

1. Title: LACTOSE MALABSORPTION IN THAILAND

I, A Prevalence Study

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Recent studies have shown a high incidence of lactose malabsorption due to lactase deficiency in Bantu tribes in Uganda (Cook and Kajubi 1966), in American Negroes (Bayless and Rosensweig 1966), and in Greek Cypriots living in London (McMichael, Webb and Dawson 1966). These findings have been interpreted to suggest a genetically determined enzyme defect. It is likely that this develops after infancy since congenital lactase deficiency is a serious illness (Holtzel et al 1959). If it is true that lactose malabsorption first occurs after infancy, the differentiation of genetic from environmental factors is critical.

In a previous study of gastrointestinal function in normal adult Thais lactose malabsorption was a universal finding. The present investigation broadens the above observation by studying the prevalence of lactose intolerance, and when possible jejunal lactase activity, in different age groups.

Subjects

Fifty male Thai Marines, 43 pregnant females in all trimesters of pregnancy, and 48 village adults residing near Bangkok comprised the adult group. Most drank no milk at all; a few used a small amount of sweetened condensed milk with coffee. For comparison, data from 58 Peace Corps Volunteers and U.S. Army personnel in Southeast Asia are included. The pediatric group consisted of 85 normal children between 1 and 24 months of age institutionalized at birth because their parents had tuberculosis or Hansen's disease, and 30 children 3-6 years old from a separate orphanage. All drank milk daily, Forty-one unweaned village infants 1-24 months old and 16 non-milk drinking village children, 2½-8 years of age were studied as well.

Methods

Tolerance tests using lactose or sucrose, 1.5 gm/kg body weight in adults, and 2 gm/kg in the pediatric group, were performed in the fasting state. Glucose tolerance tests utilized half the amount of disaccharide, except for the orphanage group who received 2 gm of glucose/Kg. Venous blood was obtained fasting and at 30, 45, 60, and 90 minutes following ingestion of the sugar. In the first 40 adults and 30 children, a 2 and 3 hour blood specimen was also taken. In no case did this change the maximum rise of blood sugar and these samples were thereafter not obtained. Blood total reducing substance, hereafter termed blood sugar, was determined by a ferricyanide method adapted to the autoanalyzer (Hoffman 1937). A rise in blood sugar of 20 mg or more in any of the carbohydrate tolerance tests was considered normal.

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Jejunal biopsy tissue was obtained with the adult (9.5 mm) or pediatric (8 mm) Crosby-Kugler biopsy instrument from the region of the ligament of Treitz after x-ray verification of the position of the capsule. Specimens were wrapped in aluminum foil and immediately frozen and kept at -60°C until determination of disaccharidase activity. Enzyme assay was performed by the method of Dalqvist, modified as previously reported (Sheehy and Anderson 1965). Enzyme activity was calculated as units (μ moles of lactose hydrolyzed per minute at 37°) per gram of protein.

Results

Figure 1 shows the maximum rise in blood sugar during the lactose tolerance test in Thai and American adults. The response of the two groups was clearly different. The median rise in blood sugar among the Thais was highest in the Thai Marines. However, only 2 of the 50 marines had a normal test. Table 1 and figure 2 show the results of the lactose tolerance test in institutionalized and village children. The percentage of abnormal responses increased with age. There was a significant decrease in lactose absorption in the institutionalized children after one year of age although milk intake continued. In the village children the change did not occur until after 2 year of age. Lactose absorption in the 1 to 2 year old group was significantly better for the village than the institutionalized children.

Table II show glucose and sucrose and sucrose tolerance test data. There were no abnormal sucrose tolerance tests and in 83 subjects the glucose tolerance test was normal. These results show that sugars other than lactose are normally adsorbed.

Disaccharidase activities are summarized in Table III and Figure 3. In 82% of the 112 Thai specimens examined, lactase activity was less than 5 units per gram of protein. By contrast only 9% of the 23 American specimens were below this level. Maltase and sucrase activity were somewhat lower in the Thai subjects, particularly in the pediatric group. Pediatric biopsies were generally taken proximal to the ligament of Treitz where lower disaccharidase activity is expected (Newcomer, A.D. and McGill D.B. 1966). Enzyme activity was lowest in the orphanage children. In contrast to all other subjects, tissue specimens in this group were frozen and stored on filter paper and some loss of activity might have occurred.

Table III shows the ratios between median disaccharidase activities. In the Thai subjects only the maltase/sucrase ratio was similar to the American value, while the sucrase/lactase and maltase/lactase ratios were both high due to disproportionate lowering of lactase activity.

Comments

It is apparent that lactase deficiency and an abnormal lactose tolerance test is present in nearly all Thai adults. Similar data in American Negroes have been interpreted to indicate a genetic etiology for isolated lactase deficiency (Bayless and Rosensweig 1966). In support of this hypothesis is the demonstration of a tribal distribution of lactase deficiency in Uganda (Cook and Kajubi 1966). The data from children above the age of 2 years in the present study could be interpreted to favor a similar etiology in the Thai. However, when one studies Thais between 1 month and 2 years of age two facts emerge. Firstly, lactose absorption is normal in infancy, which is presumptive evidence of normal lactase activity (Dunphy et al 1965, Peternel 1965). While these results are inconsistent with the syndrome of congenital lactase deficiency, they do not rule out delayed expression of a genetically controlled trait. Secondly, the delayed age of onset of lactose malabsorption in village children compared to institutionalized children strongly suggests the intervention of environmental influences. Genetic interaction may or may not be present, but cannot be proven from these data.

Overt protein-calorie malnutrition, which may underlie lactase deficiency (Brock, 1966), was not a factor in the institutionalized infants and children who had adequate milk intake. Enzyme adaptation to

substrate withdrawal cannot be considered in this population either. Repeated diarrhea was observed to be exceedingly common in the infants and might be related to deficiency of lactase (Sunshine & Kretchmer 1965). In 3 of 4 infants with lactose malabsorption shortly after acute diarrhea, a normal test was obtained 3-4 weeks later, while in the 4th the rise in blood sugar went from 0 to 13 mg% (unpublished data).

There are 4 possible explanations for persistent hypolactasia and lactose malabsorption in adult Thais: 1) genetically controlled loss of enzyme activity, 2) irreversible intestinal injury acquired in early childhood 3) continued active intestinal injury 4) acquired intestinal injury in childhood with adaptation to the lactose-free Thai diet. There is little pertinent information available in considering these alternatives. Other racial groups or upper class Thais living in Thailand, or young Thais living abroad have not been studied and the question of genetic influences cannot be fully resolved. The present study indicates that with or without genetic interaction, environmental influences can alter the age at which the abnormality develops.

Brock (1966) has raised the interesting possibility that protein malnutrition in infancy may lead to permanent lactase deficiency. Why lactase should fail to return to normal with therapy in kwashiorkor (Cook and Lee 1966) is unknown. It is difficult to explain how a single enzyme system can be permanently damaged in a rapidly regenerating tissue like the small bowel epithelium.

There is no evidence to bear on the 3rd possibility, persistent injury to the intestinal mucosa. Although the intestinal mucosa in adult Thais is not normal by North American standards and thought to represent a pre-sprue lesion (Sprinz et al 1962), function as assessed by a variety of tests is clearly different than in malabsorptive disease (Troncale et al 1967). The epithelial cell brush border, the site of abnormality in primary deficiency of lactase (Crane 1966), is normal as delineated by histochemical techniques (Bhamarapravathi et al 1967). Epidemiologic data are necessary before a continuous environmental factor can be implicated.

The 4th possibility involves two concepts. Several authors have related lactase deficiency to lack of substrate in the diet (Durand 1965, Cuatrecasas et al 1965). The Thai adult diet contains little milk or milk products. However, the data presented here indicate that hypolactasia may develop while milk consumption is uninterrupted. It is possible that loss of lactase activity may occur in childhood due to an unknown cause as discussed above and that low activity is sustained because of secondary adaptation to absence of substrate in the adult diet. The inducibility of lactase in healthy young adult Thais was studied by us and will be reported separately (Keusch et al).

Summary

One hundred forty one normal Thai adults, 172 normal Thai infants and children, and 58 Americans in Southeast Asia were studied to determine the prevalence of lactose malabsorption and lactase deficiency. Lactose malabsorption and lactase deficiency were present in Thai adults. The abnormality was not congenital but occurred after early childhood. Environmental factors are implicated although genetic interaction cannot be excluded.

Table I
Percent of Institution and Village Children with an Abnormal Lactose Tolerance Test*

Age (years)	Percent Abnormal		"p" value ⁺ between Institution and Village Children
	Institution Children	Village Children	
(a) 1/12-1	36.8 (49) [#]	15 (20)	NS
(b) > 1-2	76.5 (34)	29.6 (21)	0.01
(c) > 2	86.7 (30)	87.5 (15)	NS
"p" a-b	<0.01	NS	
"p" a-c	<0.01	<0.01	
"p" b-c	NS	<0.01	

* Maximum rise in blood sugar less than 20 mg%
⁺ Significance of difference between groups compared.
[#] Number of individuals studied in parentheses.

Table II
Mean maximum rise of blood sugar after glucose and sucrose administration in Thais

Group	Glucose			Sucrose		
	No.	Dose	Mean max. rise blood glucose	No.	Dose	Mean max. rise blood glucose
<u>Children</u>						
Orphanage	30	2g/Kg	51.9 ± 20.2 mg%*	10	2g/Kg	51.8 ± 17 mg%
Village	7	1g/Kg	44.9 ± 21.9 mg%*	9	2g/Kg	54.6 ± 18.5mg%
<u>Adults</u>	51	0.75g/Kg	46.0 ± 26.1 mg%*	16	1.5g/Kg	66.9 ± 29.7mg%

* ± 1 S.D.

Table III

Disaccharidase Level*, Median and Range, and Ratios of the Median

Subject Group	Lactase	Maltase	Sucrase	$\frac{\text{Sucrase}}{\text{Lactase}}$	$\frac{\text{Maltase}}{\text{Lactase}}$	$\frac{\text{Maltase}}{\text{Sucrase}}$
<u>Children</u>						
Institution	2.4 (0-47.2)*	170 (43-338)	38 (6-103)	16	50	4.5
Village	2.5 (0-16.26)	265 (83-472)	60 (18.7-140)	24	106	4.4
Thai Marine Adults	2.5 (0.16-58.31)	262 (89-490)	73 (17.8-149)	29	105	3.5
Thai Village Adults	1.7 (0.-7.97)	307 (87-566)	85 (14-142)	50	181	3.6
American Adults	37.5 (2.47-129)	375 (124-600)	108 (34-231)	2.9	10	3.5

* Units per gram of protein (1 unit=1 umole substrate hydrolyzed/minute at 37°C)

FIG.1. MAXIMUM RISE IN BLOOD SUGAR AFTER LACTOSE (1.5 G / Kg) IN HEALTHY ADULTS DURING A 90 MINUTE TOLERANCE TEST

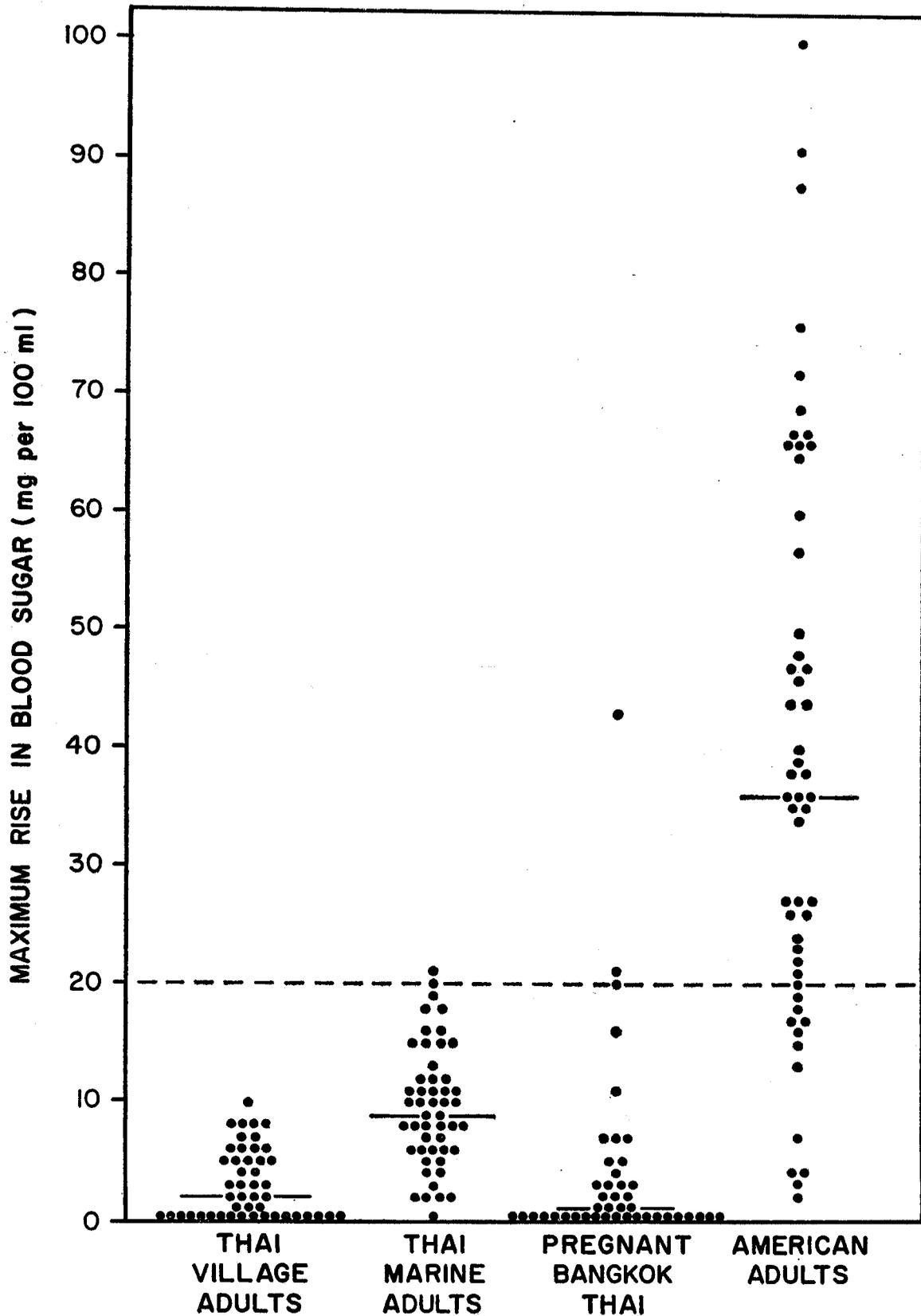
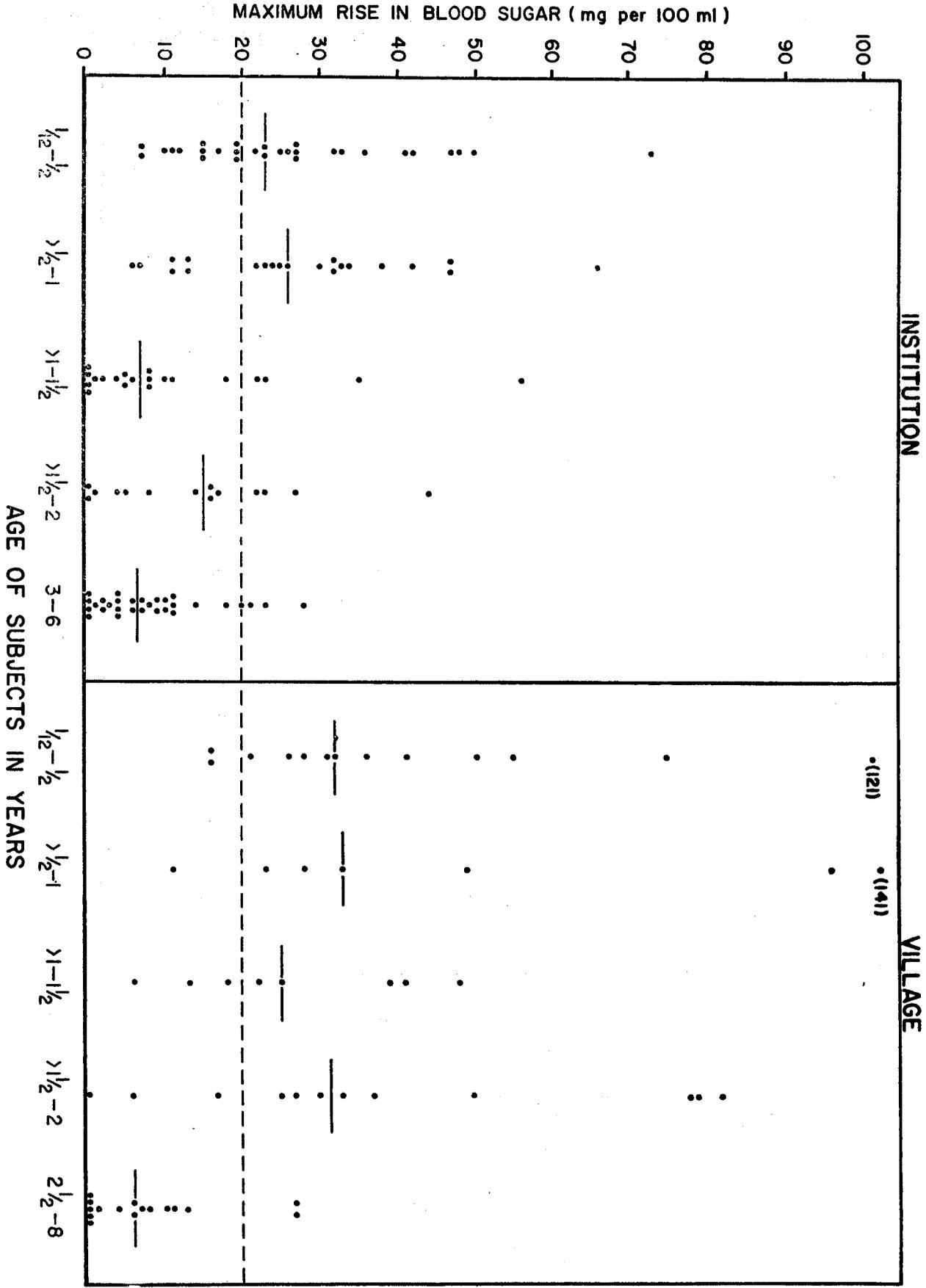


FIG. 2. MAXIMUM RISE IN BLOOD SUGAR AFTER LACTOSE (2 G/Kg) IN INSTITUTIONALIZED AND VILLAGE THAI INFANTS AND CHILDREN DURING A 90 MINUTE TOLERANCE TEST



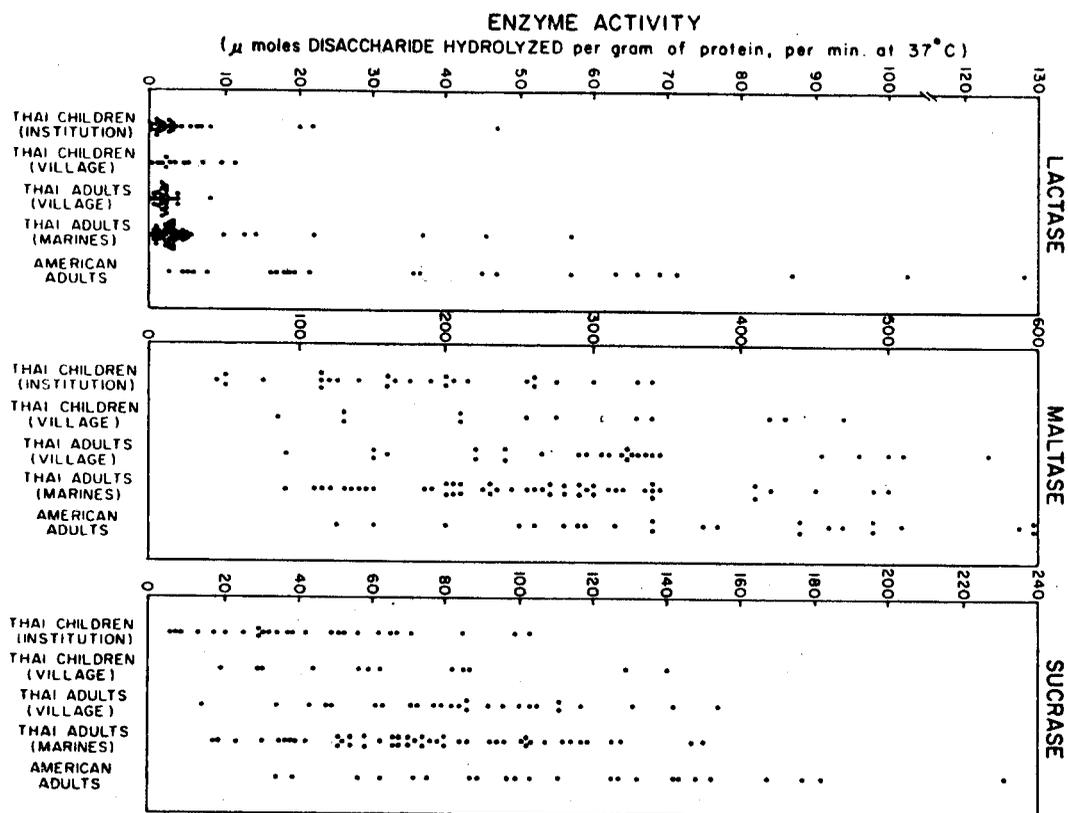


FIG. 3. JEJUNAL DISACCHARIDASE ACTIVITY (UNITS PER GRAM OF PROTEIN) IN THAI CHILDREN AND ADULTS AND AMERICAN ADULTS

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