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CURRENT CONCEPTS IN LACTOSE MALABSORPTION AND INTOLERANCE

J. M. Saavedra and J. A. Perman

Division of Gastroenterology and Nutrition, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

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INTRODUCTION

Lactose is the principal carbohydrate of mammalian milk. This disaccharide is hydrolyzed in the intestine by the brush border enzyme lactase, and the

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resultant monosaccharides glucose and galactose are absorbed into the bloodstream. In most mammals, including the majority of humans, intestinal lactase levels are at their highest immediately after birth, decreasing with weaning until very low levels of lactase are present in the adult. However, a minority of human groups maintain high levels of lactase and the capacity to digest and absorb lactose throughout adult life.

Whether due to the normal post-weaning decrease or any injury to the intestinal mucosa, low lactase levels are responsible for limited hydrolysis of lactose. The nonabsorbed carbohydrate exerts an osmotic effect in the intestinal lumen inducing increases in luminal water and sodium. Lactose escaping small bowel absorption becomes a substrate for fermentation by bacteria in the colon, resulting in production of gas and short chain fatty acids. The hallmarks of lactose intolerance are abdominal distention and pain plus acidic watery stools. Lactose malabsorption is confirmed by excretion of hydrogen in breath following an oral lactose load. Lactose intolerance is treated by removing lactose from the diet, using lactose-reduced milk products, or consuming products that promote in vivo hydrolysis of lactose.

This chapter reviews current concepts of the physiology of lactose absorption, recent advances in characterizing lactase (including its developmental aspects), and the pathophysiology of lactose malabsorption. Recent advances in the diagnosis of lactose malabsorption and its treatment are also reviewed. A glossary of terms associated with lactose digestion and absorption appears at the end of the chapter.

LACTOSE

Except in a few pinnipeds such as sea lions, lactose is the primary sugar of mammalian milk. It constitutes 70% by weight of the whey solids of milk. Human milk consists of 7% lactose, while whole cow's milk contains 4.8% lactose.

The food industry has made wide use of the characteristics of lactose: its limited sweetness relative to sucrose, fructose, and glucose and its solubility and crystallization enhance its use in the candy and confection industries. Its browning properties make it useful in the manufacture of baked products. Lactose is often present in commercially made nondairy products: breads, cereals, breakfast drinks, salad dressings, and cake mixes (144, 163), and it is found in up to 21% of prescription and 6% of over-the-counter drugs because of its excellent tablet-forming properties (33).

Nutritionally, lactose is the primary source of carbohydrate calories in breast-fed and most formula-fed infants. Although the mechanism is unknown, lactose appears to promote calcium absorption both in animals (62,

131) and in humans (43, 193), independent of the action of vitamin D. In rats, lactose stimulates phosphate absorption (50). Lactose also appears to promote magnesium and manganese absorption in healthy infants (193).

While milk is not an indispensable food after weaning, its palatability, high protein quality, calcium content, and availability make it a high-quality staple food in many industrialized societies with strong dairying industries. Thus, ingestion of lactose continues throughout life in many populations, and lactose malabsorption and intolerance become important health issues, sometimes responding to economic, cultural, and political factors (146).

PHYSIOLOGY OF LACTOSE ABSORPTION

Dietary carbohydrates other than monosaccharides require digestion prior to absorption as simple sugars. Starch, composed of amylose and amylopectin, is first hydrolyzed into maltose, maltotriose, and alpha-dextrins (branched oligosaccharides averaging 6 to 10 units) by salivary and pancreatic amylases. These oligosaccharides, together with the dietary disaccharides lactose and sucrose, are then hydrolyzed by brush border enzymes with active hydrolytic sites exposed to the luminal surface of the enterocyte (Figure 1). The human

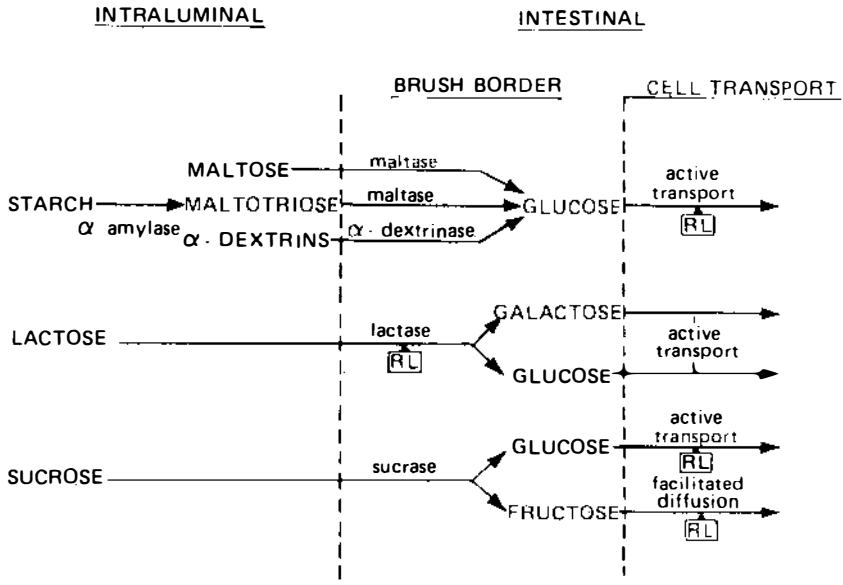

Figure 1 Schematic diagram of absorption of dietary carbohydrate at the level of the intestinal brush border. *RL* indicates the rate-limiting step in the overall digestion and absorption of the sugar. See text for explanation. Modified with permission from Ref. 69.

intestine has five distinct disaccharidases: lactase, sucrase, maltase, isomaltase (also called alpha-dextrinase), and trehalase. Except for the beta-galactosidase lactase, these enzymes are alpha-glucosidases. The brush border disaccharidases are high-molecular-weight proteins ranging between 130,000 and 500,000 daltons, containing up to 40% carbohydrate by weight. Montgomery et al (132) have reviewed the structure and function of intestinal disaccharidases.

Hydrolysis of dietary sugars with the exception of lactose is a rapid process yielding sufficient monosaccharide to saturate transport pathways. In contrast, lactose hydrolysis rather than glucose or galactose transport is the rate-limiting step in its overall process of digestion and absorption (70). Hydrolysis of lactose proceeds at approximately one half the rate of sucrose hydrolysis. This relative lack of reserve of lactase activity is pertinent to an understanding of the vulnerability of lactose digestion and absorption in humans (69). The characteristics of lactase and lactose digestion are reviewed in the following sections.

CHARACTERISTICS OF LACTASE

The characterization of lactase has advanced considerably in recent years. Three separate beta-galactosidase activities have been demonstrated in the intestinal mucosa of rat and human, but only one of these is present in the brush border membrane (2, 71). Subsequently, rat lactase was purified and found to exhibit both lactase and phlorizin hydrolase activity, either within a single unit or on separate subunits (169). Lactose-phlorizin hydrolase is a glycoprotein of molecular weight 130,000 to 140,000 containing approximately 17% carbohydrate (23, 87, 101, 137, 182).

Lactose-phlorizin hydrolase appears to be formed as an initial precursor, which after complex glycosylation, undergoes intracellular cleavage leading to a mature brush border form. This is supported by work from several investigators; Skovbjerg et al (172) worked with human lactose-phlorizin hydrolase from explants, Hauri et al (74) utilized cell lines derived from colon adenocarcinoma, and Danielsen et al (47) studied pig small intestine. More recently, Buller et al (37) and Naim et al (135) concluded that lactose-phlorizin hydrolase is synthesized as a glycosyllated precursor of 215,000 molecular weight that undergoes intracellular cleavage and is transported to the microvillus membrane, where it yields a mature form of lactose-phlorizin hydrolase of 130,000 to 160,000 molecular weight. The nature, number, and site of these cleavages are still unclear. Further studies of the biosynthesis and structure of human lactase, and of the regulation of its expression, are necessary.

ONTOGENETIC DEVELOPMENT OF LACTASE

Lactase Activity in the Fetus and Newborn

In contrast to the alpha-glucosidases sucrase, alpha-dextrinase, and maltase, lactase appears very late in fetal life. Approximately 10% of adult lactase activity is present in the proximal jejunum of fetuses at 23 weeks gestation (46), rising to 30% between 26 and 34 weeks gestation (5). Auricchio et al (8), on the basis of lactase concentration and intestinal lengths and assuming a milk intake of 120 kcal/kg/day, estimated a premature newborn after 6 month's gestation could absorb only 3% of the lactose. Superimposing data of several studies of lactase in the mid-jejunum, Grand et al (68) concluded that lactase levels are approximately 30% of full-term levels between 26 and 34 weeks gestation and that they rise rapidly in the third trimester to approximately 70% of full-term levels at 35–38 weeks gestation. Full-term lactase levels are 2–4 times the levels found in infants 2–11 months of age (5). The regulatory mechanisms that cause these maturational changes in lactase during gestation are unknown. In animals, the gestational rise in lactase activity correlates with an increase in the level of circulating corticosteroids (75), and cortisol production does increase late in human gestation (134). However, any causal association remains to be proven. Interestingly, Buller et al (38) were able to demonstrate lactase activity in the proximal colon of suckling rats. Whether this is also the case in human newborns and what role this may have in lactose absorption remain to be defined.

As indicated above, most studies of lactase development have been performed in fetuses or stillborns. There appears to be at least some evidence that premature infants who survive even for short periods may quickly increase their lactase levels beyond what would be expected for a fetus of similar gestational age. Auricchio et al (8) reported three preterm infants 7–8 months of gestation surviving more than one day whose lactase activity was 50% higher than stillborns of the same gestational age; and Antonowicz et al (4) reported a preterm infant of 28 weeks who survived for 10 days and whose lactase activity was that of a full-term infant. Finally, Mayne et al (127) measured lactase activity in three preterm infants using disaccharidase levels in jejunal fluid to extrapolate for levels of brush border enzyme; they found that normal enzyme levels were present by the first week of extrauterine life. Unfortunately, reference ranges for enzyme concentrations in jejunal fluid of infants are not yet available to establish clearly the reliability of these results. Nevertheless, it is likely that postnatal events could influence lactase levels independently of postconceptional age. Any influence of feedings on neonatal lactase levels remains to be proven.

Lactase Adaptation

The preponderance of current evidence indicates that lactase activity cannot be induced to any clinically significant degree by lactose. Initial studies of lactose absorption in different racial and ethnic groups indicated an association between the level of consumption of dairy foods and the prevalence of malabsorption within a given population (24, 25). These observations led Bolin & Davis (26) to propose the "induction or adaptative hypothesis," which stated that presence of lactose in the diet influenced lactase activity and its persistence beyond the age of weaning. Evidence to support this hypothesis arose largely from animal studies. Very high-lactose diets fed to rats for periods of up to 10 weeks caused statistically significant increases in lactase activity (27, 58, 67), and studies in newborn rabbit small intestinal explants exposed to lactose showed similar results (85). Prolonged nursing of rat pups past the age of weaning delayed, but did not prevent, a decline in lactase activity levels (106). It has been suggested that the presence of lactose may protect lactase from degradation by a process of "substrate stabilization" (85). Any such induction of lactase may not be substrate specific. Koldovsky et al (97) fed high-starch or -sucrose diets to rats previously fed low-carbohydrate diets; they found increased levels of both lactase and sucrase activity.

On the other hand, abundant evidence points to the fact that the development, and particularly the decline, of lactase in the post-weaning period of mammals, including humans, are independent of adaptation to dietary patterns. Even though substrate-induced rat lactase activity as discussed above may double upon prolonged exposure to large amounts of lactase, it does not approach the tenfold difference observed between pre- and post-weaning levels. Prolonged nursing of rat pups delayed the decline in lactase activity, but it did not ultimately prevent it (106). Ferguson et al (56) showed that implanted isografts of fetal mouse intestine into adult mice followed similar changes in disaccharidase activity as those of normally developing animals, even though the isografts were never exposed to any dietary substrate.

Ample evidence in humans further refutes the likelihood of any clinically significant dietary-induced adaptation in lactase activity. Multiple studies have documented that continued lactose consumption enhances neither lactase activity nor lactose absorption (44, 65, 99). Furthermore, prevalence of lactose malabsorption has been found to be independent of the degree of milk consumption (90). Patients with galactosemia maintained on lactose-free diets for prolonged periods of time continue to have normal lactase levels (95), and experimental withdrawal of lactose from the diet of human adults for two months does not induce a decrease in enzyme activity (93).

In conclusion, the bulk of available evidence indicates that the normal post-weaning decline of lactase activity in most mammals and humans

appears to be independent of the presence of lactose or other dietary substrate. Some interaction does exist between lactase and lactose and possibly other carbohydrate substrates by which small increases in activity of the enzyme can be elicited. However, the clinical significance, if any, and the mechanisms for this interaction remain to be determined.

Decline of Lactase Expression

Age-specific prevalence data indicate that the normal ontogenetic course of lactase activity in the mammalian gut is characterized by a decrease in the post-weaning period. Lactase activity measured by Lebenthal et al (104) in 172 morphologically normal jejunal biopsies from a general childhood population declined gradually to low levels by age 5 years. Data on Pima Indians showed a prevalence of malabsorption of 40% by age 3–4 years, 71% by 4–5 years, 92% by 5–7 years, and 100% at more than 8 years (84). The onset of malabsorption and intolerance is influenced by ethnicity. Malabsorption occurs as early as 2–4 years in Thais (90), and as late as 15 years in Finns (166).

The mechanisms associated with decline of lactase expression have yet to be elucidated. Four potential factors have been considered: diet, hormonal factors, altered enzyme synthesis, and cytokinetic factors.

DIET As discussed above, clinically significant induction of lactase activity utilizing lactose-containing diets has not been demonstrated. Thus, dietary influences leading to a decline in lactase expression are unlikely.

HORMONAL FACTORS The gestational rise of lactase correlates with an increasing level of corticosteroids in animals (75, 134), which suggests a regulatory effect of hormones on lactase activity. The post-weaning decrease in lactase activity can be prevented by hypophysectomy or thyroidectomy (192), and in rats thyroxine caused an early decline when given during nursing (192). Thyroid hormones decrease lactase levels in the adult rat intestine (32, 40, 76), and the increase in lactase activity following starvation is thought to result from a fall in the concentration of circulating thyroid hormone (161). The decrease in enzyme activity caused by thyroid hormone does not appear to be associated with structural alterations nor altered migration rates of enterocytes (76); this leaves unclear the mechanism by which thyroid hormones exert their action on lactase activity and the clinical significance of this effect in humans.

ALTERATIONS IN ENZYME SYNTHESIS It is possible that lactase synthesis continues after weaning but in a different or less active form. Enzymatic, chromatographic, and electrophoretic characteristics of lactase are identical in

infants and in adults with low levels of activity (7, 107). Using immunoprecipitation and pulse-chase techniques with labeled leucine, Jonas et al (85) attribute the decrease in lactase activity in adult compared to suckling rats to a decrease in the rate of lactase synthesis.

CYTOKINETIC FACTORS A reduction in enterocyte lifespan could lead to a subsequent decline in lactase activity. Boyle et al (31) demonstrated that lactase activity increases in enterocytes along the villus length, reaching its maximum as the enterocytes reach the villus tip. Since enterocyte migration rates accelerate from crypt to villus as rats mature toward their weaning age (183), it has been suggested that relative immaturity of the enterocyte leads to the decline in lactase activity post-weaning. Using immunoprecipitation techniques and accumulation patterns of ^{3}H-leucine to study brush border enzyme synthesis in weaning rats, Tsuboi et al (182) provided further evidence that reduced lifespan of the enterocyte rather than decreased lactase synthesis causes decreased lactase accumulation and explains lactase decline.

Observations by Smith & James (173) incorporate both synthetic and cytokinetic factors in explaining the maturational decline in lactase activity. Using quantitative cytochemistry to determine changes in lactase activity occurring as the enterocytes migrate from crypt to villus, they suggested that lactase decline occurs in two stages. The first is characterized by a shortening of the time allowed for enzyme expression with no change in the capacity of the cells to express lactase at maximal rate, which supports the findings of Tsuboi et al. The second stage of regulation is characterized by inhibition of the rate at which lactase is expressed by young enterocytes, which supports the findings of Jonas et al. This unifying hypothesis requires confirmation.

PATHOPHYSIOLOGY OF LACTOSE MALABSORPTION

The pathophysiologic events resulting from lactose malabsorption are indicated in Figure 2. Lactose escaping hydrolysis can be absorbed in small amounts into the bloodstream at high luminal concentrations, or under conditions of increased intestinal permeability resulting from mucosal damage. Even under these conditions, it is estimated that only 1% or less of intact disaccharide reaches the blood stream, followed by excretion into the urine unmetabolized (69). Lactosuria and galactosuria have been used to assess levels of lactase activity (6, 187).

The presence of unabsorbed carbohydrate in the jejunum exerts an osmotic effect, increasing secretion of water and sodium into the lumen (103). The volume of chyme is increased (42), and transit of small bowel contents is accelerated (29, 102). Nutrient absorption may be affected, as indicated by abnormally high quantities of protein, calcium, magnesium, and phosphate in

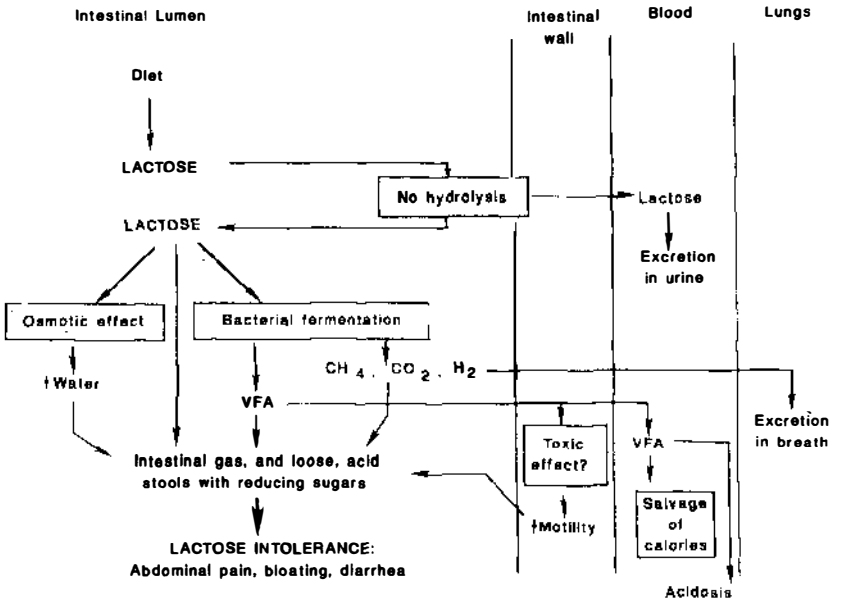

Figure 2 Pathophysiologic events following lactose malabsorption. *VFA* indicates volatile fatty acids. See text for explanation.

the ileum of lactase-deficient subjects studied by infusion-aspiration techniques (51).

When lactose is malabsorbed, large amounts enter the colon. Bond & Levitt (30) recovered from 42 to 75% of a 12.5-g lactose dose in the distal bowel of lactase-deficient individuals as compared with 0–8% in healthy controls. Upon reaching the colon, nonabsorbed carbohydrate can be fermented by colonic flora. It is estimated that 65 to 85% of mono- and disaccharides reaching the colon can be metabolized to short chain organic acids, the gases H_2, CH_4, CO_2, and other larger molecules (28, 30). Thus, relatively little osmotically active carbohydrate remains in feces. Volatile fatty acids are absorbed across the colonic mucosa (129, 165), which further decreases the osmotic activity that might otherwise be exerted by nondigested sugars plus the products of fermentation. Colonic absorption of organic acids may represent a salvage pathway for energy escaping small bowel absorption and thus be beneficial, particularly in normal neonates, in whom significant amounts of lactose are not absorbed (41, 120). However, the presence of organic acids in the bloodstream has led to severe metabolic acidosis in small infants (117, 170). Some organic acids are excreted in the feces to form acidic stools.

Gas formed from bacterial fermentation may cause abdominal distention

and bloating and be partially passed as flatus. The gaseous products of fermentation also readily diffuse into the portal circulation and are eventually exhaled in the breath. The presence of hydrogen in expiratory air, whose only source in the body is intestinal bacterial metabolism, is the basis for the lactose hydrogen breath test discussed below.

Distention caused by the additional water content in the lumen and the gaseous products of fermentation, plus the possible effects of volatile fatty acids on colonic motility, lead to the characteristic signs and symptoms of lactose intolerance. These are watery acid diarrhea, abdominal distention, pain, and flatulence.

RELATIONSHIP BETWEEN MALABSORPTION AND INTOLERANCE

The chief determinant of the capacity for lactose absorption is lactase activity, which can decrease depending on age, ethnicity, and the integrity of the intestinal mucosa. Thus, lactose absorption is not an all-or-none phenomenon. The threshold dose of lactose causing symptoms in a group of individuals with low lactase levels ranged from 3 to 90 g of lactose (19). In a review of multiple studies, Newcomer (138) found the prevalence of intolerance to a 12-g dose of lactose ranged from 0 to 75% of subjects. However, for practical and clinical purposes, we tend to classify individuals as "absorbers" or "malabsorbers" based on the results of direct or indirect measurements of lactase activity. In general, it would be expected that the presence or degree of malabsorption would parallel the capacity to tolerate lactose. However, this is not always the case.

A history of intolerance or tolerance to milk products does not predict an individual's capacity to absorb lactose (12, 17, 52). Similarly, the history of milk consumption by an individual is not predictive of his or her capacity to absorb lactose (61, 148, 164, 175), even though there may be a tendency for individuals who malabsorb to withdraw milk from their diets (17, 148). Finally, even within individuals, tolerance to a dose of lactose can be modified depending on the form in which it is given, as discussed below. A number of factors and interactions are responsible for the lack of correlation between malabsorption and intolerance. These are discussed in the following section.

RATE OF DELIVERY OF LACTOSE TO THE SMALL BOWEL For a given amount of available lactase activity and a given load of lactose, the longer the time over which the substrate is presented to the absorptive surface, the greater the likelihood of adequate hydrolysis and therefore better tolerance. The rate at which substrate is delivered to the stomach or small intestine can

be important. For example, enteral tube feedings delivered by continuous drip enhance the chances for carbohydrate hydrolysis and absorption, as indicated by decreased amounts of breath hydrogen when compared to bolus feedings (112). Welsh & Hall (188) found that lactase-deficient subjects emptied lactose from the stomach faster than equivalent doses of glucose. Presumably, this was due to the lesser osmotic regulatory effect of lactose compared with glucose on gastric emptying. Rapid emptying of lactose increases the chances for a greater osmotic effect in the small bowel. Surgical gastrectomy can "unmask" intolerance in lactase-deficient subjects, or it can cause intolerance in subjects with normal lactase activity by accelerating gastric emptying time (21). The osmotic effect of unabsorbed lactose increases the volume of chyme (42), which may in turn accelerate transit through the small bowel (29, 102). The degree to which faster transit itself impairs further absorption is not known.

VEHICLE OF DELIVERY OF LACTOSE Intolerance is greatest when similar amounts of lactose are delivered as an aqueous solution, intermediate with skim milk, and lowest when lactose is ingested as whole milk (108). The symptoms of intolerance are decreased when lactose in the form of milk is ingested with a meal, compared with milk ingested alone (18, 125). Tolerance will also improve when lactose is ingested as chocolate milk rather than whole milk (188). These differences in intolerance are most likely due to the difference in fat content, osmolarity, and presence of other sugars, which may delay gastric emptying. The role of fiber in lactose tolerance is currently under investigation, since dietary fiber may slow gastric emptying and flatten glucose tolerance curves in diabetics (59, 83).

METABOLIC ACTIVITY OF COLONIC FLORA Prolonged administration of nonabsorbable carbohydrate decreases fecal pH and the rate of production of hydrogen in vivo and in vitro in fecal incubations (158). It has been speculated that long-term maintenance of an acid colonic pH by dietary means could eventually result in conversion of the enteric flora to acidophilic types capable of degrading carbohydrate effectively by alternative fermentative pathways (156). Prolonged exposure to nonabsorbed lactose could thus lead to quantitative and qualitative changes in fermentation by individual colonic ecosystems, causing variations in the degree of diarrhea and gas production. This "colonic bacterial adaptation" has been observed both in animals and in humans (68a, 136). In rats, diarrhea will cease over time after a continued ingestion of 17% lactose, and Nigerian blacks introduced to ice cream reported initial symptoms that disappeared after several months of consumption (136). Finally, it has been postulated that bacterial lactase could be inducible. Thus, the population of colonic flora may increase with time and become

capable of metabolizing increasing amounts of lactose (136). While no direct proof exists, such effects on the colonic microflora may in turn influence tolerance.

SUBJECTIVITY Malabsorption can be easily identified by objective testing. Intolerance, on the other hand, ultimately depends on the individual's perception of symptoms except when diarrhea is prominent. Therefore, psychodynamic factors need to be taken into account when intolerance to lactose is suspected as a cause of gastrointestinal symptoms, and the diagnosis should rely on objective evidence of malabsorption, e.g. a positive breath hydrogen test. It is evident that there is a large population with lactose malabsorption capable of tolerating nutritionally significant amounts of milk without developing any significant symptoms (35, 82, 142, 175).

CLINICAL PRESENTATIONS OF LACTOSE MALABSORPTION

Congenital Lactase Deficiency

In this extremely rare condition, lactase activity is decreased or absent at birth, a deficiency that persists throughout life. Levels of other disaccharidases are normal, as is monosaccharide absorption. The histology of the small bowel mucosa is normal. Few cases have been described that satisfy all criteria for congenital lactase deficiency (168). Freiburghaus et al (60) found no difference in the electrophoretic characteristics of lactase in patients with congenital deficiency and in patients with adult-onset lactase deficiency. Treatment of this condition consists of withdrawing all lactose from the diet.

Primary Lactase Nonpersistence

Although the mechanisms responsible for lactase nonpersistence in the adult remain obscure, considerable work has accumulated on the geographic and ethnic distribution of primary lactose malabsorption (171). Such studies yield insight into the genetics of the normal post-weaning decrease of lactase levels in humans. Initial studies in the 1960s revealed large differences between white and black adults in their capacity to absorb and tolerate lactose (12, 44). Based on their findings that 70% of the American black population and 8% of American whites were lactose malabsorbers, Bayless et al (15) proposed that intestinal lactase deficiency was inherited as an autosomal recessive trait. Their findings fit the assumption that 100% of West African blacks, from which most American blacks are descended, were lactose malabsorbers and that American blacks had a 30% Western European gene mixture. Family studies by Sahi et al in Finland (167), Ransome-Kuti et al in Nigeria (160), and Johnson et al in American Pima Indians (84) are consistent with inheritance of lactose malabsorption as an autosomal recessive trait, while

lactose absorption is inherited as a completely penetrant autosomal dominant characteristic. It may be postulated that a regulatory gene is altered and thus fails to "shut off" and depress the expression of lactase activity at the programmed time, which would delay the reduction of lactase activity or completely eliminate it (151).

Secondary Lactase Deficiency

Since lactose is a brush border enzyme, any condition that injures the intestinal mucosa is likely to induce a decrease in lactase activity. Similarly, any surgical intervention that reduces the amount of available mucosal absorptive surface will decrease total lactase activity. Secondary lactase deficiency is most often transient, its duration depending on the nature and course of the underlying primary condition. The most important disease entities associated with secondary lactase deficiency are discussed below.

DIARRHEAL DISEASE Acute diarrheal disease usually of infectious origin is the most common cause worldwide of secondary lactase deficiency. The prevalence of lactose intolerance in infants with acute or chronic gastroenteritis was found to be 50% or more in numerous studies (34, 49, 77, 80, 100, 116). Any infectious organism that disrupts mucosal anatomy and produces an inflammatory response will thereby decrease activity of lactase and other disaccharidases. It is also postulated that the action of bacteria upon foodstuffs and host secretions may yield products that further damage small bowel mucosa. Among these are deconjugated bile acids and products of fermentation such as short chain fatty acids or alcohol (113). Lactase activity can also be decreased by bacterial overgrowth in the small bowel (63, 86). This may be due not only to ultrastructural villous abnormalities associated with bacterial overgrowth but also to direct degradation of exposed brush border disaccharidases (86).

Particularly important among the infectious etiologies of diarrhea leading to lactose malabsorption is rotaviral disease. Based on the observation in experimental animals that mature enterocytes at the tip of the intestinal villi were more susceptible to rotaviral infection than immature cuboidal epithelial cells, it was suggested that lactase, a component of the brush border membrane of mature enterocytes, acted as a receptor for this virus (78). This hypothesis is consistent with the high prevalence of rotaviral-related lactase deficiency in infants with gastroenteritis as opposed to adults, who appear to be less susceptible or to have milder symptoms of rotaviral diarrhea. Proof for the "lactase-as-receptor" hypothesis remains to be developed.

Secondary malabsorption of lactose and other carbohydrates due to gastroenteritis poses a major problem in the nutritional management of diarrheal disease of infancy. This is particularly true in areas of the world where malnutrition is also prevalent, and forms part of the vicious cycle of diarrhea-

malnutrition-infection that is responsible for more than 5 million deaths each year worldwide (174). Since chronic diarrhea and malnutrition commonly coexist, the relative contribution of each to the development of lactose malabsorption is difficult to discern.

Continued intake of milk, especially as the sole source of nutrients in a child with gastroenteritis, can potentially cause significant increases in stool output, in losses of bicarbonate leading to metabolic acidosis, and in the risk of severe dehydration (103, 116, 119, 122, 155). The increased volume and rate of purging may also lead to further nutritional depletion, increasing fat and nitrogen losses with significant losses in body weight (100, 149). The duration and the severity of diarrhea correlate with the capacity to tolerate lactose during the illness (116). Finally, prolonged diarrhea associated with lactose malabsorption may lead eventually to monosaccharide intolerance (115) and thereby perpetuate the cycle of diarrhea and malabsorption.

Given these potential complications, lactose-free formulas are generally recommended for infants with severe or persistent gastroenteritis, particularly in those who show evidence of lactose malabsorption (3, 45, 114). However, lactose in infant formulas may be acceptable and might even promote tolerance in children with mild diarrheal disease, especially in those with no evidence of carbohydrate malabsorption (53, 61, 72).

An exception to the recommendation of lactose exclusion in children with gastroenteritis is the breast-fed infant. Continued breast feeding during diarrhea is usually well tolerated and most likely improves the nutritional outcome (36, 145).

PARASITOSIS Giardiasis and ascariasis have been associated with lactose malabsorption (9, 177, 178). Histologic changes of the upper small bowel mucosa may occur in the presence of giardia, an indication of damage sufficient to deplete lactase activity (1, 191). Electron microscopy has shown that the parasites align their adhesive disc toward the mucosa close to the microvilli and these "coat" the mucosa. The reduction in available absorptive surface produced in this way could be responsible for lactose malabsorption (9).

COW'S MILK PROTEIN INTOLERANCE Protein in cow's milk can be responsible for lactose malabsorption (118). The mechanism underlying development of lactase deficiency appears to be immune-mediated injury of the intestinal mucosa. Maluenda et al (121) found that intestinal disaccharidase levels were low at the time of cow-milk-induced enteritis, rose during recovery from enteritis, but subsequently fell when cow's milk was reintroduced.

INFLAMMATORY BOWEL DISEASE Absorptive defects have been documented to occur in patients with inflammatory bowel disease (IBD),

particularly in those with Crohn's disease (20, 153) involving the small bowel. However, Kirschner et al (92) reported that lactose malabsorption occurs no more frequently in children with IBD than in the general population. Restriction of dairy products may be necessary in IBD patients when lactose malabsorption is objectively documented. Otherwise, unnecessary restriction may occur in patients who, because of their general malabsorptive syndrome and the use of steroids, are already at increased risk for metabolic bone disease and therefore in need of appropriate calcium intake.

AIDS A general malabsorptive condition has been reported in acquired immunodeficiency syndrome and may contribute to the diarrhea observed in these patients (54, 66, 98). Whether this is an effect of enteric pathogens on the intestinal mucosa or is caused by the underlying disease itself awaits further study.

Other Clinical Conditions

RECURRENT ABDOMINAL PAIN OF CHILDHOOD AND IRRITABLE BOWEL The ill-defined syndrome of recurrent abdominal pain of childhood (RAP), which compromises daily home and school routines and characteristically resolves completely between episodes, has been associated with lactose malabsorption (11, 16, 107, 111). Though some have concluded that lactose malabsorption contributes significantly to the symptomatology of RAP of childhood (12, 111), others tend to exclude lactose as the single or most important pathogenic agent in RAP. It is generally accepted that RAP results from an interaction between lifestyle and habit, environment, temperament, and learned response patterns, with somatic predisposition or dysfunction (109) in which lactose malabsorption and intolerance can clearly play an aggravating or triggering role. On balance, it appears reasonable to exclude lactose temporarily from the diet of RAP patients as a therapeutic trial once lactose malabsorption has been documented by objective testing.

Similarly, multiple studies find that the frequency with which lactose malabsorption can be associated with symptoms of irritable bowel ranges from as low as 5–6% to as high as 95% (55, 73, 154, 189). The wide variation is probably due to lack of adequate control for ethnic background and lack of blinded studies. When these variables are taken into account, the prevalence of lactose malabsorption in adults with irritable bowel appears to be low (140).

LACTOSE ABSORPTION BY PREMATURE INFANTS Premature infants are a unique population in the sense that they absorb lactose suboptimally but do not show signs of intolerance. Newborn infants who receive breast milk or modified cow's milk formulas frequently excrete significant amounts of reducing sugars in their stool (48). Full-term infants receiving lactose as the

sole source of carbohydrate excrete significant amounts of hydrogen in breath by one week of age, which indicates lactose malabsorption (41). MacLean & Fink (120) found that 75% of infants 29–38 weeks of gestational age excreted significant amounts of hydrogen by two weeks of age, and amounts that would clearly be indicative of malabsorption by three weeks. Nevertheless, these infants did not have any symptoms of intolerance and gained weight normally. The authors estimated that the amount of lactose malabsorbed equalled 64% of intake. Auricchio et al (8) estimated that up to 97% of lactose could be malabsorbed in premature infants. Given the normal nutritional course of these infants, it is postulated that a large proportion of these calories are salvaged in the colon by absorption of the products of fermentation; this constitutes an extreme form of "colonic adaptation" to lactose malabsorption. Accordingly, there is no justification for removing lactose as the primary source of carbohydrate in these infants.

ADAPTATION OF LACTASE DURING PREGNANCY Villar et al (185) found that 44% of women demonstrating malabsorption with breath hydrogen tests before the 15th week of gestation developed the capacity to digest and absorb lactose at term. The mechanism is unknown. These authors suggested that this adaptative improvement could have positive effects on calcium intake, absorption, and balance during gestation.

EFFECT OF LACTOSE MALABSORPTION ON ABSORPTION OF CALCIUM AND RELATIONSHIP TO OSTEOPOROSIS Several authors have documented the fact that lactose improves calcium absorption (43, 131, 193). Others, however, have found no change in calcium absorption when given together with intact or hydrolyzed lactose (179, 180). Debongnie et al (51) actually found that four subjects with lactose malabsorption absorbed calcium better from lactose-free milk. Balance studies in adults with primary lactose malabsorption have found no significant effect of lactose ingestion on the absorption of nitrogen, calcium, phosphate, or magnesium (57, 139). The association between lactose malabsorption and osteoporosis in postmenopausal women is still unclear (79, 184). Kocian et al (94) found that the cortical thickness of the clavicle in subjects after gastric resection was decreased in patients with lactose malabsorption. On the other hand, blacks, who have an increased prevalence of lactose malabsorption, usually have a decreased prevalence of osteoporosis. This could be secondary to an increased bone density at maturity (181). Whatever the mechanisms, the association between lactose malabsorption and osteoporosis is not one of cause and effect.

DIAGNOSIS OF LACTOSE MALABSORPTION

Commonly used screening tests for the diagnosis of lactose malabsorption are described in Table 1. In recent years, the lactose breath hydrogen test has

become the "gold standard" for the diagnosis of lactose malabsorption (81, 141). This method is sensitive, noninvasive, and inexpensive, and it can be performed in patients of all ages. Hydrogen (H_2) in breath results exclusively from the fermentation of carbohydrate by colonic bacteria if lactose, or any other dietary sugar, is malabsorbed. H_2 is absorbed into the portal circulation and excreted in breath (39, 110). The original, somewhat cumbersome, techniques for continuous collection of breath have been replaced by interval sampling of expired air using masks, cannulas, or nasal prongs (13, 157). Samples of breath taken at intervals following administration of lactose are analyzed by gas chromatography or other analytical methods using relatively inexpensive dedicated instruments that are now commercially available for this purpose. Samples can be collected in plastic syringes for relatively rapid analysis, or stored in specialized containers for periods of 30 days or more (157). An increase in breath H_2 of >10–20 ppm above the baseline value is considered abnormal and indicative of fermentation of nonabsorbed carbohydrate. Additional information obtainable in the course of performing the lactose H_2 breath test includes evidence of small bowel bacterial overgrowth, which may contribute to lactose malabsorption (130). Newcomer et al (141) demonstrated complete separation between biopsy-proven lactase-deficient and lactase-sufficient individuals. Lactose breath hydrogen tests have been shown to correlate better with intolerance than with mucosal lactase activity, which suggests that direct assay of lactase activity on intestinal biopsy is not consistently representative of the total capacity for lactose absorption (13, 89).

Several factors can interfere with the sensitivity and specificity of breath hydrogen testing. First, it is essential that the colonic bacterial flora be capable of producing hydrogen as a metabolic product. Both in vivo and in vitro studies have shown that between 2 and 20% of individuals may lack hydrogen-producing flora (64, 186). Antibiotic treatment can also modify colonic flora and therefore alter the capacity for hydrogen production (64). Acidification of contents by continued delivery of carbohydrate to the colon may depress hydrogen production (158, 186). Since hydrogen requires absorption and transport in the blood stream, impaired gut circulation decreases its excretion in breath (159). Finally, smoking rapidly increases the peak of hydrogen production, which returns to baseline values shortly after smoking ceases (176).

MANAGEMENT OF LACTOSE MALABSORPTION

Several options are available for the management of lactose malabsorption. The first is exclusion of lactose from the diet. However, substantial numbers of individuals with primary lactose malabsorption can consume nutritionally significant amounts of milk without developing intolerance. Totally eliminat-

Table 1 Methods for detecting lactose malabsorption

Test and technique	Results
Sugar in feces	
1. Place small amount of liquid stool in test tube. 2. Dilute with twice its volume of water. 3. Place 15 drops of the resulting suspension in a second tube together with a Clinitest tablet. 4. Compare the resulting color with the chart provided for testing urine.	Negative < 0.25% Equivocal 0.25–0.5% Positive > 0.5%
Fecal pH	
1. Dip Nitrazine paper into liquid part of stool. 2. Compare resulting color of paper with chart provided.	Positive < 5.5
Breath hydrogen	
1. Patient is fasted (overnight if possible). 2. Obtain fasting sample of expired air. 3. Administer oral load of lactose, usually 2 g/kg; maximum 50 g as a 20% solution. Doses and concentration should be reduced when severe intolerance is suspected.	Negative < 10 ppm above baseline Equivocal 10–20 ppm Positive > 20 ppm

ing lactose or dairy products from the diet of these individuals is therefore unnecessary and could in some cases compromise nutritional status. This is particularly true in societies such as those in North America in which dairy products represent a substantial portion of high-quality protein in the diet and contribute up to 10% of food energy, 74.5% of calcium, 37% of riboflavin, 34% of phosphorus, 20% of magnesium, and 20.5% of vitamin B_{12} available for human consumption (123). Prominence of milk in the North American diet results from culturally acceptable feeding patterns and aggressive marketing by the dairy industry.

Because of its acceptability, nutrient bioavailability, and nutrient density, milk is usually chosen as a nutritional supplement in feeding programs in developing countries. This poses a problem since a high prevalence of primary lactose malabsorption and an even greater prevalence of lactose malabsorption secondary to malnutrition and diarrheal disease exist in such areas. Nevertheless, milk can often be tolerated and utilized by young lactose malabsorbers when given in small amounts and together with other nutrient sources (35, 82, 142, 175). In children with severe diarrheal disease and evidence of carbohydrate malabsorption, alternative nutrient sources or lactose-free formulas are the treatment of choice.

In addition to reduction or elimination of lactose-containing foods, several

additional strategies are available for the continued consumption of dairy products. Consumption of whole milk (108) or chocolate milk (188) rather than skim milk, and consuming milk with meals (18, 125) may reduce symptoms of intolerance. Consumption of products in which lactose has been fermented or hydrolyzed may be beneficial to symptom response. Fermented milk products such as aged cheeses (e.g. cheddar and swiss) usually contain significantly less lactose since the lactose-rich whey is separated from cheese during manufacturing.

Prehydrolyzed milk treated with lactase enzyme derived from microorganisms is now available. Multiple trials have demonstrated its effectiveness in improving absorption and tolerance (88, 147, 162). The increased cost and sweetness may affect acceptability of these products by some. Lactase may also be purchased to hydrolyze milk. Two lactases are commercially available. One is obtained from the yeast *Kluyveromyces lactis* (Lactaid®, Sugar Lo Company, Pleasantville, NJ) and another is derived from the fungus *Aspergillus oryzae* (Lactrase®, Kremers Urban Company, Milwaukee). These enzymes are not only effective in hydrolyzing milk by incubating it for a period of 12–24 hours prior to consumption, but they have also been effective in aiding hydrolysis and improving absorption in vivo when consumed just prior to ingestion of milk (10). Improved absorption has been shown in both adults (133) and children (22). Although initially promising (91), adding *Lactobacillus acidophilus* containing beta-galactosidase activity to milk was subsequently shown not to improve absorption or tolerance significantly when compared to untreated milk (143, 152).

Finally, much attention is now being given to yogurt as an adequate alternative for patients with lactose intolerance. Kolars et al (96) showed that ingestion of 18 g of lactose in yogurt resulted in one third of the breath hydrogen response compared with the same amount of lactose in milk or water, and it also improved signs and symptoms of tolerance. Yogurt is usually made by inoculating milk with *Lactobacillus bulgaricus* or *Streptococcus thermophilus*. Some of the lactose is consumed by these organisms, but since commercial yogurt is usually cultured from a stock containing 30% additional milk solids, the final concentration of lactose in yogurt sold in North America is roughly equivalent to that of native cow's milk, i.e. 4.6–5%. The beneficial effect on lactose digestion results from inherent activity of lactase in the microorganisms contained in yogurt that survive gastric digestion and become active at the temperature and pH of the duodenum.

Unflavored yogurts appear to have a better effect than flavored yogurts (126), and frozen yogurt as manufactured by current commercial methods contains little lactase activity with little effect on absorption. Thus, the manufacturing process determines the degree of effect on absorption by a

specific yogurt product (190). Acidification of milk and pasteurization of yogurt hinder the absorption and tolerance of the ingested lactose (124). Finally, modification of milk absorption and intolerance by the addition of *Bacillus acidophilus* (128) may be a therapeutic alternative. Initially promising results need to be confirmed.

DIRECTIONS FOR THE FUTURE

Because lactose malabsorption occurs in the majority of the world's population, it has wide clinical, nutritional, and socioeconomic implications. The analysis of these implications is beyond the scope of this review. Further work is needed in many areas, including the basic mechanisms that govern the expression of lactase activity and its decline in the human intestine; adequate education regarding proper dietary management of individuals who have lactose intolerance; efficacy of managing such patients with cultured dairy products; the development of products that promote in vivo hydrolysis of lactose; the effect of dietary fiber on lactose tolerance since fiber consumption is increasing in western societies; and the nutritional impact of the maintenance or withdrawal of lactose from the diet of infants and children with acute and chronic diarrhea, particularly in underprivileged societies.

GLOSSARY OF TERMS

Lactase deficiency: A subnormal level of lactase activity in the brush border membrane. Lactase activity can be measured directly in vivo only by small bowel biopsy. The lactose tolerance test and the breath hydrogen test for lactose absorption are indirect measurements of total intestinal lactase activity.

Congenital lactase deficiency: An extremely rare condition caused by a genetic enzymatic defect in which lactase activity is extremely low at birth.

Primary lactase nonpersistence: Synonyms include adult lactase deficiency, ontogenetic adult lactase deficiency, primary adult hypolactasia, and racial-ethnic lactase deficiency. This condition describes the normal developmental decrease in lactase activity beyond the age of weaning in most mammals including the majority of humans. Therefore, strictly speaking, it should not be considered an abnormality or a "deficiency." The World Health Organization recommends that the term lactase nonpersistence be used to refer to this condition.

Lactase persistence: The less common condition by which some adults have genetically maintained the capacity to express lactase activity and absorb lactose beyond the age of weaning.

Secondary lactase deficiency: Synonyms include secondary hypolactasia.

This is a true deficiency of lactase activity and refers to temporarily low enzyme activity in infants or in lactase-persistent individuals, most commonly due to an intestinal mucosal injury.

Lactose malabsorption: Decreased hydrolysis of lactose in the intestinal lumen usually, but not always, attributable to low lactase activity. Strictly speaking, lactose is not normally absorbed as such, but as its components, glucose and galactose. The more correct terminology would be lactose digestion or nondigestion.

Lactose intolerance: Refers to the clinical signs and symptoms following lactose nondigestion including diarrhea, bloating, flatulence, and abdominal pain. "Tolerance" and "intolerance" are not synonyms with absorption and malabsorption, and should be used only in reference to the symptomatic response to a defined amount of lactose delivered in a specific vehicle, since both the dose and the vehicle in which it is given (aqueous solution vs milk) can play an important role in the development of symptoms of intolerance.

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