun concurrent with dietary supplements of 40 g/day of butter. Fecal fat was measured by the method of van de Kamer et al. (9).

**Adult group**

Quantitative studies of the jejunal microflora were made in a subpopulation of 56 adults studied in detail by our laboratory and previously reported (2, 10). Intestinal fluid was aspirated through one opening of a double lumen polyethylene tube attached to a Crosby-Kugler capsule located beyond the ligament of Treitz. Serial dilutions from $10^{-4}$ to $10^{-6}$ were made and plated by surface inoculation for aerobic (within 2 hr) and anaerobic (within 1 hr) incubation. Aerobic studies used the following media: blood, MacConkey, mannitol salt, SF, tellurite, and Sabouraud-dextrose agars. Anaerobic studies utilized blood, neomycin-blood, and lactobacillus agars. Plates were incubated at 37°C for 24 hr except for SF agar (96 hr) and the anaerobic studies (48 hr). The highest count for each species of organism isolated was recorded.

**Results**

Base-line laboratory value for the two groups of children are shown in Table 1 and are compared with previously reported data from Thai adults (2). Serum carotene, cholesterol, and albumin were significantly lower in the village children compared with the institution children. Vitamin A levels were lower in the village group as well, but the difference was not statistically significant. Serum albumin in the milk-drinking orphanage children was higher than the level in adults.

The results of the absorption tests in the three sets of subjects are presented in Table 2 (11). The data were remarkably similar in all. The distribution of xylose tolerance test results in the 45 Thai children is shown in Fig. 1 compared with a previously reported large series of Thai adults (10). The shift towards lower values in the children may be attributed in part to differences in dosage of the pentose, because adults weighing over 50 kg would receive less than 0.5 g/kg with a resulting increase in the percent excreted. In 13 village children, a repeat xylose test was performed from 7 to 10 days after the first. Mean urinary xylose excretion in the first test was 17.5 ± 1.6% and 17.5 ± 1.9% in the second. To estimate the 95% confidence limit for a single test in this group, the standard deviation of the experimental error was first calculated as the square root of the error term in an analysis of variance. The 95% confidence limit, defined as ± 2 sd, was 9.8%. The distribution of carbohydrate tolerance test values for institution and village children is shown in Fig. 2.

Bacteriologic studies are summarized in Table 3. Gram-positive cocci (both anaerobic and aerobic, including enterococci) were the most prevalent organisms (median count 2 × $10^4$/ml; range 10^2–2 × 10^9). Coliforms were present in 50% fewer subjects, and in smaller numbers (median count 3 × 10^3; range 10^2–4 × 10^6). The only other organisms isolated with high frequency were Candida species (median count 9 × 10^2; range 10^2– 8 × 10^4). The yeasts were found in associ-

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**TABLE 1**

Comparison of laboratory studies in two groups of Thai children and adults

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Children</th>
<th>P Value</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Village</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Institution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>37.2 ± 0.7c</td>
<td>37.5 ± 0.4</td>
<td>NSd</td>
</tr>
<tr>
<td>Carotene, μg/100 ml</td>
<td>54.5 ± 6.6</td>
<td>67.0 ± 5.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vitamin A, μg/100 ml</td>
<td>49.2 ± 4.3</td>
<td>57.6 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol, mg/100 ml</td>
<td>143.6 ± 5.5</td>
<td>164.2 ± 5.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Albumin, g/100 ml</td>
<td>3.9 ± 0.2</td>
<td>4.5 ± 0.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Iron, μg/100 ml</td>
<td>76.6 ± 7.6</td>
<td>70.0 ± 6.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Data from (2).  
* Significance of the difference between village and institution children by Student's t test.  
* Mean ± 1 SEM.  
* Not significant at $P = 0.05$ level.
TABLE 2
Comparison of absorption tests in two groups of Thai children and adults

<table>
<thead>
<tr>
<th>Absorption test</th>
<th>Children</th>
<th>Adults*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Village</td>
<td>Institution</td>
</tr>
<tr>
<td>Xylose, $\mu g$</td>
<td>17.9 ± 1.4</td>
<td>21.3 ± 1.5</td>
</tr>
<tr>
<td>Lactose, mg/100 ml</td>
<td>7.4 ± 2.2</td>
<td>8.4 ± 1.4</td>
</tr>
<tr>
<td>Sucrose, mg/100 ml</td>
<td>54.6 ± 6.2</td>
<td>51.8 ± 5.4</td>
</tr>
<tr>
<td>Glucose, mg/100 ml</td>
<td>44.9 ± 8.3</td>
<td>51.9 ± 3.7</td>
</tr>
<tr>
<td>Fecal fat, g/day</td>
<td>3.0 ± 0.5</td>
<td>2.8 ± 0.4</td>
</tr>
</tbody>
</table>

* Significance of the difference between village and institution children by Student's t test.  
* Data from (2, 11).  
* Five-hour urinary excretion expressed as $\mu g$ dose (0.5 g kg for children, 25 g for adults).  
* Mean ±1 SEM.  
* Not significant at $P = 0.05$ level.  
* Maximum rise in blood sugar during 90-min tolerance test.

Fig. 1. Comparison of xylose tolerance test results in Thai children and adults (data recalculated as percent of dose excreted). From (10).

Fig. 2. Comparison of carbohydrate tolerance test results in Thai children from a village (V) or orphanage (I) within the city of Bangkok.

TABLE 3
Microbiological studies of proximal intestinal fluid from adult Thais

<table>
<thead>
<tr>
<th>Culture result</th>
<th>Percent of subjects</th>
<th>Percent with significant growth*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>Gram + cocci</td>
<td>33.6</td>
<td>46.6</td>
</tr>
<tr>
<td>Coliforms</td>
<td>26.8</td>
<td>18</td>
</tr>
<tr>
<td>Yeast</td>
<td>32.1</td>
<td>16</td>
</tr>
</tbody>
</table>

* ≥10^9 ml.

Discussion

We have previously reported lactose malabsorption and isolated lactase deficiency in the present study group of children (12). In that report there was virtually no difference between enzyme levels in children above 2 years of age and in Thai adults. A similar conclusion is now warranted for intestinal function, as assessed by a series of carbohydrate tolerance tests and fecal fat determinations. It seems reasonable to suggest that xylose malabsorption, which begins within 8 months in American visitors to Thailand (10), is also acquired by the indigenous population within the first 2 years of life. The nonspecific abnormalities of jejunal morphology in persons living in the tropics probably also occur during this period (13).

Other data have shown a progressive increase from birth in the incidence of lactose malabsorption independent of the continued inclusion or absence of milk in the diet (12). Although neither group of children showed evidence of protein malnutrition, the significantly higher serum albumin level in the institutionalized children was undoubtedly related to the increased content of animal protein in their diet in the form of milk. In spite of this advantage, their intestinal function was no better than that in the village children.

A comparison was also made between xylose excretion in the present series and data
from the literature. Clark (14) reported 40 normal children in the tropics in Kingston, Jamaica, tested with a dose of 15 g/m² (a slightly higher dose than employed in this study). Mean 5-hr urinary excretion, 24.2 ± 7% (range 10 to 41), was not significantly different from that of the Thai children \( (t = 0.546, P > 0.05) \). On the other hand, Jones and di Sant'Agnese (15) reported 12 normal children in North Carolina tested with a dose of 0.5 g/kg who excreted 29 ± 1.2% (range 24 to 36), which was significantly higher than that of the Thai institution children \( (t = 3.3, P < 0.001) \) or village children \( (t = 5.59, P < 0.001) \). Tropical malabsorption, therefore, does not discriminate between the generations as tropical sprue appears to do (16). Unlike the reports for overt sprue (17), the severity of the lesion in Thailand would also appear not to correlate with its duration, because children and adults have a similar degree of malabsorption.

Gorbach and colleagues (18) have recently commented on the intestinal microflora and absorptive function. They found an abnormal coliform flora in the proximal gut in virtually all patients with diagnosed tropical sprue and in 60% (often in small numbers) of a group of subjects with protein–calorie malnutrition. Our data underscore the statement made by the authors (18) that malabsorption is not necessarily a consequence of the mere presence of enteric bacteria in the upper small bowel. Furthermore, our data indicate that adults not suffering from protein–calorie malnutrition may also have an abnormal coliform flora in the jejunum, possibly related to continuous environmental contamination. Our technique of necessity underestimates the number of positive subjects because we sampled only from the first loop of jejunum (18). If an abnormal jejunal flora contributes to the clinical manifestations of tropical sprue, then we agree with Gorbach et al. (18) that the sequence involves an abnormality of the small bowel mucosal cell first, which may then be rendered particularly sensitive to the products of bacterial metabolism. Previous studies of neomycin-induced malabsorption in Thai subjects have also suggested the central role of damage to the epithelium (19). We were unable to detect any heightened sensitivity to the effects of the antibiotic in Thai subjects compared with Americans recently arrived in Thailand, although it is possible that the tropical environment had already affected the small bowel epithelial cell in the latter group. Finally, we have noted no abnormalities in small bowel enzyme activity in either Thai children or adults with asymptomatic malabsorption studied by histochemical techniques (N. Bhamarapravathi, G. T. Keusch, F. J. Troncale, unpublished observations).

Summary

Intestinal absorptive function was studied in two apparently healthy groups of Thai children, one receiving daily protein supplements in the form of milk. Malabsorption of xylose and lactose was present to the same degree in both groups and did not differ from previous studies in Thai adults. Absorption of glucose, sucrose, and fat was normal in all three populations.

An abnormal coliform flora in the proximal small intestine was found in 18% of 56 adults studied, without any suggestion of overt tropical sprue or protein–calorie malnutrition. These studies serve to distinguish further the findings in subclinical tropical malabsorption from those of overt sprue.

The support of the nursing and laboratory staffs of the SEATO Clinical Research Center was an indispensable factor in the completion of these studies. Drs. Howard Noyes and Priya Kanchanavate performed the bacteriologic studies. Dr. Varuni Promadhat supervised some of the pediatric studies.

References


