THE NUTRITIONAL IMPLICATIONS OF LACTOSE INTOLERANCE

by

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ABSTRACT

Adult lactose intolerance due to low lactase levels is often associated with varying degrees of abdominal distress ranging from bloating and distension to severe cramps and diarrhea. Recent studies have suggested that these gastrointestinal disturbances may interfere with normal absorption of nutrients in addition to lactose. In order to investigate this possibility, both human and animal studies were conducted.

Twenty-three healthy Caucasian adults were used to study the effect of lactose on the absorption of vitamin A, ascorbic acid and protein. Eight of the 23 subjects were lactose intolerant on the basis of a maximum rise of blood glucose of less than 20 mg/100 ml over the fasting blood glucose level after ingestion of 50 g of lactose in 300 ml water. In each study, blood samples were drawn after an overnight fast and at intervals up to 4 hours after consuming 50 g lactose in an aqueous solution or test meal containing gelatin, vitamin C or vitamin A. Sucrose replaced lactose as a control.

The results from the human studies failed to demonstrate that lactose had an effect on the absorption of ascorbic acid, vitamin A or protein in lactose intolerant subjects. It may be that the composition of the test drink which contained fat and protein, may have affected the rate of absorption of

the nutrients tested through a delay in gastric emptying time. However, the finding that absorption of vitamin C remained unaffected even when consumed with an aqueous solution of lactose, is attributed to the possibility that the level of ascorbic acid given was too low to show measurable differences in blood levels of that nutrient.

To study the effect of lactose on the absorption of calcium, fat and protein, balance studies were conducted using postweaning rats. The experimental groups received either 10%, 20% or 30% lactose diets, while an equivalent amount of sucrose replaced the lactose in the control diets.

In addition, postweaning rats were given vitamin A intragastrically with either lactose or sucrose to investigate the effect of lactose on vitamin A absorption.

From the balance studies with rats, the results indicate that fecal nitrogen and fat excretion was significantly ($p < 0.05$) higher in all the animals fed lactose as compared to the controls. However, fecal calcium excretion was found to be generally lower for each lactose group relative to the controls, but the difference was statistically significant ($p < 0.05$) only at the 30% level of lactose intake. Improved calcium absorption may have important nutritional implications where dietary calcium intake is low. It appears though, that the level of dietary lactose would most likely have to exceed the limits of normal lactose consumption to have an effect on the absorption of nutrients.

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I would like to thank my parents for the love, understanding and encouragement that they have always given me. This work is dedicated to them.

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TABLE OF CONTENTS

PAGE

PAGE

LIST OF TABLES

I. INTRODUCTION

Adult lactose intolerance due to low levels of intestinal lactase activity is common in the majority of adults throughout the world. It is particularly evident in certain races and ethnic groups (1), a fact that accounts for its high incidence on a worldwide basis. In Eskimos (2,3), Jews (4-7), Asians (8-15), Negroes (16-27) and North American Indians (3, 21,28-29), the incidence of lactose intolerance is generally greater than 70% and may even be as high as 90%. On the other hand, in some peoples, including northwestern Europeans, the incidence of lactose intolerance is often below 20% (1).

In those individuals with low lactase levels, consumption of one or more glasses of milk will induce various degrees of abdominal distress ranging from bloating and distension to severe cramps and diarrhea (30,31). The symptomatic response of a lactose intolerant individual is associated with the accumulation of lactose in the intestinal lumen. Since lactase levels are low, the ability to hydrolyze lactose to its constituent monosaccharides, glucose and galactose, which are readily absorbed, is reduced. Consequently, lactose accumulates in the lumen of the small intestine causing fluid and electrolyte changes which increase intestinal motility. In the colon, fermentation products resulting from bacterial action on the unabsorbed lactose impair absorption of the fluid load and intestinal motility is further enhanced. Therefore, the distension of the small intestine and the increased motility

of both the small and large intestine are responsible for the abdominal discomfort seen in lactose intolerance.

Although the incidence and the etiology of adult lactose intolerance have been investigated extensively, little is known about the effect of lactose intolerance on the absorption of nutrients other than lactose. Since rapid transit of food through the gastrointestinal tract may not afford sufficient time for the absorption of dietary nutrients, a lactose intolerant individual may not be deriving full nutritional benefits when consuming only milk or other lactose-containing products. Recently, Paige and Graham (32) noted that lactose intolerant subjects receiving a lactose-based diet, showed an increase in stool water, fat and nitrogen excretion as compared to values obtained on a sucrose-based diet. Similarly, Calloway and Chenoweth (33) investigated nutrient absorption and retention in lactose intolerant subjects. Their results indicated increased fecal energy losses that were lactose dose dependent in four intolerant subjects each fed diets of varying lactose content over 12 day periods, as compared to the two control subjects. Both studies suggest that consumption of milk or other lactose-containing products might result in impaired absorption of nutrients in addition to lactose.

The purpose of the present work was to examine the effect of dietary lactose on nutrient absorption in lactose intolerant individuals as well as in postweaning rats, which have low levels of intestinal lactase activity.

Human subjects were used to assess the effect of lactose on the absorption of vitamin A, ascorbic acid, and protein.

Balance studies were carried out using postweaning rats to examine the effect of lactose on the absorption of fat, protein and calcium.

In addition, postweaning rats were given vitamin A intragastrically with either lactose or sucrose to investigate the effect of lactose on vitamin A absorption.

II. LITERATURE REVIEW

A. Adult Lactose Intolerance

1. Diagnosis

Intolerance to lactose has been found in many adults who were able to consume milk freely during infancy and childhood (51). Most adults who are lactose intolerant are able to tolerate small quantities of milk, as in coffee or tea. However, ingestion of one or more glasses of milk (30,31) may induce symptoms ranging from flatulence and bloating to severe cramps and diarrhea. Intestinal lactase activity as low as 7 units/g protein may be found in an intolerant individual as compared to approximately 70 units/g protein in a lactose tolerant subject (30,34). Because of the diminished levels of lactase activity in the intestinal brush border cells, a load of lactose will not be sufficiently hydrolyzed to its component units, glucose and galactose. Clinically, a flat lactose tolerance curve is seen in an intolerant subject as indicated by a rise of blood glucose of less than 20 mg/100 ml over the fasting blood glucose level after a 50 g oral lactose load (35). This low rise in blood glucose may be accompanied by gastrointestinal symptoms.

2. Pathogenesis of Symptoms

The symptoms associated with low lactase levels are caused by the accumulation of lactose in the intestinal lumen. The unabsorbed lactose attracts a net osmotic movement of water

out into the lumen (36). This is associated with changes in the sodium gradient of the small intestine (37) so that absorption of water and electrolytes is impaired. Abdominal distension and bloating results causing an acceleration in transit time (37-39). The osmotic effect of the accumulated disaccharide in the small intestine is enhanced in the colon. Here the lactose is subjected to bacterial degradation to a number of organic acids, especially lactic and acetic acid (38-41). These are not well absorbed in the large intestine and interfere with absorption of the fluid load presented to the colon (38,40). The symptoms seen then, are due to distension of the small intestine (42) and the increased motility of both the small and large intestine (42) induced by the increased fluid load (38). Diarrhea and occasionally steatorrhea may be seen in lactose intolerance (40,43-45). Fecal pH drops due to the presence of the organic acids (46), bacterial counts may be increased (46), lactose as well as glucose and galactose may be found in stools (47).

3. Etiology

a. Genetic Theory

One of the most widely accepted theories to explain the etiology of adult lactose intolerance is the genetic theory (31). It would account for the equally high incidence of lactose intolerance in those groups of people within their native environment and those same peoples who have lived for generations in countries of a totally different environment

than their native land. Gilat et al. (5) for example, found a high incidence of lactose intolerance among Israeli Jews irrespective of their origin, that is, Ashkenazi, Sephardi, Yemenite, Iraqi and Oriental. It has since been noted that there is also a high incidence of intolerance among Canadian and American Jews (6,7).

Investigation of the familial incidence of lactose intolerance also suggests a genetic etiology of adult lactose intolerance (8,40,48-51). In one study, Neale (50) found that all members of two generations of a Pakistani family in Britain exhibited clinical symptoms of lactose intolerance and/or had low levels of intestinal lactase activity. Other workers (8,40, 48-49,51) have noted that subjects who were lactose intolerant usually had a parent or sibling who had experienced intolerance to lactose.

In addition, Cook and Kajubi (23) found a Bantu tribe in East Africa having a high incidence of lactose intolerance, the "Hamitic" Hima and Tussi tribe with a low incidence and the Hutu and Iru tribes with an intermediate incidence who are believed to be of mixed Bantu/Hamitic origin. These studies suggest that lactose intolerance is of genetic origin. If this is so, then there should be no correlation between milk drinking habits and levels of lactase activity. The second hypothesis concerning the etiology of lactose intolerance disputes this assumption.

b. Lactase Induction by Milk Consumption

This theory states that the postweaning decline in lactase activity in most mammals is a normal consequence of decreased milk consumption. If the enzyme is adaptive, as this theory implies, then varying the lactose content of the diet should increase intestinal lactase activity. In lactose intolerant subjects, attempts at induction of the lactase enzyme by gradually increasing the lactose content of the diet have not been successful (52-56). Conversely, in healthy adult subjects, denial of milk over a period of time did not reduce intestinal lactase activity (57-58). A correlation between the levels of intestinal lactase activity and milk drinking habits has also been difficult to establish (59,60-64). In man, therefore, adaptation of intestinal lactase activity to dietary lactose seems unlikely as a causative factor in adult lactose intolerance.

Data from animal studies of the adaptation of intestinal lactase however, have been conflicting (65). A number of workers have found that lactase activity could be influenced by increasing the lactose content of the diet or by prolonged lactose feeding (66-75). Bolin et al. (66-67) demonstrated the adaptive nature of intestinal lactase in the adult rat, when an increase in lactase activity was produced after 5-8 weeks on a 30% lactose diet (66), as well as on a 10% lactose diet (67). However, the postweaning decline in lactase activity could not be prevented by feeding a 10% lactose diet up to 5 weeks of age (67). Jones et al. (69) reported significantly higher levels of lactase in 40 day old rats fed a 68% lactose diet for one

to twelve weeks than in rats fed glucose, sucrose or a lab chow. A number of other investigators have obtained similar results (70-74). An equally large number of workers have been unsuccessful in inducing the specific activity of lactase or preventing its decline after weaning (76-80). The discrepancies in the findings are most likely due to differences in methodology: length of experimental period, level of dietary lactose fed, and the enzyme assay method used.

c. Dietary Inhibitors

Proponents of another theory to explain the etiology of adult lactose intolerance, claim that certain foods or drugs ingested are lactase antagonists or inhibitors (81). As a result, lactose intolerance may develop. Alterations in the intestinal mucosa due to consumption of particular foods, for example highly spiced foods and betel nuts, may affect lactase activity (82). Also, drugs such as colchicine may cause a decreased lactase production which will impair lactose absorption. However, further studies to investigate dietary habits and drug usage of those races and ethnic groups exhibiting a high incidence of lactose intolerance would determine the validity of this theory.

d. Disease Hypothesis

This theory suggests that lactose intolerance in certain population groups may be a secondary manifestation of some subclinical infection indigenous to that particular area.

In other words, where the incidence of lactose intolerance is high, for example in tropical countries, infection (83-84) and/or malnutrition (85-86) may alter the intestinal mucosa and its enzymes and thus impair its absorptive capacity. Bowie et al. (87-89) have attempted to link kwashiorkor in African children to adult lactose intolerance. They suggest that low lactase levels may result from intestinal mucosa damage due to protein deprivation in childhood. However, the children in Bowie's studies may have been lactose intolerant independent of the kwashiorkor, that is, before its onset. In addition, work with rats revealed that protein deprivation did not affect intestinal lactase levels (90-91).

It appears that no single theory may account for the marked differences in the occurence of adult lactose intolerance in various population groups. Primary adult lactose intolerance is probably a manifestation of genetic factors influencing lactase levels in the intestine. Where disease and/or drugs or certain foods have damaged the intestinal mucosa, lactase levels may also be affected resulting in another, secondary type of adult lactose intolerance.

B. The Effect of Intestinal Motility, Gastric Emptying and Diet Composition on Nutrient Absorption in Lactose Intolerance

1. The Effect of Intestinal Motility on Nutrient Absorption

The parasympathetic nervous system is largely responsible for normal gastrointestinal function (92,93).

Vagal stimulation of the cholinergic fibers that are present within the intestinal wall tends to increase the overall degree of activity by promoting peristalsis of the intestinal tract. Distension, presence of food or specific chemical substances can stimulate the nerve endings and extreme irritation can elicit the "peristaltic rush". This begins in the duodenum and passes down the entire length of small intestine to the ileo-cecal valve in a matter of minutes. In this way, the small intestine is relieved of excessive irritation or distension as its contents are swept into the colon. On the other hand, strong stimulation of the sympathetic nerve supply can totally block movement of food through the gastrointestinal tract. The effect of either extreme of intestinal motility on nutrient absorption is discussed below.

Clinical as well as experimental investigations have revealed that transit time through the small intestine is a critical factor in optimal nutrient absorption (94-108). In 1936, Wade (94) first noted the relationship between motility and absorption. He suggested that normal gastrointestinal absorption is dependent upon normal gastrointestinal motility. In his treatment of two celiac children, he administered a peristaltic stimulant to correct the reduced motility of the intestinal tract and to cause a period of more rapid absorption of the chyme from the lumen. The result was an increase in body weight and height, the elevation of previously flat glucose tolerance curves and the eventual return to normal intestinal peristalsis. In 1940, May and McCreary (95)

conducted an experiment to prove that low blood sugar in celiac disease was in fact related to hypomotility of the small intestine. They found a definite improvement in glucose tolerance curves where a peristaltic stimulant had been administered intraduodenally with the glucose load. The authors concluded that the efficiency of absorption depends upon intimate contact of the mucosa with the intestinal contents and that this may be accomplished by the constant segmenting activity of the intestine. Therefore, they suggest that either a decrease or increase in peristaltic activity would likely result in a reduction in nutrient absorption.

Subsequent studies have since confirmed that altered intestinal motility, whether drug- or disease-induced, plays a direct role in the malabsorption of certain nutrients (96-98, 102,105-107). Where hypomotility has been induced by administration of a peristaltic inhibitor (96-102) absorption of vitamin A (96), ^{24}sodium and water (97-98), and fat (in man) (102) have been found to be impaired. However, in other studies, absorption appeared to be at least unaffected (99,101) or even improved (100). The conflicting results are probably due to the experimental procedure used to study absorption. Where absorption seemed to be unaffected (99,101) or enhanced (100), a slow intraduodenal infusion procedure of the test substance had been used. Therefore, although the segmenting activity of the duodenum was reduced, the quantity of perfusate available to the mucosal surface per unit of time was sufficiently small to allow absorption to proceed normally.

Conversely, where nutrient absorption was impaired (96-98,102), the test solution had been injected directly into the duodenum and like the clinical state of hypomotility (celiac disease), the load to the mucosal surface exceeded its peristaltic capacity. It appears then that absorption is in fact reduced where intestinal motility is decreased.

The reports concerning the effect of hypermotility on nutrient absorption have also been conflicting (102-108). Reduced absorption of glucose (104), fat (102,105), and water, sodium and chloride (106-107), have been cited in drug- or hormone-induced intestinal hypermotility in man and animals. Similar studies have obtained contradictory results to those mentioned above (99,103,108). This may be due to differences in the intestinal segment chosen for study. An apparent increase in nutrient absorption may reflect the absorptive activity of that particular segment of the intestine. In fact, the total amount of material absorbed per unit of time, rather than per unit of length, may have actually been decreased.

Clinical investigations of absorption in a "natural" hypermotile state, such as in thyrotoxicosis and congenital sucrose-isomaltose malabsorption syndrome, indicate that absorption of nutrients is reduced. Steatorrhea is common in hyperthyroidism (104). Launiala (37-38) has reported a decrease in palmitate, xylose and arginine absorption in a child with congenital sucrose-isomaltose malabsorption. The accumulation of lactose in the intestinal lumen of lactose

intolerant individuals may be considered analogous to the sucrose-isomaltose malabsorption seen in CSIM. It follows then, that the lactose-induced hypermotile state in lactose intolerance might be interfering with absorption of dietary nutrients in addition to lactose. Paige and Graham (32) recently conducted a balance study using four intolerant and two tolerant subjects between 22 months and 6 years of age. They noted that the lactose intolerant children receiving a lactose-casein diet did not retain nutrients as well as they did on a sucrose-casein diet. Their findings include:

a) a decrease in apparent nitrogen absorption from 93% to 83% of intake
b) a reduction in nitrogen retention from 15% to 5% of intake
c) a decrease in fat absorption as indicated by an elevation in stool fat from 3 g/day to 5 g/day
d) an increase in stool weight from a mean of 38 g/day to 147 g/day.

Nutrient absorption did not appear to be affected by either diet for the tolerant subjects. According to these results, it appears that lactose intolerant subjects may be sustaining fecal losses of nutrients in addition to lactose itself. Calloway and Chenoweth (33) have also examined this possibility. Four intolerant and two tolerant subjects were confined to a metabolic ward for 48 days during which each subject received each of 4 diets for twelve day periods. The diets consisted of:

a) 1000 g of homogenized low-fat milk divided into four meals per day, supplying a total of 50 g lactose

b) 1000 g of modified low-fat milk enzymatically processed so as to reduce lactose content by approximately 50%

c) 1000 g simulated low-fat milk with glucose and galactose instead of lactose

d) wheaten foods only because they affect nutrient absorption regardless of intestinal lactase levels.

Calloway and Chenoweth (33) found that two of the intolerant subjects had increased hydrogen levels in the breath as well as higher fecal losses of moisture, dry solids and energy, that were lactose dose dependent. These results concur with those of Paige and Graham (32) that lactose feeding may lead to nutritionally significant fecal losses of nutrients in subjects with low lactase levels.

It should be noted that all these studies have purposefully eliminated the effect of gastric emptying time in order to examine the effect of intestinal motility alone on nutrient absorption. Under normal conditions, gastric emptying time in addition to the peristaltic activity of the small intestine determine the rate of intestinal absorption (109-113).

2. The Effect of Gastric Emptying on Nutrient Absorption

The volume of gastric contents transferred to the duodenum is generally under the inhibitory influence of neural and hormonal factors originating in the duodenum (92,109,111). In decreasing order of potency: fatty acids, fats, proteoses, peptones, amino acids, sugars, other starch digestion products, and low pH present in the duodenum will stimulate the intra-

muscular plexi to transmit the enterogastric reflex to the stomach and consequently inhibit gastric evacuation. For example, the greater the concentration of solutes in the small intestine, the stronger will be the excitation of the receptors and the smaller the volume of material pumped from the stomach into the duodenum. The presence of fat in the small intestine will also delay gastric emptying via a hormone (enterogastrone) synthesized in the intestinal wall. Gastric distension alone will accelerate the rate of gastric emptying. It is not surprising therefore, that large deviations in the rate of this transfer would influence nutrient absorption especially where the absorptive capacity of the mucosa of the small intestine is impaired in some way.

Studies have shown that a decrease in the rate of transfer of gastric contents in healthy animals results in a reduced rate of nutrient absorption (114-116). An increase in the volume of gastric contents pumped per minute into the duodenum results in decreased nutrient absorption only where the absorptive capacity of the small intestine is impaired (117). For example where lactase levels are low, an acceleration in the rate of gastric emptying will lead to a reduction in absorption of nutrients (118-120). In other words, the lactose load presented to the intestine will exceed the capacity of the intestinal lactase levels to cleave the lactose molecule and its absorption will be impaired. Consequently, a delay in gastric emptying time in these individuals is beneficial to the absorption process. In their study of calcium absorption in

lactose intolerant individuals, Kocian et al. (121) note:

> The slower supply of chyme protects the small intestine against lactose overloading although the lactase activity of the intestinal epithelium is relatively low and thus renders a better utilization of calcium possible. The slower supply of calcium reduces the amount offered per unit of time and thus also increases the percentage of absorbed calcium.

Therefore, if absorption is improved through a delay in gastric emptying time, the abdominal distress symptoms associated with lactose intolerance may be modified too, to some extent. The relationship of dietary modification of gastric emptying time and the appearance of clinical symptoms of lactose intolerance is discussed in the proceeding section.

3. The Effect of Diet Composition on Symptoms of Lactose Intolerance and Nutrient Absorption

The symptomatic response of a lactose intolerant individual depends on the composition of the meal in which the lactose is given. A number of workers (122-127) have shown that the fat and/or protein content of a meal or even the milk itself, may reduce the abdominal discomfort of an intolerant individual. Bayless and Paige (123) note that milk consumed alone seems to induce greater abdominal discomfort than if taken with a meal. They suggest that the different components of a meal may delay gastric emptying time. In this way the low level of intestinal lactase is not "overloaded" with lactose and fluid and electrolyte balance is not disturbed. Normal peristalsis can be maintained, thus avoiding or at least reducing the symptomatic response that would otherwise be seen in lactose intolerance.

Other investigators have shown (124-126) that the composition of the milk itself may be sufficient to modify symptoms of lactose intolerance also through a delay in gastric emptying time. In one study (125), symptomatic responses of 8 intolerant subjects were compared after receiving 500 ml skim milk and after receiving an equivalent amount of whole milk. Less discomfort was experienced after the whole milk was consumed. Therefore, the fat and protein levels of a meal or milk may alleviate the symptoms of lactose intolerance by delaying gastric emptying time and reducing intestinal motility (124). Whether or not nutrient absorption remains impaired is less evident.

Kocian et al. (121) suggest that where low lactase levels are present, a delay in gastric emptying time after a lactose load may be important for absorption to occur properly. However, Leichter (125) showed that although the symptomatic response was less intense, the rise in blood glucose did not improve in lactose intolerant individuals who received whole milk as compared to skim or an aqueous lactose solution. It should be noted though, that the whole milk may have effectively delayed gastric emptying so as to reduce the rate of lactose absorption, and eventually increase the absolute quantity of lactose absorbed. This might have been evident had absorption been followed for a longer period than the time of the lactose tolerance test which lasted only one hour.

Paige et al. (127) found that feeding lower levels of lactose to intolerant subjects was also effective in

reducing their symptomatic response, however, lactose tolerance curves still did not improve. Bedine and Bayless (128) demonstrated that in lactose intolerant subjects who were asymptomatic, as little as 3 and 6 g of lactose in 200 ml of electrolyte solution (21.7 mEq sodium/l, 37.1 mEq potassium/l) resulted in net fluid and sodium accumulation in the small intestine.

From these studies, it appears that the fat and protein levels of a meal or milk (123-126), or the lactose content itself (127-130), may be altered so as to alleviate the symptoms of lactose intolerance. However, it is still not clear whether or not nutrient absorption is concurrently improved. On the other hand, studies of the effect of altered intestinal motility on nutrient absorption (Section II.B.1) suggest that the symptomatic response induced when lactose is consumed alone may interfere with absorption of nutrients in addition to lactose. The present work is concerned with investigation of this latter possibility; that the lactose-induced state of hypermotility in a lactose intolerant individual may not afford sufficient time for absorption of dietary nutrients. Consequently, an individual with low lactase levels may not be deriving full nutritional benefits when consuming only milk or other lactose-containing products.

III. MATERIALS AND METHODS

A. Human Studies

In order to study the effect of lactose on the absorption of vitamin A, ascorbic acid and protein, twenty-three residents of Vancouver, British Columbia were used. All were Caucasians; nine females between 21 and 31 years of age, mean = 25 years, fourteen males between 22 and 33 years, mean = 28 years. Each subject was questioned about his general physical condition and on this basis was considered to be healthy. None reported a family history of diabetes.

Following an overnight fast, each subject received a lactose tolerance test. Venous blood samples were drawn while the subjects were fasting and at 15, 30 and 60 minute intervals after oral ingestion of 50 g lactose[1] dissolved in 300 ml water. Development of any symptoms such as flatulence, bloating, gas, cramps or diarrhea were recorded. A maximum rise in blood glucose of less than 20 mg/100 ml and gastro-intestinal symptoms were considered indicative of lactose intolerance. On this basis, eight of the subjects were lactose intolerant, and the remaining fifteen were tolerant.

The nutrients chosen for study were based on the following considerations:

a) the drink or meal should be acceptable to the subjects

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1) α-lactose, Fisher Scientific, N.J.

b) peak absorption of the nutrient should occur within a four hour period

c) absorption of the nutrient should not be affected by the other nutrients present in the test solution

d) absorption of the nutrient should vary proportionally with the quantity ingested.

It was decided that vitamins A and C seemed to meet the above considerations. Gelatin was also given in order to measure changes in blood urea levels as an indicator of protein absorption (131). The levels of vitamins A and C and protein ingested and the time intervals at which blood samples were drawn were based on studies reported in the literature (132). The tolerant and intolerant subjects served as their own controls. Sucrose replaced the lactose in the control studies.

1. Experimental Procedures

a. The Effect of Lactose on the Absorption of Protein and Vitamin A

In order to study the effect of lactose on protein and vitamin A absorption, a preliminary study using 5 tolerant and 8 intolerant subjects was carried out. After an overnight fast, venous blood samples were drawn, while the subjects were still fasting and at 60, 120, 180 and 240 minute intervals after ingestion of a test drink. The drink consisted of 50 g lactose and 55 g gelatin[1] dissolved in 400 ml water. At the same time each subject ingested 25,000 IU vitamin A[2] in capsule form.

1) Knox unflavored gelatin, Knox Foods, Trenton, Ontario.
2) 25,000 IU vitamin A/capsule, Stanley Drug Products Ltd., Vancouver, B.C.

The following week, the procedure was repeated with the same subjects except that 50 g sucrose replaced the lactose in the test drink. The volunteers were instructed to consume the fluid as quickly as possible because the gelatin had a tendency to congeal.

b. The Effect of Lactose on the Absorption of Vitamins A and C

Another preliminary experiment involving 9 subjects, 3 intolerant and 6 tolerant, was conducted to follow the effect of lactose (without gelatin) on the absorption on vitamins A and C. The procedure was similar to the first experiment except that each subject ingested 50 g lactose dissolved in 400 ml water with 500 mg vitamin C[1] in tablet form and 25,000 IU vitamin A in capsule form. Blood samples were drawn while the subjects were fasting and at 60, 120, 180 and 240 minute intervals after ingestion of the test drink. This was repeated the following week with sucrose instead of lactose.

c. The Effect of Lactose on the Absorption of Vitamins A and C

Since vitamin A is fat soluble, it was decided to give our subjects the vitamin with a test meal, rather than a drink, to study the effect of lactose on its absorption. The meal, adopted from Barrowman et al. (133) contained 45 g lactose,

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1) 500 mg vitamin C/ tablet, Stanley Drug Products, Vancouver, B.C.

15 g casilan[1] and 25 ml olive oil as well as 200,000 IU vitamin A[2] in capsule form. Each subject also received 1 g vitamin C because the previous dose of 500 mg was thought to be too low to show measurable differences in blood vitamin C levels. Venous blood samples were drawn after an overnight fast and at 90, 180 and 240 minute intervals after ingestion of the meal. At a later date these same subjects received a similar meal except sucrose replaced the lactose.

2. Methods

a. Plasma Glucose Determination

Blood samples were drawn and transferred to test tubes containing potassium oxalate, centrifuged at 2000 RPM for 20 minutes and plasma was removed and frozen. The glucose was determined within a few days by the glucose oxidase method (134).

b. Plasma Urea Nitrogen Determination

Blood samples were drawn and transferred to heparinized test tubes and treated as above. Plasma urea nitrogen levels were determined according to Hyland test kit No. 030-010 (135).

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1) Casilan, Glaxo-Allenburys, Toronto, Ontario.
2) 50,000 IU vitamin A/capsule (Afaxin), Winthrop Lab., Div. of Sterling Drugs Ltd., Aurora, Ontario.

c. Plasma Vitamin A Determination[1]

Vitamin A was measured by the Carr Price (136) method with slight modifications. Instead of 2 ml plasma and 2 ml 96% ethyl alcohol, 1 ml of each was used for the analysis. After evaporation under nitrogen 0.2 ml chloroform was added instead of 0.1 ml to each cuvette and 2 ml of chromogen reagent was used in place of 1 ml. Optical density readings were taken in a Coleman Junior Spectrophotometer, Model 6C at a wavelength of 620 mμ.

d. Plasma Vitamin C Determination

Plasma was analysed for ascorbic acid using the dinitrophenylhydrazine method adapted from Roe and Kuether (137). One ml of plasma was added to 9 ml of 5% trichloroacetic acid, instead of 2 ml plasma and 8 ml trichloroacetic acid. Blood samples drawn were frozen immediately after centrifugation and analysis was carried out within 24 hours so as to avoid destruction of vitamin C. Optical density readings for plasma glucose, urea nitrogen and ascorbic acid were taken in a Coleman Hitachi Spectrophotometer, Model 101 at wavelengths of 450 mμ, 630 mμ, and 515 mμ, respectively.

3. Statistical Analysis

The paired t test was performed in order to evaluate the results obtained when the different sugars were consumed

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1) Vitamin A Standard was run using USP Vitamin A Reference Solution distributed by The United States Pharmacopeial Convention.

by the same group of subjects. The generalized t test was used to assess the responses of the controls and the intolerant subjects after consuming the same sugar. Statistical significance was assumed at or below the 5% level.

B. Animal Studies

1. Experimental Procedures

a. The Effect of Lactose on the Excretion of Fat, Nitrogen and Calcium

To investigate the effect of 10%, 20%, and 30% lactose diets on the absorption of protein, fat and calcium, three balance studies were carried out on postweaning rats (initial weight = 164 g) for ten day periods. The procedure for each balance study was similar: twelve male Sprague-Dawley rats[1] were housed singly in metabolic cages. Six served as controls and received the diet containing an amount of sucrose equivalent to the level of lactose in the diet fed to the six experimental animals. The composition of the experimental diet in each balance study in shown in Table I. Food and water were fed ad lib. Weight gain and food consumption were recorded. Daily urine and feces collection started after the rats had been on the diets for 48 hours.

For each animal, urine was collected in a 125 ml Erlenmeyer flask containing 0.5 ml 6N HCl and transferred daily to a larger bottle for storage in a freezer. After 10 days, the pooled volume of urine collected was measured and

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1) Obtained from Bio Breeding Laboratories, Ottawa, Canada.

Table I. Composition of Diets.			
	10% Lactose	20% Lactose	30% Lactose
CORNSTARCH, %	53	43	33
VITAMIN FREE CASEIN, %	20	20	20
SALT MIXTURE, %[1]	5	5	5
VITAMIN MIXTURE, %[2]	2	2	2
CORN OIL, %	10	10	10

1) Rogers-Harper Salt Mix, purchased from General Biochemicals, Chagrin Falls, Ohio. The salt mixture contained: $CaCO_3$, 29.29%; $CaHPO_4.2H_2O$, 0.43%; KH_2PO_4, 34.31%; NaCl, 25.06%; $MgSO_4.7H_2O$, 9.98%; $Fe(C_6H_5O_7).6H_2O$, 0.623%; $CuSO_4$, 0.156%; $MnSO_4.H_2O$, 0.121%; $ZnCl_2$, 0.020%; KI, 0.0005%; $(NH_4)_6MO_7O_{24}.4H_2O$, 0.0025%; $Na_2SeO_3.5H_2O$, 0.0015%.

2) Vitamin Diet Fortification Mix., purchased from Nutritional Biochemicals Corp., Cleveland, Ohio. The vitamin mixture contained in g/kg: vitamin A concentrate, 4.5 (200,000 units/g); vitamin D concentrate, 0.25 (400,000 units/g); alpha tocopherol, 5.0; ascorbic acid, 45.0; inositol, 5.0; choline chloride, 75.0; menadione, 2.25; p-aminobenzoic acid, 5.0; niacin, 4.5; riboflavin, 1.0; pyridoxine hydrochloride, 1,0; thiamine hydrochloride, 1.0; calcium pantothenate, 3.0; and in mg/kg: biotin, 20; folic acid, 90; vitamin B_{12}, 1.35.

made up to volume. To obtain a uniform sample, the bottle containing the urine was well shaken prior to analysis. Aliquots were taken directly for nitrogen determination. For calcium determination urine samples were filtered through filter paper Whatman No. 41.

Feces were collected daily and stored in a freezer. After 10 days, the pooled feces for each rat were weighed and then dried to a constant weight at 60°C in a vacuum oven, so that moisture content could be determined. The dried feces were then ground to a powder and aliquots were taken directly for nitrogen and fat determination. In order to determine calcium content, the dried feces were ashed overnight in a muffle furnace at 600°C. The ash was dissolved in concentrated HCl, diluted to make a known volume, then filtered (as urine samples) and aliquots were used for calcium determination by atomic absorption spectrophotometry.

b. The Effect of Lactose on the Absorption of Vitamin A

Postweaning rats were used to study the effect of lactose on the absorption of vitamin A. In this study, 72 male Sprague-Dawley rats (average weight = 263 g) were randomly divided into two groups. Each group was then subdivided into nine lots of four animals each. After an overnight fast, the experimental group received 500 mg lactose and 2500 IU vitamin A[1]

1) Trans Retinol Palmitate Type VII water dispersable, Sigma Chemical Co., St. Louis, Mo.

in 2 ml water by stomach tube while the control group was given sucrose instead of lactose. Four rats from each group were sacrificed and blood was drawn by heart puncture at the following time intervals: prior to receiving the test solution and at 1, 2, 2½, 3, 3½, 4, 4½, and 5 hours after administration of the test solution.

2. Methods

a. Nitrogen Determination

Urinary and fecal nitrogen were determined by the Kjeldahl method (138).

b. Calcium Determination

Urinary (139) and fecal calcium (140) were determined by atomic absorption spectrophotometry.[1]

c. Determination of Fat Content

Fat content of feces was measured using the Goldfisch fat extraction apparatus (141).

d. Plasma Vitamin A Determination

As in Human Studies (III.A.2).

3. Statistical Analysis

The generalized t test was used to assess the significance of mean values obtained for each experimental

1) Unicam Atomic Absorption Spectrophotometer, Model SP90.

group as compared to their controls for each parameter studied. Analysis of variance was also performed to test the significance of the differences between the type as well as the level of carbohydrate in each balance study and the possible interaction of both. Statistical significance was assumed at or below the 5% level.

IV. RESULTS

A. Human Studies

1. The Effect of Lactose on the Absorption of Protein

The mean maximum rise in plasma urea above the fasting plasma urea level after ingestion of 55 g gelatin by the lactose tolerant and intolerant subjects is shown in Table II. (The individual values for each subject are in Table I, Appendix.) There are no statistically significant differences in the maximum rise in plasma urea in either the tolerant or intolerant group whether lactose or sucrose was consumed. The plasma urea values obtained when the same sugar was consumed by either group of subjects also did not differ significantly. In addition, the mean plasma urea levels at each time interval were similar for the intolerant subjects and the controls (Fig. 1, Appendix). Consequently, peak plasma urea levels occurred at the same interval (240') for both groups. Symptoms of bloating, gas, cramps or diarrhea were not evident in any of the subjects.

2. The Effect of Lactose on the Absorption of Ascorbic Acid

The results for the mean maximum rise in plasma ascorbic acid levels in those subjects who received 500 mg of ascorbic acid are shown in Table III. (The individual values are shown in Table II, Appendix.) There were no significant differences in the mean rise in plasma ascorbic acid between the lactose intolerant and tolerant subjects whether vitamin C

Table II. Mean Maximum Rise ± S. D. in Plasma Urea in Lactose Tolerant and Intolerant Subjects Given 55 g Gelatin and 25,000 IU Vitamin A with Either 50 g Lactose or 50 g Sucrose.

	PLASMA UREA (mg urea/100 ml)		
	Lactose	Sucrose	P
Tolerant (7)	11.7 ± 5.57	10.3 ± 2.78	> 0.05
Intolerant (5)	9.8 ± 3.16	10.5 ± 5.03	> 0.05
P	> 0.05	> 0.05	

Table III. Mean Maximum Rise ± S. D. in Plasma Ascorbic Acid in Lactose Tolerant and Intolerant Subjects Given 500 mg Vitamin C and 25,000 IU Vitamin A with Either 50 g Lactose or 50 g Sucrose.

	PLASMA ASCORBIC ACID (mg vitamin C/100 ml)		
	Lactose	Sucrose	P
Tolerant (6)	0.97 ± 0.31	1.02 ± 0.28	> 0.05
Intolerant (3)	0.93 ± 0.21	0.90 ± 0.40	> 0.05
P	> 0.05	> 0.05	

was administered with sucrose or lactose. In the tolerant subjects, the peak in absorption of vitamin C for 5 out of 6 subjects occurred at the 180 minute interval when the vitamin was consumed with lactose and at the 120 minute interval when consumed with sucrose (Fig. 2, Appendix). This difference is not considered statistically significant. The values for the maximum rise in plasma vitamin C with sucrose or lactose are similar in the intolerant subjects. In addition, the ingestion of lactose or sucrose seemed to have no effect on the mean maximum rise in plasma ascorbic acid when the subjects served as their own controls. Symptoms of gas and bloating, cramps and diarrhea were reported in some of the intolerant subjects.

The results in Table IV show the maximum rise in plasma ascorbic acid levels in 4 intolerant subjects who received 1 g vitamin C with a test meal. (The individual values are shown in Table III, Appendix.) The mean rise in plasma ascorbic acid after the lactose meal, 1.05 mg vitamin C/100 ml plasma, does not differ significantly from that obtained when these subjects consumed the sucrose meal, 1.03 mg vitamin C/100 ml plasma. Absorption rates also remain unaffected (Fig. 3, Appendix). Because of the small sample size, one must always be careful in drawing conclusions from such data. In addition, the symptomatic response of our subjects in this experiment was reduced probably due to consumption of the lactose in the form of a meal rather than a drink.

Table IV. Mean Maximum Rise ± S. D. in Plasma Ascorbic Acid in Lactose Intolerant Subjects Given 200,000 IU Vitamin A and 1 g Vitamin C with a Test Meal Containing 15 g Casilan, 25 ml Olive Oil and Either 45 g Lactose or 45 g Sucrose.

PLASMA ASCORBIC ACID (mg vitamin C/100 ml)			
	Lactose	Sucrose	P
Intolerant (4)	1.05 ± 0.048	1.03 ± 0.232	> 0.05

Table V. Mean Maximum Rise ± S. D. in Plasma Vitamin A in Lactose Intolerant Subjects Given 200,000 IU Vitamin A and 1 g Vitamin C with a Test Meal Containing 15 g Casilan, 25 ml Olive Oil, and Either 45 g Lactose or 45 g Sucrose.

PLASMA VITAMIN A (mg vitamin A/100 ml)			
	Lactose	Sucrose	P
Intolerant (4)	0.012 ± 0.0085	0.031 ± 0.0239	> 0.05

3. The Effect of Lactose on the Absorption of Vitamin A

The mean rise in plasma vitamin A levels when four lactose intolerant subjects consumed a meal with 200,000 IU vitamin A are shown in Table V. (Values for each subject are shown in Table IV, Appendix.) The mean maximum rise in plasma vitamin A was slightly lower after the lactose meal as compared to the value obtained after the sucrose meal. The difference however, between these two values is not statistically significant at the 5% level. In addition, the peak absorption for vitamin A was reached after the same time interval whether or not lactose or sucrose was consumed with the vitamin.

B. Animal Studies

1. The Effect of Lactose on the Excretion of Fat, Nitrogen and Calcium

a. Body Weight Gain and Food Consumption

The mean cumulative weight gain and food consumption of each group of rats on the various diets are shown in Tables VI and VII. Weight gain was significantly lower ($p < 0.05$) in the experimental animals fed the 20% and 30% lactose diets as compared to their corresponding controls. Food consumption was also lower for these same animals, although the difference between the controls and experimental animals is statistically significant ($p < 0.05$) only on the 30% disaccharide diets. This would suggest that feed efficiency is reduced at the higher levels of dietary lactose.

Table VI. Mean Weight Gain ± S. D. of Experimental and Control Animals Over a Ten Day Period. (N = 6)		
DIET	WEIGHT GAIN (g/10 days)	P
10% Lactose	87.3 ± 4.63	> 0.05
10% Sucrose	86.2 ± 8.02	
20% Lactose	73.8 ± 5.93	< 0.05
20% Sucrose	83.8 ± 8.90	
30% Lactose	53.1 ± 18.83	< 0.05
30% Sucrose	74.4 + 6.71	

Table VII. Average Food Consumption ± S. D. of Experimental and Control Animals Over a Ten Day Period. (N = 6)		
DIET	FOOD CONSUMPTION (g/10 days)	P
10% Lactose	174.0 ± 6.75	> 0.05
20% Sucrose	178.7 ± 16.77	
20% Lactose	177.9 ± 5.75	> 0.05
20% Sucrose	191.9 ± 15.95	
30% Lactose	142.0 ± 26.57	< 0.05
30% Sucrose	173.7 ± 14.42	

Loose stools were apparent in the 30% lactose group, indicating that diarrhea was induced by the high level of lactose intake. These rats, too, as a group, appeared to be slightly more irritable than those in any of the other groups. However, there were usually one or two animals in the other dietary groups whose behavior was slightly erratic. Spillage of food into excreta often occurred in such cases and accounts for the large standard deviations in the results. It was also observed that the urine volume was consistently greater as dietary lactose levels increased, while the reverse was true as sucrose levels increased. At the 30% level of disaccharide intake, the difference in urine volume between the controls (mean = 135.0$\pm$ 14.14 mls/10 days) and the experimental group (mean = 255.8 $\pm$ 79.08 mls/10 days) is statistically significant at the 5% level. The reason for this finding is not clear.

b. The Effect of Lactose on Fecal Fat Excretion

The values for fecal fat excretion as per cent of fat intake in the control and experimental animals are shown in Table VIII. Significant differences ($p < 0.05$) in fecal excretion of fat are associated with both the type of carbohydrate and level of carbohydrate in the diets. In other words, fat excretion was greater for the experimental animals relative to their controls; also fat excretion was least for both groups on the 10% disaccharide diets, as compared to the animals on the 20% and 30% disaccharide diets. In addition there is no interaction between the type of disaccharides and

Table VIII. Effect of Different Levels of Dietary Lactose on Fecal Excretion of Fat.

(N = 6)

DIET	Mean Fecal Fat Excretion as % Fat Intake ± S.D.
10% Lactose	3.75 ± 0.94
10% Sucrose	2.30 ± 0.14
20% Lactose	6.54 ± 2.36
20% Sucrose	3.42 ± 1.03
30% Lactose	4.43 ± 0.72
30% Sucrose	3.51 ± 0.55

Source of Variation	F*	P**
1. Type of carbohydrate	21.5393	0.00006
2. Level of carbohydrate	8.2274	0.00142
3. Interaction of 2 and 3	2.8247	0.07526

* F = ratio of mean squares of treatment to mean squares of error

** P = probability that effect of treatments is due to chance

their level in the diet; so that the presence of lactose alone would be sufficient to affect fecal excretion of fat.

c. The Effect of Lactose on Fecal and Urinary Nitrogen Excretion

The values for fecal nitrogen excretion as per cent of nitrogen intake are presented in Table IX. Excretion of nitrogen in feces is significantly ($p < 0.05$) affected by the type and level of dietary carbohydrate although there is no interaction between the two. Those animals fed the lactose diets showed a greater excretion of fecal nitrogen relative to the sucrose-fed rats; as dietary lactose levels increased, fecal excretion of nitrogen was greater.

As seen in Table X, urinary nitrogen excretion as per cent of nitrogen intake is significantly ($p < 0.05$) affected only by the level of carbohydrate in the diet. Therefore, either lactose or sucrose may increase nitrogen excretion in urine, and this effect is more apparent as levels of these disaccharides in the diet are increased.

d. The Effect of Lactose on Fecal and Urinary Calcium Excretion

The results for fecal calcium excretion as per cent of calcium intake are shown in Table XI. Fecal calcium excretion for each lactose group is significantly lower ($p<0.05$) not only from its corresponding sucrose group but also from each sucrose group in the two other balance studies.

Table IX. Effect of Different Levels of Dietary Lactose on Fecal Excretion of Nitrogen.

(N = 6)

DIET	Mean Fecal N Excretion as % N Intake ± S. D.
10% Lactose	5.02 ± 0.91
10% Sucrose	3.71 ± 0.55
20% Lactose	5.23 ± 0.32
20% Sucrose	3.68 ± 0.19
30% Lactose	6.11 ± 0.92
30% Sucrose	4.22 ± 0.48

Source of Variation	F*	P**
1. Type of carbohydrate	57.4257	0.00000
2. Level of carbohydrate	5.9170	0.00683
3. Interaction of 2 and 3	0.6343	0.53795

* F = ratio of mean squares of treatment to mean squares of error

** P = probability that effect of treatments is due to chance

Table X. Effect of Different Levels of Dietary Lactose on Urinary Excretion of Nitrogen.
(N = 6)

DIET	Mean Urinary N Excretion as % N Intake ± S.D.
10% Lactose	36.97 ± 2.51
10% Sucrose	38.95 ± 3.65
20% Lactose	42.67 ± 5.55
20% Sucrose	43.96 ± 4.54
30% Lactose	36.88 ± 6.97
30% Sucrose	42.06 ± 4.18

Source of Variation	F*	P**
1. Type of carbohydrate	3.1281	0.08725
2. Level of carbohydrate	4.0019	0.02884
3. Interaction of 2 and 3	0.5651	0.57496

* F = ratio of mean squares of treatment to mean squares of error

** P = probability that effect of treatments is due to chance

Table XI. Effect of Different Levels of Dietary Lactose on Fecal Excretion of Calcium.

(N = 6)

DIET	Mean Fecal Calcium Excretion as % intake ± S.D.
10% Lactose	45.12 ± 13.15
10% Sucrose	51.42 ± 4.10
20% Lactose	38.14 ± 7.00
20% Lactose	44.05 ± 3.50
30% Lactose	28.20 ± 6.10
30% Sucrose	56.07 ± 7.03

Source of Variation	F*	P**
1. Type of carbohydrate	28.5810	0.00001
2. Level of carbohydrate	3.2055	0.05481
3. Interaction of 2 and 3	8.4349	0.00124

* F = ratio of mean squares of treatment to mean squares of error

** P = probability that effect of treatments is due to chance

According to the results in Table XII, urinary calcium excretion is significantly affected by the type and level of carbohydrate in the diet, as well as the interaction of both. At the 10% level of dietary lactose, calcium excretion in urine is lower than at the 20% and 30% dietary lactose levels. On the 20% and 30% lactose diets, urinary calcium excretion is not only higher relative to their corresponding controls, but also as compared to the controls in the two other balance studies. This might be due to the finding that fecal calcium excretion is lower (Table XI) when lactose is present in the diet. This indicates an increase in calcium uptake, which might account for higher levels of calcium in urine.

2. The Effect of Lactose on the Absorption of Vitamin A

The mean plasma vitamin A levels reached after intragastric administration of 2500 IU of retinol palmitate with either 500 mg lactose or sucrose to postweaning rats are shown in Table XIII. Peak absorption occurred for both groups at the two hour time interval. Although this value is higher in the lactose group, the difference is not statistically significant ($p > 0.05$). The maximum mean plasma vitamin A rise (difference between the mean fasting plasma vitamin A value and the maximum mean plasma vitamin A rise) in the experimental group (0.1936 mg vitamin A/total blood volume) is slightly higher as well relative to the controls (0.1476 mg vitamin A/ total blood volume). The values between the corresponding

Table XII. Effect of Different Levels of Dietary Lactose on Urinary Excretion of Calcium.

(N = 6)

DIET	Mean Urinary Calcium Excretion as % Ca Intake ± S. D.
10% Lactose	1.28 ± 0.27
10% Sucrose	1.38 ± 0.71
20 % Lactose	1.64 ± 0.59
20% Sucrose	0.62 ± 0.23
30% Lactose	2.87 ± 0.48
30% Sucrose	1.34 ± 0.84

Source of Variation	F*	P**
1. Type of carbohydrate	20.5826	0.00009
2. Level of carbohydrate	17.5576	0.00001
3. Interaction of 2 and 3	10.0167	0.00047

* F = ratio of mean squares of treatment to mean squares of error

** P = probability that effect of treatments is due to chance

Table XIII. Mean Plasma Vitamin A Levels in Postweaning Rats After Intragastric Administration of 2500 IU of Vitamin A with Either 500 mg Lactose or 500 mg Sucrose (4 animals per subgroup).

Time Interval (hrs)	mg vitamin A/total blood volume* Lactose ± S.D.	Sucrose ±S.D.	P
Fasting	0.0702 ± 0.023	0.0669 ± 0.070	> .05
1.0	0.1725 ± 0.073	0.2082 ± 0.090	> .05
2.0	0.2638 ± 0.124	0.2145 ± 0.180	> .05
2.5	0.2435 ± 0.064	0.1686 ± 0.040	> .05
3.0	0.1249 ± 0.027	0.1822 ± 0.097	> .05
3.5	0.0932 ± 0.020	0.1227 ± 0.057	> .05
4.0	0.1215 ± 0.018	0.1273 ± 0.015	> .05
4.5	0.1506 ± 0.046	0.1153 ± 0.058	> .05
5.0	0.1399 ± 0.016	0.0916 ± 0.016	< .05
Maximum Mean Rise in Plasma Vitamin A	0.1936	0.1476	

* Total blood volume = (mg vitamin A/ ml) x (4.3%** x body weight/rat)

** This figure represents the ratio of blood volume to body weight (4.3 ml/100 g) in the rat. (Rowett, H.G.Q. The rat as a small mammal. London. John Murray (Publishers) Ltd., 1960. p.40.)

points on the vitamin A absorption curve (Fig. 5, Appendix) differ significantly ($p < 0.05$) for controls and the experimental animals only at the 5 hour interval. In addition, the rats that received the sucrose solution appeared to be more easily excitable and showed signs of diarrhea which sets certain limitations in interpretation of these findings.

V. DISCUSSION

A. Human Studies

Results obtained in this study with human subjects do not indicate that lactose has any effect on the absorption of vitamin A, ascorbic acid or protein in lactose tolerant and intolerant subject. The findings with regard to protein do not agree with those of Paige and Graham (32), or Calloway and Chenoweth (33), who found that lactose intolerant subjects had higher fecal losses of moisture, dry solids and energy which were related to the level of dietary lactose. Because of differences in experimental procedure, it is difficult to compare their results with those of the present study.

Paige and Graham (32), as well as Calloway and Chenoweth (33), conducted balance studies of nutrients over an extended period of time. In the present study, changes in plasma urea levels only over a four hour period were used as a measure of protein absorption. Therefore the fact that lactose had no effect on plasma urea levels does not necessarily mean that there were no differences in the absolute absorption of the protein. The use of balance studies is more suitable for assessing the nutritional significance of the effect of lactose on protein absorption. Similar studies of the effect of lactose on the absorption of vitamin A and ascorbic acid have not been reported. Therefore, there is no basis for comparison.

As pointed out in the literature review (Section II. B.3.) the fat and protein components of a meal, or the milk itself, may alleviate the symptomatic response of a lactose intolerant individual, probably due to a delay in gastric emptying time and a dilution effect (122,123-127). In the present study, most of the intolerant subjects who consumed lactose in the test drink containing gelatin or in a test meal, reported little or no abdominal discomfort during the testing period. The presence of the protein in the test drink, or the fat and protein contained in the test meal, may have delayed gastric emptying and thus reduced the abdominal distress symptoms in these subjects, as compared to the symptomatic response of those intolerant individuals who received the aqueous lactose solution alone. In addition, as Kocian et al. (121) suggest, this delay in gastric emptying is important for nutrient absorption to occur in individuals with low lactase levels. This may also be the reason why the rate of absorption of vitamins A and C, and protein in the intolerant subjects did not differ significantly whether lactose or sucrose was consumed in the test drink containing protein or in the test meal.

However, when vitamin C was given with an an aqueous lactose solution (without gelatin and vitamin A), plasma vitamin C levels did not differ from those after the sucrose drink in lactose intolerant subjects. The explanation for this finding is not really clear. The test solution here did not contain any fat or protein components that may have caused a

delay in gastric emptying and thus alleviated the symptomatic response and possibly improved absorption of acorbic acid. Perhaps 500 mg was too small an amount to show measurable difference in blood levels of vitamin C which might have been manifest with larger amounts of ascorbic acid.

From these studies with human subjects, it would appear that protein, ascorbic acid and vitamin A absorption is not affected by lactose intolerance. One may conclude that under normal dietary conditions a lactose intolerant individual would probably not experience significant losses of nutrients when consuming milk or lactose-containing products.

B. Animal Studies

1. The Effect of Lactose on the Excretion of Nitrogen, Fat and Calcium

The balance studies indicate that postweaning rats on lactose-containing diets show greater excretion of nitrogen, and fat but not calcium, as compared to postweaning rats on sucrose diets. Furthermore, as dietary lactose levels increased, feces were of softer consistency and fecal losses of nitrogen and fat increased. Medler et al. (142) also noted that feeding an infant milk formula to weanling rats results in diarrhea and a decrease in net protein utilization from 88% to 67% as compared to feeding a formula that was treated with lactase. Our findings also agree with those of Paige and Graham (32) and Calloway and Chenoweth (33) who observed similar losses with respect to fecal nitrogen and fat excretion in lactose intolerant individuals. The effect of lactose on calcium excretion was not investigated by these workers.

In the balance study by Paige and Graham (32), nitrogen excretion increased from 7% in lactose intolerant children who received sucrose-based diets to 17% when these same children received lactose diets. In the present balance study, fecal nitrogen excretion in the controls was 3.71%, 3.68% and 4.22% of nitrogen intake on the 10%, 20% and 30% disaccharide diets respectively, while in the experimental groups, mean fecal nitrogen excretion was 5.02%, 5.23% and 6.11% of nitrogen intake. Although these differences in nitrogen losses are statistically significant ($p < 0.05$), it is doubtful

that they are of practical significance. In terms of an average daily loss of nitrogen, a loss of 1 or 2% of the nitrogen intake would not be serious. The nutritional consequences of a 10% increase in fecal nitrogen excretion, as reported by Paige and Graham (32), would be significant in an intolerant individual whose dietary protein was marginal. In addition, Paige and Graham (32) fed their subjects a diet containing almost 60% lactose as compared to the highest dietary level of lactose of 30% in the present study. This may account for the more pronounced effect of lactose on fecal nitrogen excretion seen in their study.

Paige and Graham (32) also noted an increase in stool fat from 3 g to 5 g/day when lactose intolerant children were given lactose diets after receiving sucrose-based diets. The results from the present balance studies with rats indicate that fat excretion expressed as per cent of fat intake (Table VIII) was significantly greater in the experimental groups than in the controls. However, the figures reported in Table VIII represent a maximum difference in fecal fat excretion of only 3.12% (at the 20% level of lactose intake) between the controls and the experimental animals.

Finally, Paige and Graham (32) reported an increase in daily stool weight from 38g/day to 147g/day when the lactose intolerant children received a lactose diet as compared to a sucrose diet. It is likely that intense abdominal distress symptoms, such as diarrhea, were present in these children due to the

high level of dietary lactose. In the present balance study, stool weight increased by approximately 23% in the rats fed the lactose diets relative to the controls. As dietary lactose levels increased, looser stools and softer fecal consistency were evident. The rats fed the 20% lactose diet had softer feces than those fed the 10% lactose diet. Only the rats receiving the 30% lactose diet seemed to suffer from diarrhea.

With respect to calcium absorption, the results from the present balance study indicate that lactose reduced fecal losses of calcium in rats, particularly at the 30% level of lactose intake. These findings are in agreement with those of a number of workers (143-147) who have repeatedly found that lactose stimulates calcium uptake from the rat intestine. One of the hypotheses proposed to explain this phenomenon is that lactic acid produced by bacterial action on the lactose in the intestinal lumen lowers the pH, creating conditions more favourable to calcium uptake. Pansu and Chapuy (143) noted that in humans as well, calcium absorption was improved by lactose consumption in individuals with low lactase levels. They suggested that lactose will cause:

> a hyperosmolar intraluminal effect,
> water secretion into the lumen and
> inverse transfer across the membrane.

Conditions then, favoring lactose accumulation in the intestinal lumen would enhance calcium uptake. Such conditions existed in the present work due to feeding large levels of dietary lactose. As the level of dietary lactose increased, the intensity of the gastrointestinal disturbances increased.

There was also a concomitant improvement in calcium absorption. Therefore, the theories proposed above to explain the effect of lactose on calcium absorption seem to be supported by the results obtained in the present balance study.

However, according to these same criteria it is difficult to explain the results of Kocian et al. (121) that lactose seemed to improve the rate of calcium uptake in lactose tolerant subjects. In addition, these same investigators noted no difference in calcium uptake in lactose intolerant subjects who consumed milk and lactose free milk.

The finding of Kocian et al. (121) that lactose had no effect on calcium absorption in lactose intolerant subjects may be explained in the following way. Because the milk solutions contained fat and protein, gastric emptying time was probably delayed and in this way, intestinal lactase was not overloaded with lactose. Consequently, there was little change in gastrointestinal motility and calcium absorption was not improved. However, it may also be argued that calcium absorption was in fact increased after the milk was consumed because the probable delay in gastric emptying allowed sufficient time for calcium absorption to occur. If one accepts the latter explanation, it then becomes possible to account for the results obtained by Kocian et al. (121) with tolerant subjects. This suggests that lactose enhances calcium absorption in tolerant and intolerant individuals, however, the theories proposed to explain this phenomenon which are based on the accumulation of lactose, must be rejected.

If lactose enhances total calcium absorption, as the results from the present balance studies indicate, and this effect is proportional to the level of lactose in the diet, such an effect may have important nutritional implication where dietary calcium intake is low. However, the practical significance of the effect of lactose on fat and protein absorption is doubtful. It appears not only from the present study but also from the work of Paige and Graham (32) that the level of dietary lactose necessary to interfere with nutrient absorption would far exceed the limits of normal dietary consumption.

2. The Effect of Lactose on the Absorption of Vitamin A

The results from the vitamin A absorption study in rats indicate that lactose did not impair vitamin A absorption and even seemed to improve it. However, as compared to the lactose group, the rats that received the sucrose solution appeared to be more excitable, which may have contributed to the observation that they were also suffering from diarrhea. These gastrointestinal disturbances which were evident in the sucrose group may have nullified the effect of lactose on vitamin A absorption in the lactose group.

VI. RECOMMENDATIONS

In Canada, it is estimated that some 6.5 million people, or approximately 30% of the total Canadian population, are lactose intolerant[1]. If all these individuals are sustaining losses of important nutrients due to lactose consumption, as suggested by recent studies (32,33) then this might become an area of public health concern in Canada. The results of the present work suggest that under normal dietary conditions, absorption of nutrients may not be affected by lactose intolerance. However, future research is needed to determine the validity of this suggestion.

Attention should be focused on the dietary modification of the symptomatic response of a lactose intolerant individual, and what effect this modification has on absorption. It should be established whether or not alleviation of gastrointestinal symptoms by consuming lactose with a meal, is related to improved nutrient absorption in individuals with low lactase levels.

A larger number of subjects should be used to study the effect of lactose on the absorption of various nutrients in order to obtain significant results. In addition, conducting balance studies with humans, besides measuring blood levels of the various nutrients, would aid in the interpretation of the

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1) These figures are based on calculations derived from (1) 1971 Statistics Canada figures for the different ethnic populations in Canada and (2) the values for the incidence of lactose intolerance for these ethnic groups that have been reported in the literature.

findings. In other words, where the rate of absorption does not appear to be affected by lactose, changes in the absolute amount of nutrient absorption could be detected.

The nutritional implications that can be drawn from the balance studies with rats are not as striking as would be suggested by Paige and Graham (92) and Calloway and Chenoweth (33). Of course, one must exercise caution in extrapolating from animal studies to humans.

Finally, in any future studies, the level of lactose administered to subjects should be maintained within the limits of normal lactose consumption. This would avoid undue concern over apparent nutrient losses due to exaggerated levels of dietary lactose.

VII. SUMMARY

Adult lactose intolerance due to low lactase levels is often associated with varying degrees of abdominal distress ranging from bloating and distension to severe cramps and diarrhea. Recent studies have suggested that these gastrointestinal disturbances may interfere with normal absorption of nutrients in addition to lactose. In order to investigate this possibility, both human and animal studies were conducted.

Twenty-three Caucasians: nine females between 21 and 31 years of age, mean = 25 years and fourteen males between 22 and 33 years of age, mean = 28 years were used to study the effect of lactose on the absorption of vitamin A, ascorbic acid and protein. Lactose tolerance tests revealed that 8 of the subjects were lactose intolerant on the basis of a maximal blood glucose rise of less than 20 mg/ 100 ml over the fasting blood glucose level and the presence of gastrointestinal symptoms after a lactose tolerance test. In each study, blood samples were drawn after an overnight fast and at intervals up to 4 hours after consuming 50 g of lactose in an aqueous solution or test meal containing gelatin, vitamin C or vitamin A. Sucrose replaced lactose as a control.

The results of the human studies failed to demonstrate that lactose had an effect on the absorption of ascorbic acid, vitamin A or protein in lactose intolerant subjects. The mean maximum rise in plasma urea (9.8 mg/100 ml), plasma

ascorbic acid (0.93 mg/100 ml) and plasma vitamin A (0.012 mg/100 ml) after lactose ingestion did not differ significantly ($p > 0.05$) from the values obtained after consumption of sucrose (10.5 mg urea/100 ml, 0.90 mg ascorbic acid/100 ml, 0.031 mg vitamin A/100 ml). It may be that the composition of the test drink which contained fat and protein, may have affected the rate of absorption of those nutrients through a delay in gastric emptying time. However, the finding that absorption of vitamin C remained unaffected even when consumed with an aqueous solution of lactose (without gelatin), is attributed to the possibility that the level of ascorbic acid given was too low to show measurable differences in blood levels of that nutrient.

In order to study the effect of lactose on the absorption of calcium, fat and protein, balance studies were conducted using postweaning rats. The experimental groups received either 10%, 20% or 30% lactose diets, while an equivalent amount of sucrose replaced the lactose in the control diets.

In addition, postweaning rats were given vitamin A intragastrically with either lactose or sucrose to investigate the effect of lactose on vitamin A absorption.

From the balance studies with rats, the results indicate that fecal nitrogen and fat excretion was significantly ($p < 0.05$) higher in all the animals fed lactose as compared to the controls. Mean fecal fat excretion expressed as percent fat intake was 3.75%, 6.54% and 4.43% for those

animals that received the 10%, 20% and 30% lactose diets respectively, while the values for the corresponding controls were 2.30%, 3.42% and 3.51%. Similarly, mean fecal nitrogen excretion expressed as percent nitrogen intake was 5.02%, 5.23% and 6.11% for the lactose groups and 3.71%, 3.68% and 4.22% for the controls on 10%, 20% and 30% sucrose diets, respectively. However, fecal calcium excretion was found to be generally lower for each lactose group relative to the controls, but the difference was statistically significant ($p < 0.05$) only at the 30% level of lactose intake. The values for mean fecal calcium excretion as percent calcium intake were 45.12%, 38.14% and 28.20% for each group on the 10%, 20% and 30% lactose diet respectively, and 51.42%, 44.05% and 56.07% for the corresponding controls.

It appears that lactose impairs nitrogen and fat absorption, but enhances calcium absorption in postweaning rats. Improved calcium absorption may have important nutritional implications where dietary calcium intake is low. It appears though, that the level of dietary lactose would most likely have to exceed the limits of normal lactose consumption to have an effect on the absorption of nutrients.

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A P P E N D I X

Table I. Maximum rise in plasma urea in lactose tolerant and intolerant subjects given 55 g gelatin and 25,000 IU vitamin A with either 50 g lactose or 50 g sucrose.

	Subject No.	(mg urea / 100 ml) Lactose	Sucrose
Lactose Tolerant	1.	9.6	9.9
	2.	16.1	12.2
	3.	7.5	11.1
	4.	8.2	12.9
	5.	20.6	12.6
	6.	13.5	7.9
	7.	6.2	5.4
Mean ± S.D.		11.7 ± 5.57	10.3 ± 2.78
Lactose Intolerant	8.	9.4	8.4
	9.	6.5	6.4
	10.	7.5	5.8
	11.	11.0	16.4
	12.	14.5	15.3
Mean ± S.D.		9.8 ± 3.16	10.5 ± 5.03

Table II. Maximum rise in plasma ascorbic acid in lactose tolerant and intolerant subjects given 500 mg vitamin C and 25,000 IU vitamin A with either 50 g lactose or 50 g sucrose.

	Subject No.	(mg vitamin C / 100ml)	
		Lactose	Sucrose
Lactose Tolerant	1	0.75	0.93
	2	0.96	0.98
	3	1.32	0.82
	4	1.17	1.49
	5	1.14	1.18
	6	0.49	0.70
Mean ± S.D.		0.97 ± 0.31	1.02 ± 0.28
Lactose Intolerant	7	1.00	1.29
	8	0.69	0.49
	9	1.09	0.93
Mean ± S.D.		0.93 ± 0.21	0.90 ± 0.40

Table III. Maximum rise in plasma ascorbic acid in lactose intolerant subjects given 200,000 IU vitamin A, 1 g vitamin C and a test meal containing 15 g casilan, 25 ml olive oil with either 45 g lactose or 45 g sucrose.

Subject No.	mg vitamin C / 100 ml	
	Lactose	Sucrose
1	0.98	1.13
2	1.05	0.71
3	1.07	1.25
4	1.09	1.03
Mean ± S.D.	1.05 ± 0.048	1.03 ± 0.232

Table IV. Maximum rise in plasma vitamin A in lactose intolerant subjects given 200,000 IU vitamin A, 1 g vitamin C and a test meal containing 15 g casilan, 25 ml olive oil with either 45 g lactose or 45 g sucrose.

Subject No.	mg vitamin A / 100 ml	
	Lactose	Sucrose
1	0.009	0.048
2	0.014	0.012
3	0.023	0.055
4	0.003	0.009
Mean ± S.D.	0.012 ± 0.00855	0.031 ± 0.0239

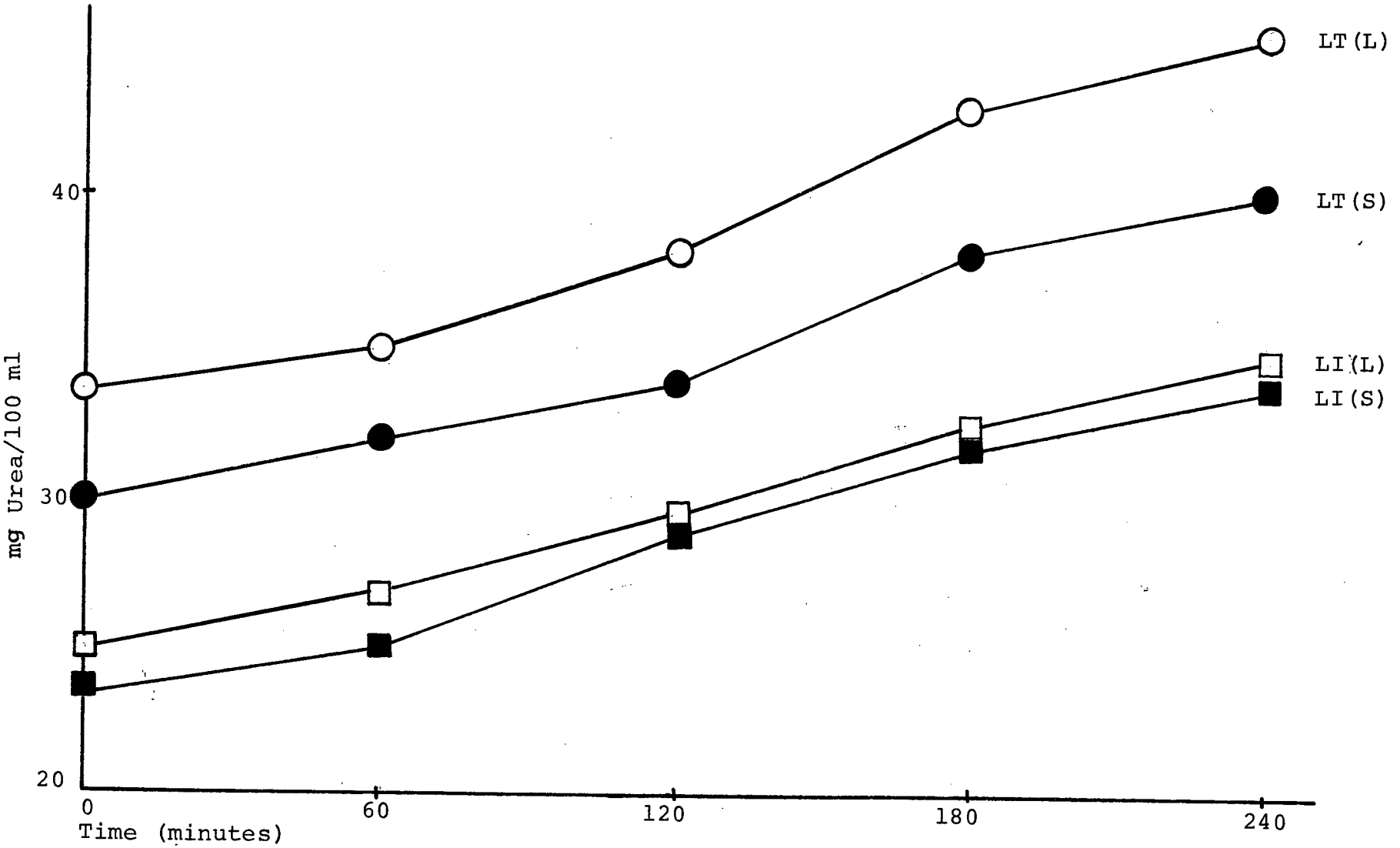

FIGURE 1. Mean Plasma Urea Levels in Lactose Tolerant (LT) and Intolerant (LI) Subjects Given 55 g Gelatin With Either 50 g Lactose (L) or 50 g Sucrose (S).

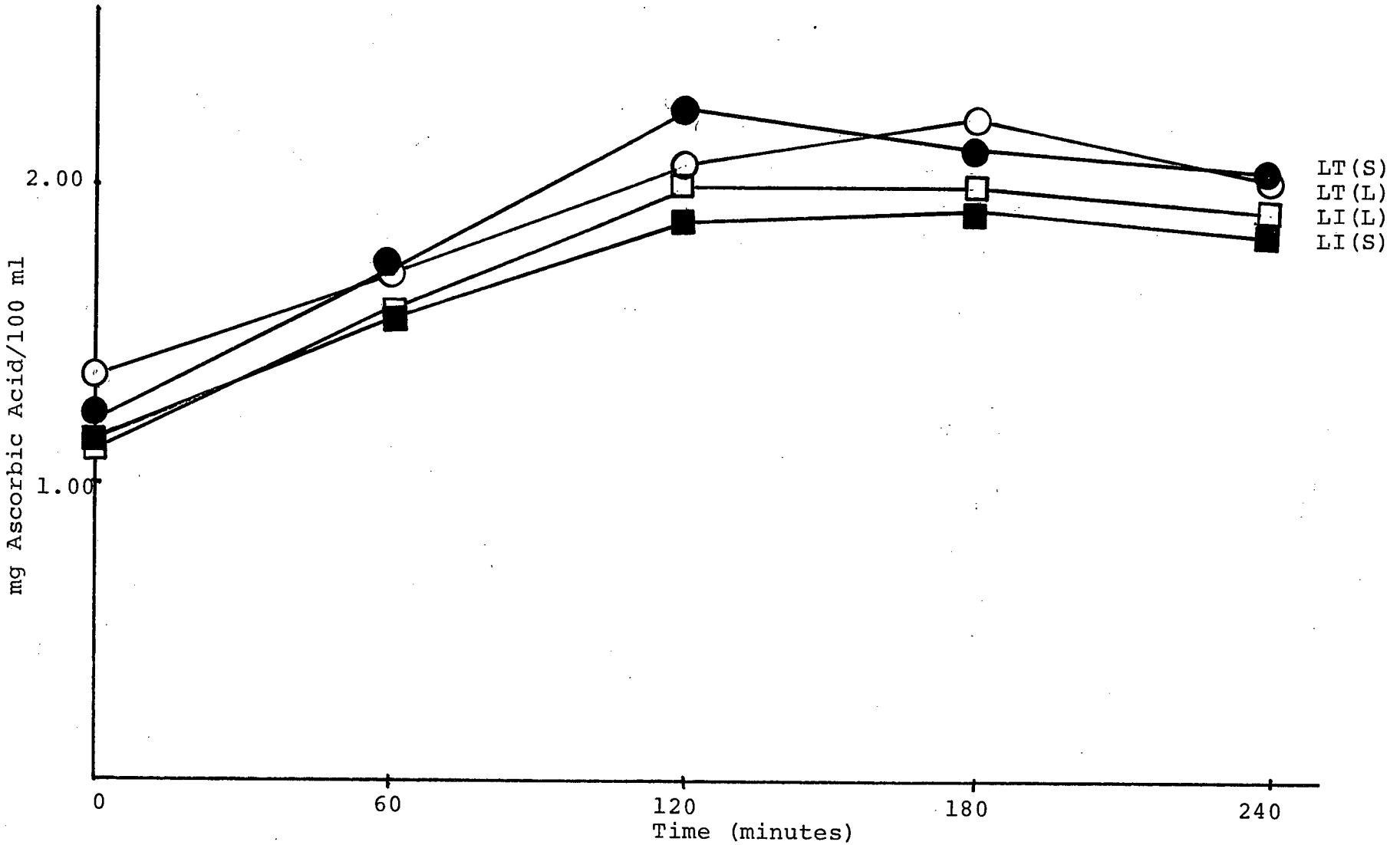

FIGURE 2 Mean Plasma Ascorbic Acid Levels in 6 Lactose Tolerant (LT) and 3 Intolerant (LI) Subjects Given 500 mg Vitamin C and 25,000 IU Vitamin A With Either 50 g Lactose (L) or 50 g Sucrose (S).

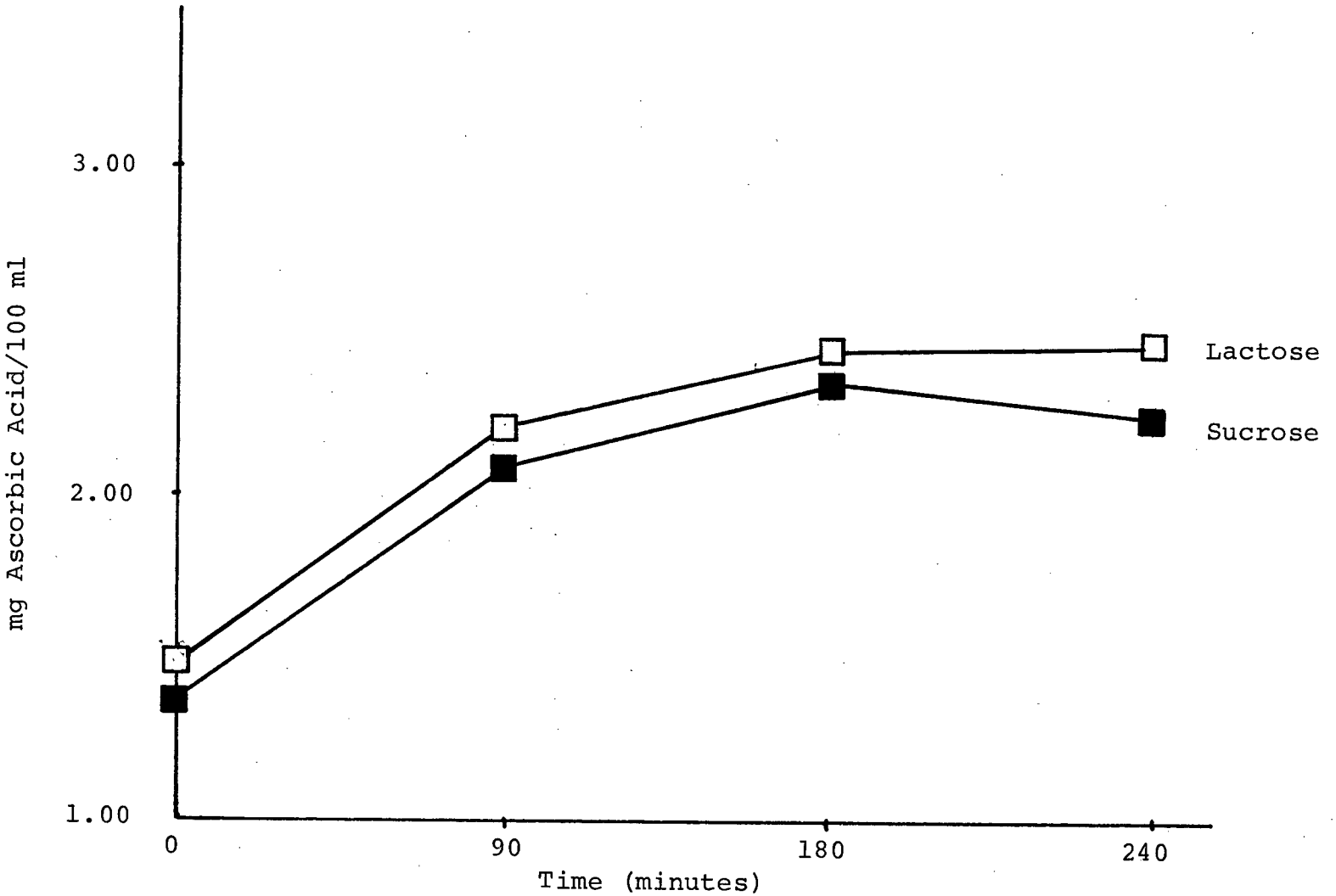

FIGURE 3. Mean Plasma Ascorbic Acid Levels in Lactose Intolerant (4) Subjects Given 200,000 IU Vitamin A and 1 g Vitamin C With a Test Meal Containing 15 g Casilan, 25 ml Olive Oil and Either 45 g Lactose or 45 g Sucrose.

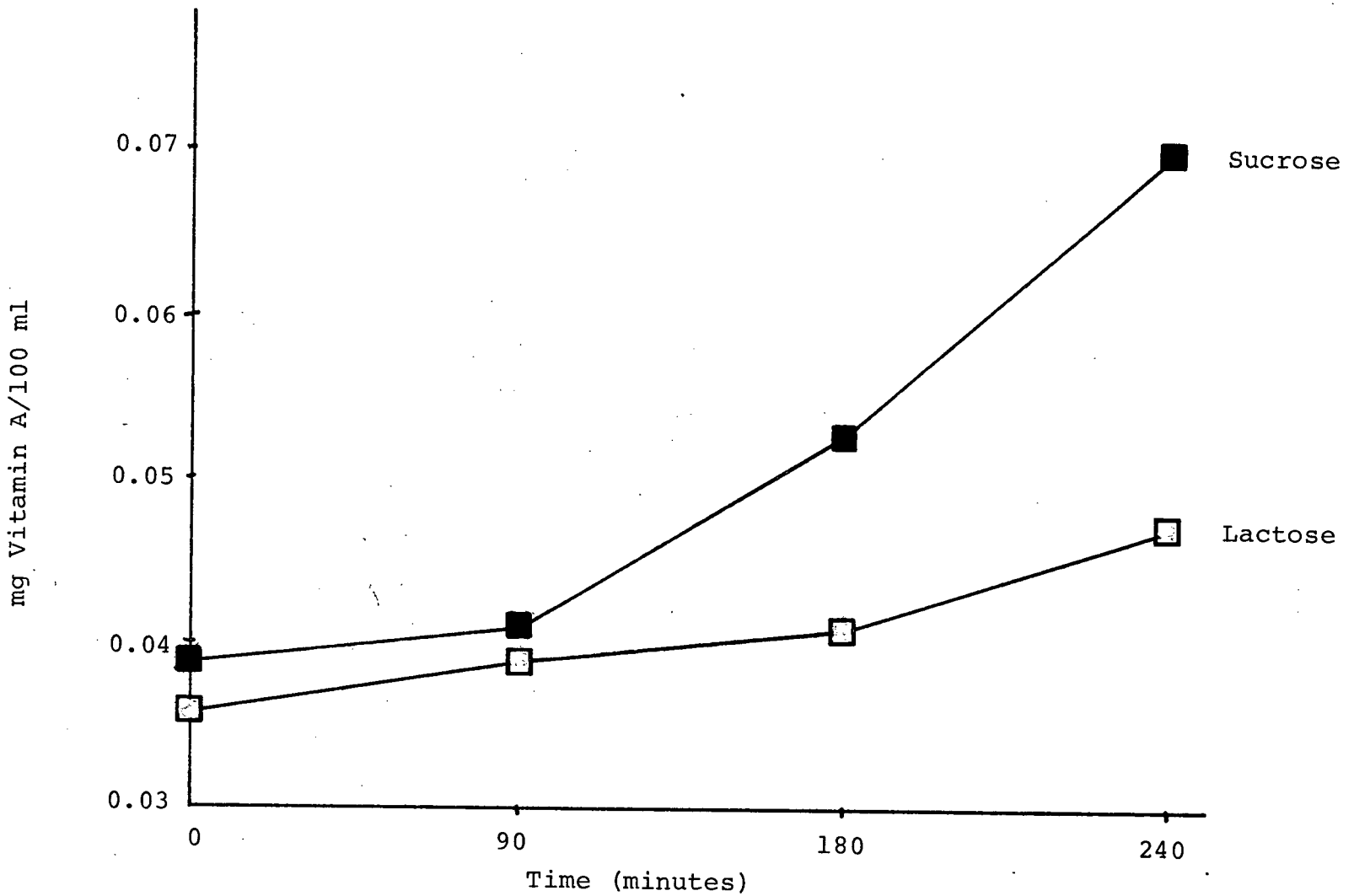

FIGURE 4. Mean Plasma Vitamin A Levels in Lactose Intolerant Subjects (4) Given 200,000 IU Vitamin A and 1 g Vitamin C With a Test Meal Containing 15 g Casilan and 25 ml Olive Oil and Either 45 g Lactose or 45 g Sucrose.

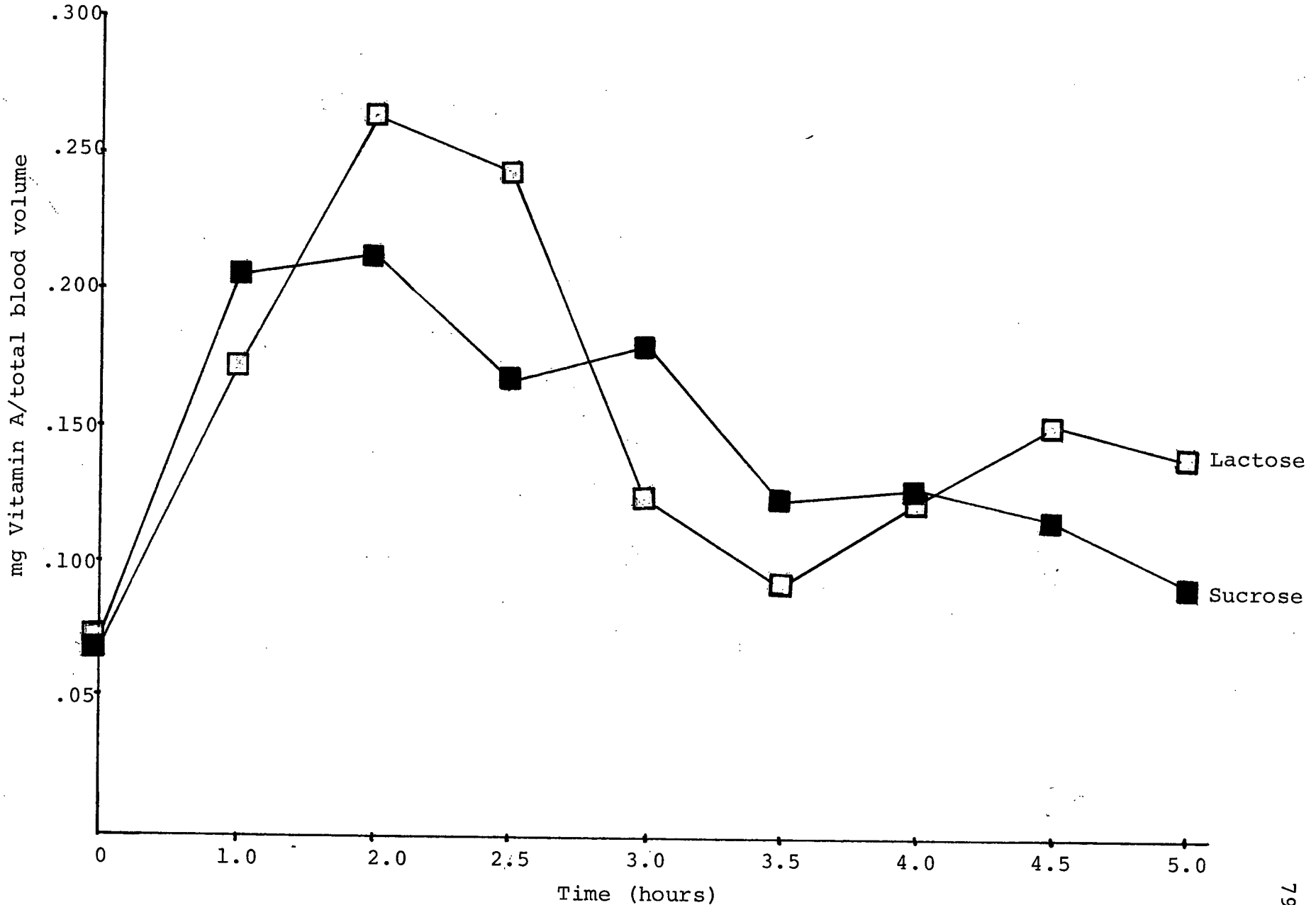

FIGURE 5. Mean Plasma Vitamin A Levels in Rats After Intragastric Administration of 500 mg Lactose or 500 mg Sucrose, and 2500 IU Vitamin A. (N = 36)