1. Title: LACTOSE MALABSORPTION IN THAILAND

II. Enzyme Induction

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In the previous report we presented evidence that lactose malabsorption and intestinal lactase deficiency occurred after infancy in the Thai population, and was independent of milk drinking. The suggestion has been made that lactase is an adaptive enzyme in man (Cuatrecasas et al 1965). Because we were unable to reject the hypothesis that near universal hypolactasia in adult Thais represented an adaptive phenomenon to the milk-free Thai diet, the present study was undertaken to examine this hypothesis further.

Subject. Fifty male Royal Thai Marine non-commissioned officers and recruits, mean age 22.8 (22-30) years, participated in the study. In 23 subjects there was no history of milk intake while the remaining men took only 1-2 teaspoons of sweetened condensed milk per day in coffee. In no subject was a history of milk intolerance elicited.

Methods: Lactose tolerance tests and disaccharidase assay (Sheehy and Anderson) on jejunal tissue were done. Each subject then began dietary supplementation with 25 grams of lactose twice daily. Complete ingestion of the sugar was verified visually. Lactose feeding was continued for approximately 4 weeks (mean 26.4 days, range 22-38 days) when a repeat tolerance test and biopsy were performed.

Results:

Biopsy. 114 attempts were necessary to obtain 100 tissue specimens for enzyme assay. The reasons for repeat biopsy included failure to pass the pylorus (6), kinking of the tube (2), closure of the capsule without obtaining a specimen (2), and failure of the knife mechanism to close (4). No complications from biopsy were encountered.

The biopsy specimens were studied after fixation in formalin under the dissecting microscope. Special attention was made to discern the presence of various forms of villi i.e., finger, tongue or leaf, short ridge, or convolutions, and the percentage of each form if more than one was present was roughly estimated. Neither long finger villus nor flat mosaic atrophic mucosa was observed in any of the specimens. In forty specimens there was a mixture of leaf and ridge with occasional short fingers (in ten cases). In five cases, the villi consist mostly of convolutions. In another five cases, a mixture of convolution ridge and leaf was noted.

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Clinical Symptoms. Forty six of the 50 subjects had 1-8 watery stools, generally accompanied by cramps as well, within hours of the first lactose tolerance test. In 5 subjects more frequent or softer stools persisted for the entire period of study. Thirty seven subjects experienced symptoms following the second lactose tolerance test.

Tolerance Test. Figure 1 show the maximum rise in blood sugar over fasting in the 50 subjects before and after dietary supplementation with lactose. No significant change occurred after lactose feeding in the group.

Lactase Activity. Figure 2 show lactase activity in units (u moles of lactose hydrolyzed per minute at 37°C) per gram of tissue wet weight and per gram of protein. In 4 specimens (2 pre-and 2 post-lactose feeding) activity of all disaccharidases was extremely low and these results were discarded. There was no significant change in enzyme activity after lactose feeding. Seventy eight of the 96 specimens had low lactase activity, confirming the impression gained from the tolerance test. In 6 subjects normal lactase activity was found in both pre and post lactose specimens associated with abnormal tolerance tests (maximum rise of blood sugar 1-16 mg%). One subject had a normal control lactose tolerance test rise of 20 mg% with low normal lactase activity. The post feeding lactase activity was higher but the rise in the tolerance test was only 10 mg%. Two others had normal lactase before, and 4 others after, lactose feeding with a flat tolerance test (maximum rise of blood sugar of 1-11 mg%).

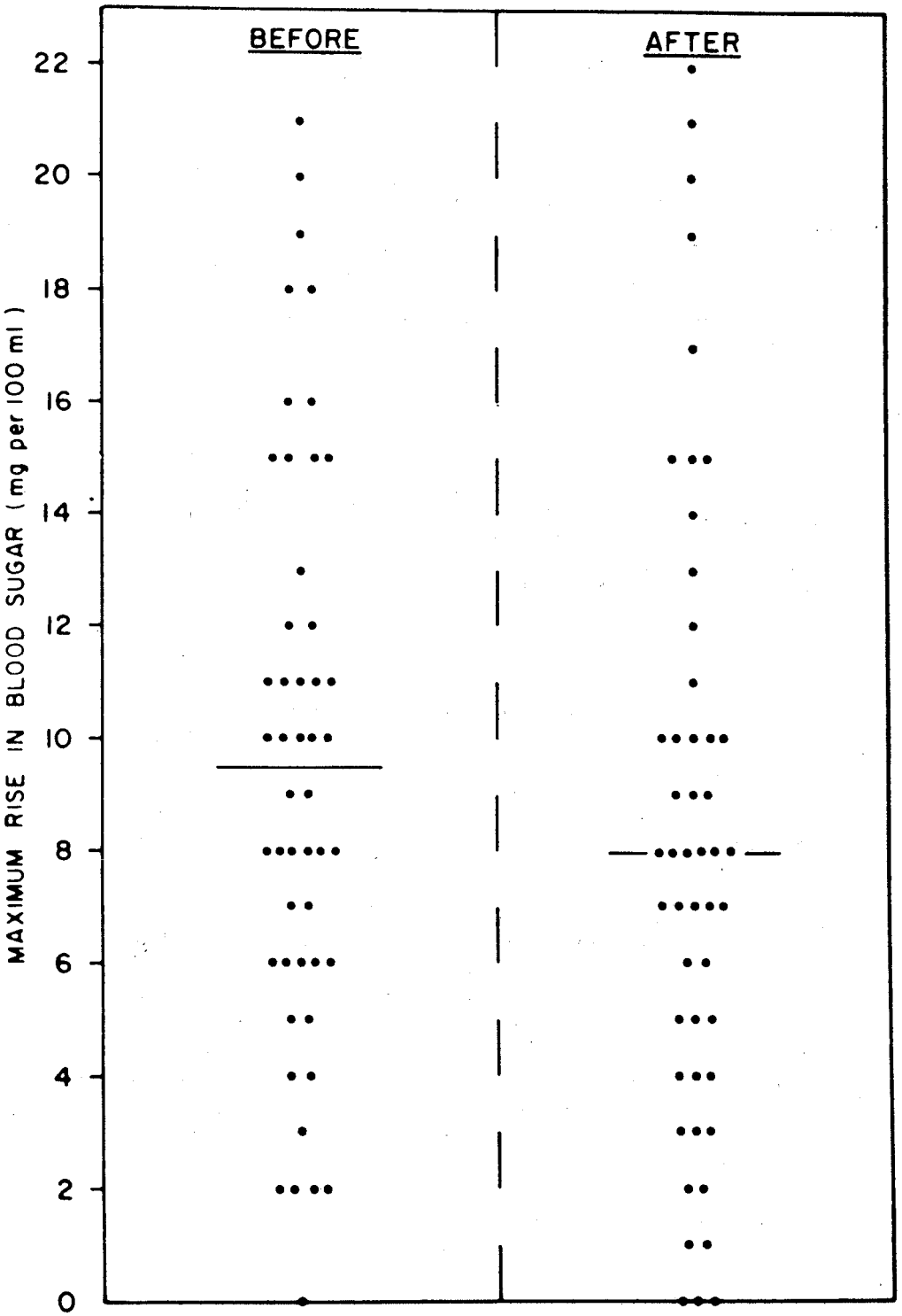
Comments: In several animal species intestinal lactase activity disappears after the weaning period when lactose is no longer a dietary constituent (Holtzel 1965). The California sea lion, whose milk is lactose-free, never develops lactase activity (Sunshine and Kretchmer, 1964). In man the data concerning lactase activity and milk intake are meager. Cuatrecasas (1965) showed an association between low lactase activity, lactose intolerance and the history of no milk ingestion. In addition, when milk was removed from the diet of 2 milk drinkers with normal lactase activity, lactose "absorption" diminished. Prolonged lactose feeding failed to increase absorption, however, in 11 subjects and no increase in enzyme activity occurred in 3 subjects serially biopsied.

The present study, utilizing a sufficiently large population to allow firm conclusions, has failed to show induction of intestinal lactase activity or improvement in lactose absorption in man after prolonged feeding of lactose. It is doubtful that a higher dose of sugar or a longer experiment would have changed the results. Induction of lactase, a very complicated phenomenon, has been extensively studied in E. coli (Cohn 1957). Briefly when inducer is introduced into an exponentially growing culture of E. coli, synthesis of lactase begins immediately and continues for as long as the inducer remains in the culture medium. When the inducer is removed lactase synthesis stops and enzyme activity per cell decreases as new protein without lactase activity is made. While strict analogy to human intestinal epithelial cells is not possible, the results in the present study give no indication of enzyme induction in man.

Because the intestinal mucosa of Thai subjects looks different than North American subjects (Sprinz et al 1962) the possibility that lactase was not induced in this study because of pre-existing, permanent damage or continuous injury to epithelial cells must be considered (Keusch et al 1967). McMichael et al (1966) have stated that the maltase/lactase ratio in primary (normal histology) lactase deficiency is considerably higher than in secondary (abnormal histology) deficiency because of the marked changes in both enzymes in the latter. The maltase/lactase and sucrase/lactase ratios in our Thai subjects were 5-18 times greater than in the Americans studied by us (Keusch et al 1967) and consistent with a primary type of deficiency. The site of this lesion is, presumably, the brush border of the epithelial cell (Crane 1966). It is not known however, if the nature of the injury in the Thai with non-specific jejunal changes is the same as in the American with normal histology and lactose malabsorption. The poor correlation between lactase deficiency and milk-drinking in these Americans (Littman and Hammond 1965) and the failure to induce enzyme activity in the present study indicate the enzyme adaptation does not occur.

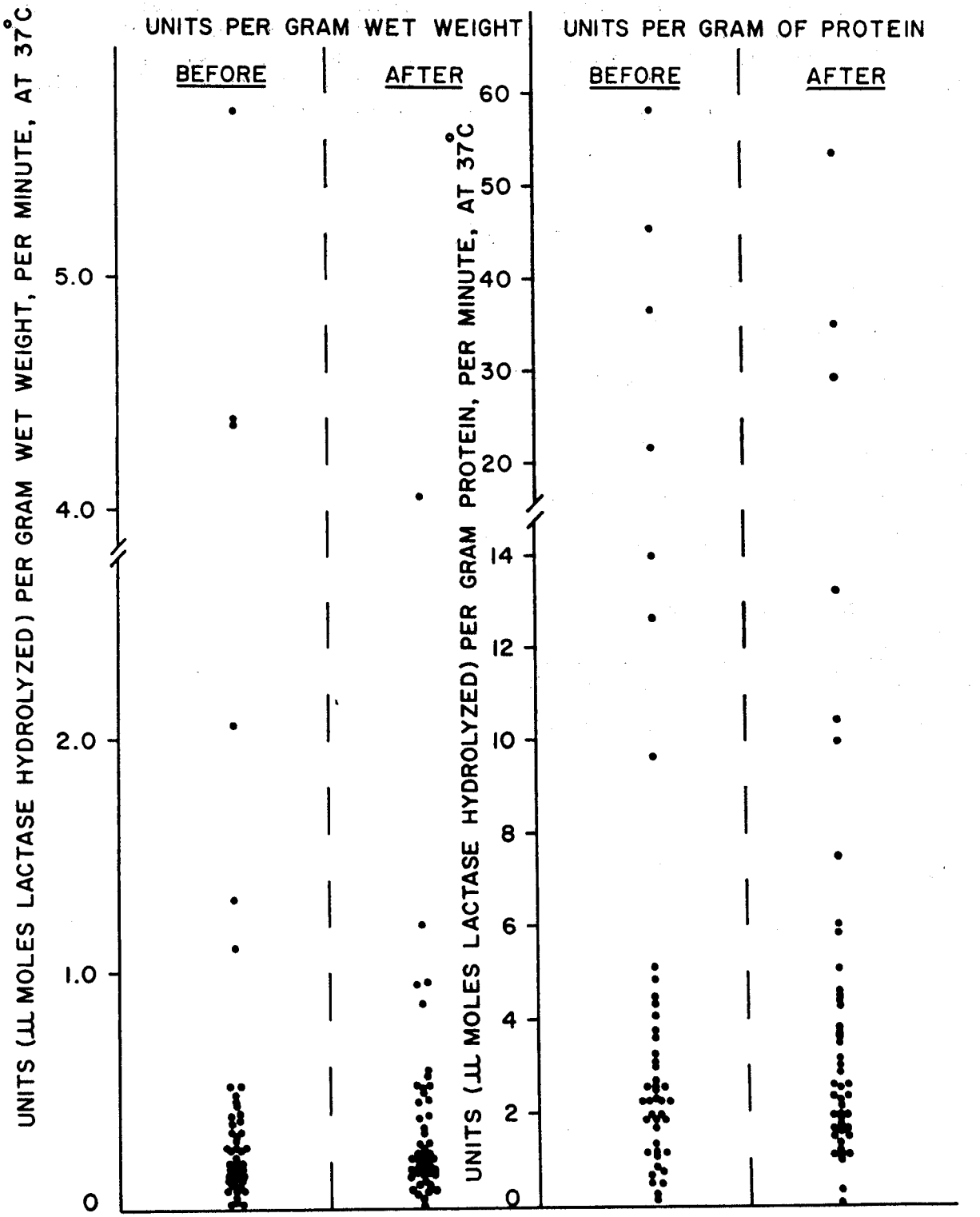
Summary. Induction of intestinal lactase activity was attempted by feeding 50 gm of lactose daily for approximately 4 weeks to 50 male Thai Marines. No change in enzyme activity occurred. The lactose tolerance test was abnormal both before and after the experimental period. It is concluded that lactase is not an adaptive enzyme in man.

FIG. I. MAXIMUM RISE IN BLOOD SUGAR AFTER LACTOSE (1.5 gm/kg) DURING A 90 MINUTE TOLERANCE TEST BEFORE AND AFTER PROLONGED LACTOSE FEEDING



(HORIZONTAL LINE INDICATES MEDIAN VALUE)

FIG. 2. JEJUNAL LACTASE ACTIVITY BEFORE AND AFTER PROLONGED LACTOSE FEEDING* TO HEALTHY THAI ADULTS



*25 GM OF LACTOSE TWICE DAILY FOR APPROXIMATELY 4 WEEKS

ACKNOWLEDGEMENTS

The assistance of R. Adm. Snit Posakrissana, Surgeon General, RTN, R. Adm. Jinawat Wongpensri, Commanding Officer Sattahip Navy Station, R. Adm. Sophon Suyarnsettakorn, Commandant, RTMC and Capt Samrit Jartinanda, Deputy Director SEATO Medical Research Projects is gratefully acknowledged. Thanks are due LCDR M.C. Pusan Swasdiwatana, MC, RTN, Mrs. Yupa Kasemsant, R.N., Mrs. Pusadee Surisook, R.N., SFC James Turner, U.S.A., Sr. Lt Nuam Pejarat, RTN, and Lt. Saweg Jaigwarng, RTN

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