Food Science and Technology International (1997) **3**, 87–92

Oral supplements to improve lactose digestion and tolerance

Aportes orales para mejorar la digestión y la tolerancia de la lactosa

D.R. Rao

Department of Food Science and Animal Industries, Alabama A&M University Huntsville, AL 35762 USA

There are two principal microbial sources of β-galactosidase (lactase): (*i*) yeast (*Kluyveromyces lactis*) and (*ii*) fungi (*Aspergillus niger* and *A. oryzae*). From these sources, several over-the-counter lactase supplements have been prepared and introduced into the US market. Controlled clinical trials have shown that these lactose digestive aids are effective. However, the results have been variable. A consistent observation in many of these is that there may be a subpopulation with very low levels of endogenous residual lactase. These people might need much higher levels of oral supplements than currently recommended. Generally, the products are expensive and research should be directed toward reducing the cost of these oral supplements.

Keywords: lactose, maldigestion, lactase, β-galactosidase, enzymes

Las dos fuentes principales de β-galactosidasa (lactasa) son: (i) las levaduras (*Kluyveromyces lactis*) y (ii) los hongos (*Aspergillus niger* y *A. oryzae*). A partir de estas dos fuentes se han elaborado preparados de lactasa que no precisan prescripción médica y que se han introducido en el mercado americano. Mediante pruebas clínicas de control se ha puesto de manifiesto la efectividad de estos productos, aunque los resultados son variables. Concretamente, en estas pruebas se ha observado que podría haber un grupo de población con niveles muy bajos de lactasa residual endógena. Estas personas necesitarían aportes administrados oralmente más grandes de lo comunmente recomendado. Generalmente, el costo de estas formulaciones es alto y la investigación debería dirigirse hacia el estudio de cómo abaratar su producción.

Palabras clave: lactosa, indigestión, lactasa, β-galactosidasa, enzimas

INTRODUCTION

Primary lactase deficiency is a genetically programmed event and develops in a vast majority of humans by adulthood (Simoons, 1970; Sahi, 1994). Of several enzymes and complexes thereof located in the brush border of small intestinal epithelial cells, β-galactosidase (EC 3.2.1.23) or lactase, hydrolyses the milk sugar lactose. Hydrolysis of lactose into its constituent monosaccharides is a prerequisite for absorption of lactose. Thus, hypolactasia may become evident as lactose intolerance symptoms after consumption of lactose or milk (Rao *et al.*, 1985; Sahi, 1994). Lactose intolerance symptoms generally include flatulence, bloating, abdominal cramps and, in severe intolerance cases, diarrhoea. Lactose intolerant subjects, therefore, avoid foods containing lactose, which might compromise the intake of many important nutrients, especially calcium.

Exogenous supplementation of the enzyme β-galactosidase to mitigate symptoms of lactose intolerance was advocated by Kobayashi *et al.* (1975). In fact, the concept of exogenous supplementation of digestive enzymes was practiced much earlier, especially

Journal article no. 338, contributed by the Agricultural Experiment Station, Alabama A & M University.
Received 18 December 1995; revised 26 November 1996.

1082–0132

Table 1. Commercial lactase preparations.

Tabla 1. Preparados de lactasa comerciales.

Source	Product	Supplier
Kluyveromyces lactis (optimum pH 6.8–7.0 optimum temp. 35–37 °C)	Lactaid	SugarLo Co.,Inc. Pleasantville, NJ, USA
	Maxilact LX 5000	Gist-Brocades NV Holland
	Lactozyme	Novo Industries Inc. Bagswaerd Denmark
Aspergillus sp. (optimum pH 3.0–7.0, optimum temp. 55 °C)	Lactase N (from *A. niger*)	GB Fermentation Products Co. Kingstree, SC, USA
	Lactase A (Takamine: from *A. oryzae*)	Miles Laboratories Elkhart, IN, USA
	Milk digestant (from *A. niger*)	Malabar Forumula, Cypress, CA, USA

Table 2. Commercial-over-the-counter lactose digestive aids.

Tabla 2. Preparados comerciales para la digestión de la lactosa de venta sin prescripción medica.

Source	Product	Supplier
Kluyveromyces lactis	Lactaid caplets	Lactaid, Inc. Pleasantville, NJ, USA
Aspergillus niger	Dairy Ease chewable tablets	Glenbrook Laboratories New York, NY, USA
Aspergillus oryzae	Lactrase capsules	Schwarz Pharmaceuticals Milwaukee, WI, USA
	Lactogest soft gel capsules	Thompson Medical Co., Inc. New York, NY, USA

with pancreatic enzymes. Rand (1981) reported an alleviation in lactose intolerance when milk was consumed along with enteric-coated β-galactosidase embedded in algin beads. Likewise, Mizote *et al.* (1978) successfully reduced diarrhoea in gastrectomized patients with lactase supplementation. Systematic studies for the sole purpose of helping lactose intolerant populations, however, were started by Solomons *et al.* (1982) in Guatemala. They demonstrated a 37% reduction in colonic lactose fermentation when β-galactosidase was added to milk prior to its consumption. This brief review focuses on the current available lactase replacement therapy strategies

LACTASE SUPPLEMENTS

Lactase preparations

Several enzyme preparations are available for substitution therapy for lactose maldigestors (Table 1) Two principal sources of food grade lactase are currently available: lactase from yeast, *Kluyveromyces lactis,* has optimum activity around neutral pH with maximum activity around 37 °C; lactase from the fungi *Aspergillus niger* or *A. oryzae* have optimum activity in an acidic environment with maximum activity at 55 °C. Table 2 lists the over-the-counter lactose digestive aids (enzymes) currently available.

Human studies with commercial oral supplements

The feasibility of effective enzyme replacement therapy for lactose intolerant individuals was demonstrated by Rosado *et al.* (1984). Figure 1 shows

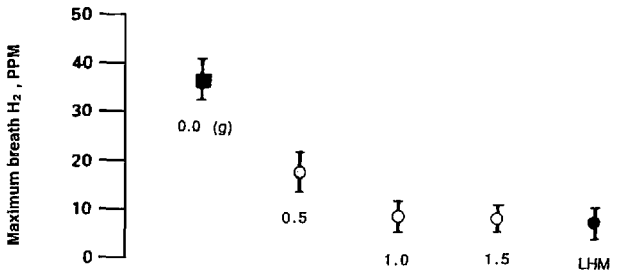

Figure 1. Breath hydrogen excretion as a function of consumption of graded levels of β-galactosidase (Lactaid) from *Kluyveromyces lactis* added to 360 ml of milk 5 min before consumption ($n = 13 \pm$ SEM). LHM, lactose hydrolysed milk (from Rosado *et al.*, 1984 with permission).

Figura 1. Hidrógeno eliminado en la respiración en función de cantidades crecientes de β-galactosidase (Lactaid) añadida a 360 ml de leche 5 minutos antes de su ingestión ($n = 13 \pm$ SEM). LHM, leche con lactosa hidrolizada (datos según Rosado *et al.*, 1984).

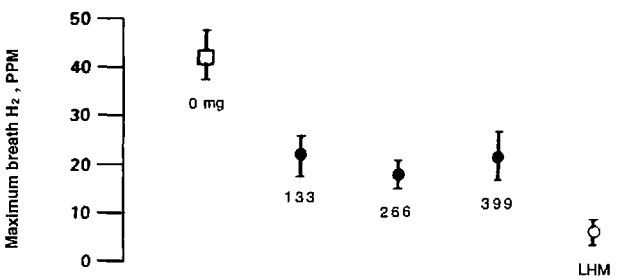

Figure 2. Breath hydrogen excretion as a function of consumption of graded levels of β-galactosidase (Lactase N) from *Aspergillus niger* added to 360 ml of milk 5 min before consumption ($n = 13 \pm$ SEM). LHM, lactose hydrolysed milk (from Rosado *et al.*, 1984, with permission).

Figura 2. Hidrógeno eliminado en la respiración en función de cantidades crecientes de β-galactosidase (Lactase N) de *Aspergillus niger* añadida a 360 ml de leche 5 minutos antes de su ingestión ($n = 13; \pm$ SEM). LHM, leche con lactosa hidrolizada (datos según Rosado *et al.*, 1984).

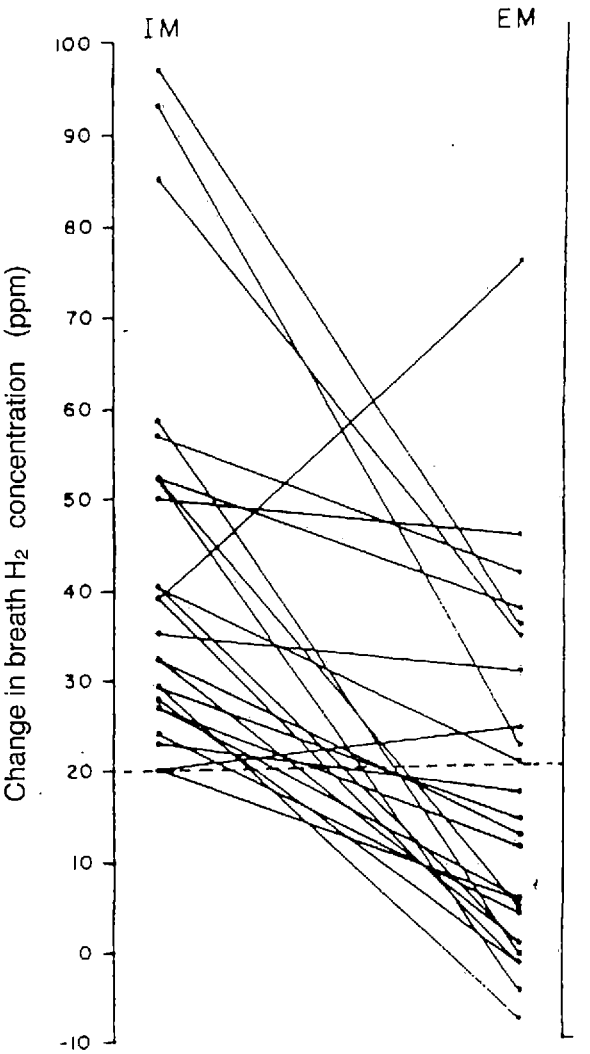

Figure 3. Change in breath hydrogen concentration in 25 lactose maldigestors after consuming intact milk (IM) or milk with added enzyme (EM), containing 1 g of Lactaid or 18 g of lactase (from Rosado *et al.*, 1984, with permission).

Figura 3. Variación de la concentración de hidrógeno eliminado en la respiración en 25 individuos con mala digestión de lactosa después de ingerir leche intacta (IM) o con adición de enzimas (EM), conteniendo 1 g de Lactaid o 18 g de lactasa (datos según Rosado *et al.*, 1984).

maximum breath hydrogen excretion as a function of consumption of graded levels of β-galactosidase (Lactaid) added to 360 ml of milk, 5 min before consumption by 13 lactose malabsorbers. Addition of 0.5 g of Lactaid to milk reduced peak hydrogen excretion substantially. Increasing the level of Lactaid further reduced the levels of breath hydrogen excretion (Figure 1). However, with 1.0 g of Lactaid, 23% of individuals still showed a maximum increase in breath hydrogen concentration of ⩾ 20 ppm; similarly with a 1.5 g dose, 15% of subjects had a positive breath hydrogen test result. Figure 2 shows the mean

Table 3. Number of subjects reporting symptoms of lactose intolerance after consuming two preparations of lactase added to 360 ml of milk 5 min before consumption. Data from Rosado *et al.* (1984); $n = 13$

Tabla 3. Número de individuos que presentaron sintomas de intolerancia a la lactasa después de consumir dos preparados de lactasa, añadidos a 360 ml de leche 5 minutos antes de su ingestión (según datos de Rosado *et al.*, 1984; $n = 13$).

Lactase preparation	Dose Lactaid (g)/Lactase N (mg)				
	0.0/0.0	0.5/133	1.0/266	1.5/399	LHM[a]
Lactaid	11	9	3	2	3
Lactase N	10	7	5	4	1

[a] Lactose-hydrolysed milk (> 90% lactose-hydrolysed)

Table 4. Milk products (20 g lactose) and lactose maldigestion. Data from Onwulata *et al.* (1989).

Tabla 4. Productos lácteos (20 g de lactosa) y la mala digestión de la lactosa (según datos de Onwulata *et al.*, 1989).

Product	Peak breath H_2 (ppm)	Flatulence[a]
Whole milk (WM)[b]	40	8
Yogurt	2	0
Lactose-hydrolysed milk (LHM)	12	0
Lactaid tablet + WM (756 FCC units/subject)	20	3
Sweet acidophilus milk	41	6

[a] No. of subjects out of 10 reporting symptoms.

[b] Treatments significantly different ($p < 0.05$)

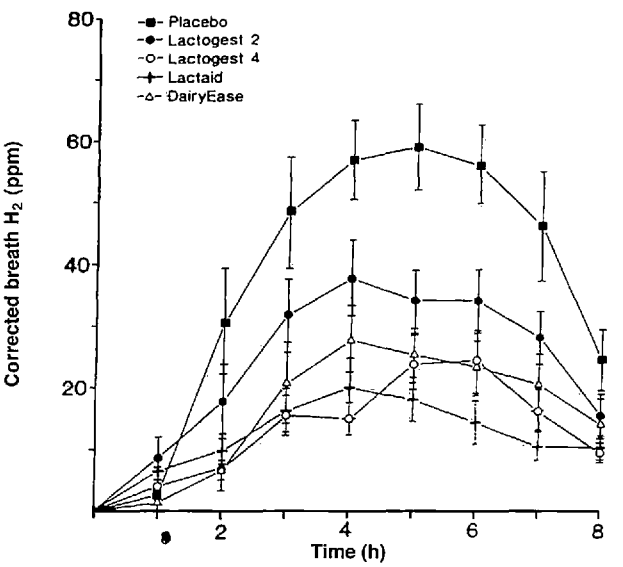

Figure 4. Temporal changes in breath hydrogen excretion in 20 lactose maldigestors in Minnesota after consuming 400 ml of 2% milk together with various lactose digestive aids (6,000 IU of lactase; 3,000 IU as two capsules of Lactogest) (from Lin *et al.*, 1993, with permission).

Figura 4. Variación con el tiempo del hidrógeno eliminado en la respiración con 20 individuos malos digestores de lactosa después de consumir 400 ml de leche al 2% con diferentes aportes de preparados para la digestión de la lactosa (6000 IV de lactasa; 3000 IN en el caso de las dos cápsulas de Lactogest). Datos según Lin *et al.*, 1993.

maximum breath hydrogen concentration after consumption of Lactase N added to 360 ml of milk 5 min before consumption. The digestive efficiency of Lactase N (fungal β-galactosidase) was less than that of Lactaid (yeast β-galactosidase) (Figure 1). Even after consuming a maximum dose of Lactase N, 30% of the subjects reported symptoms of lactose intolerance (Table 3). In another experiment, Rosado *et al.* (1984) observed that 10 of 25 Mexican lactose malabsorbers excreted > 20 ppm of breath hydrogen after consuming 360 ml of milk treated for 5 min with 1 g of Lactaid prior to consumption (Figure 3). From this study it would thus appear that the oral supplements are useful in alleviating lactose intolerance. However, a small population did not respond to the enzyme replacement therapy, which may be due to the lack of sufficient enzymes in the milk. In subsequent studies (Solomons *et al.*, 1985; Barillas and Solomons, 1987; Moskovitz *et al.*, 1987; DiPalma and Collins, 1989; Onwulata *et al.*, 1989) oral supplements of lactase proved to be helpful to various degrees in alleviating lactose maldigestion.

In our laboratory, we compared the efficacy of various milk products including the oral digestive aid, Lactaid, in alleviating lactose maldigestion (Onwulata *et al.*, 1989). Lactaid tablets (756 FCC units), when consumed with whole milk containing 20 g of lactose, reduced the peak breath hydrogen and symptoms significantly in 10 lactose maldigestors (Table 4). However, 30% of the subjects consuming Lactaid still reported flatulence. A more comprehensive study involving comparison of various commercial over-the-counter lactose digestive aids was recently reported by Lin *et al.* (1993). This study was conducted in two locations (Mobile, AL and St. Paul, MN) and compared the efficiency of Lactogest (soft gel

Table 5. Effect of ice cream (18 g of lactose) and lactase (9900 FCC units) consumption on breath hydrogen (ppm) excretion. (Data from Ramírez *et al.*, 1994).

Tabla 5. Efecto de la ingestión de helado (18 g lactosa) y lactasa (9900 FCC unidades) sobre la excreción de hidrógeno respiratorio (según datos de Ramírez *et al.*, 1994).

Test meal	Peak H_2	Cumulative H_2
Ice cream + placebo	30 ± 10	85 ± 32
Ice cream + Lactaid	2 ± 1[a]	4 ± 2[b]
Ice cream + Lactrase	22 ± 6	54 ± 16
Ice cream + Dairy Ease	24 ± 7	61 ± 21

[a] Significantly different from placebo ($p \leq 0.03$)

Table 6. Effect of ice cream (18 g lactose and lactase (9900 FCC units) consumption on gastrointestinal symptoms. Data from Ramírez *et al.* (1994)

Tabla 6. Efecto de la ingestión de helado (18 g de lactosa) y lactasa (9900 FCC unidades) sobre ciertos síntomas gastrointestinales (según los datos de Ramírez *et al.*, 1994).

Test meal	Max. pain	Max. gas
Ice cream + placebo	0.7 ± 0.26	1.2 ± 0.24
Ice cream + Lactaid	0.4 ± 0.22	0.8 ± 0.24
Ice cream + Dairy Ease	0.3 ± 0.15[a]	1.2 ± 0.29
Ice cream + Lactrase	0.2 ± 0.13[a]	0.5 ± 0.22

Symptoms scored: 0 = none; 1 = mild; 2 = moderate; 3 = severe

[a] Significantly different from placebo ($p < 0.05$)

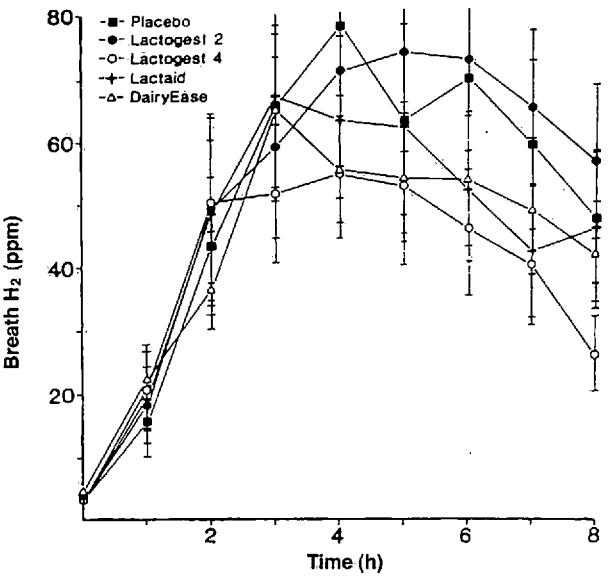

Figure 5. Temporal changes in breath hydrogen excretion in 11 lactose maldigesters in Mobile, Alabama after consuming 50 g of lactose with various lactose digestive aids. See Figure 4 for lactase dose (from Lin *et al.*, 1993, with permission).

Figura 5. Variación con el tiempo del hidrógeno eliminado en la respiración con 11 individuos mal digestores de lactosa después de la ingestión de 50 g de lactosa con varios preparados para la digestión lactosa (datos según Lin *et al.*, 1993). Ver Figura 4 para las dosis de lactasa.

capsules) from Thompson Medical Co., Inc., Lactaid (caplets) from Lactaid, Inc., and Dairy Ease (chewable tablets) from Glenbrook Laboratories, in alleviating lactose maldigestion. All enzyme preparations reduced significantly both peak (Figure 4) and total breath hydrogen secretion when given with milk containing 20 g lactose. In the case of Lactogest, the response was stoichiometric with respect to dose (two capsules vs four capsules). However, both for Lactogest and for Dairy Ease, the peak production of breath hydrogen was > 20 ppm, signifying incomplete lactose digestion. Even for Lactaid, it is evident from standard errors of mean (Figure 4) that a sizeable number of participants excreted more than 20 ppm breath hydrogen. When 50 g of lactose in water was given with 6000 units of any enzyme, the effect on small intestinal lactose digestion was minimal as measured by breath hydrogen concentration (Figure 5). More recently, Ramírez *et al.* (1994) demonstrated differing capabilities of over-the-counter lactase preparations in improving lactose digestion. In this randomized, placebo-controlled trial, 10 healthy lactose intolerant volunteers were challenged with ice cream containing 18 g of lactose together with Lactrase, Dairy Ease or Lactaid (9900 FCC lactase units). Only Lactaid reduced peak breath hydrogen excretion to less than 20 ppm (Table 5), while only Dairy Ease and Lactrase influenced symptoms significantly (Table 6).

From the available data it is evident that oral supplements of lactase are, in general, effective in improving lactose digestion and reducing lactose intolerance symptoms. However, a few individuals do not seem to respond to the exogenous source of enzyme, possibly due to very low levels of endogenous residual lactase. Future research should shed some light on possible subpopulations with very low levels of residual lactase; such subpopulations may need higher levels of exogenous lactase than currently recommended.

Cost of lactase digestive aids

The maximum cost for consuming 240 ml of milk together with the recommended maximum dose of lactase goes up by 100–150% ($0.41–0.59) compared with the cost of consuming milk alone ($0.19–0.23), while the cost of lactose-hydrolysed milk is approximately twice as much as intact milk ($0.36–0.38) (Data from Suárez *et al.*, 1995). Empirical experience shows that prohibitive cost could be one of the reasons why lactose-reduced milk or exogenous lactase supplements are under-used. Cost-reduction research might, therefore, increase the utilization of these aids.

FINAL REMARKS

Exogenous lactase preparations, in general, appear to be effective in improving lactose digestion. Several over-the-counter microbial β-galactosidase preparations are available. The efficacy of these preparations seems to be variable. There are two considerations that may be important in recommending exogenous lactase oral supplements for lactose intolerant individuals: (*i*) there is possibly a subpopulation of lactose maldigesters that either does not respond to or needs a higher dose level of exogenous lactase, and (*ii*) the cost of digestive aids may be a factor in consumer acceptance of these oral supplements.

REFERENCES

Barillas C. and Solomons N.W. (1987). Effective reduction of lactose maldigestion in preschool children by direct addition of β-galactosidase to milk at meal time. *Pediatrics* **79**: 766–772.

DiPalma J.A. and Collins M.S. (1989). Enzyme replacement for lactose malabsorption using beta-D-galactosidase. *Journal of Clinical Gastroenterology* **11**: 290–329.

Kobayashi A., Kawai S., Ohbe Y. and Nagashima Y. (1975). Effects of dietary lactose and a lactase preparation on the intestinal absorption of calcium and magnesium in normal infants. *Journal of Clinical Nutrition* **28**: 681–683.

Lin M., DiPalma J.A., Martini M.C., Gross C.J., Harlander S.K. and Savaiano D.A. (1993). Comparative effects of exogenous lactase (β-galactosidase) preparations *in vivo* lactose digestion. *Digestive Diseases Science* **38**: 2022–2027.

Mizote H., Terasaki S., Ryu T. *et al.* (1978). Clinical study of lactose intolerance after gastrectomy. *Kuremi Medical Journal* **25**: 295–300.

Moskovitz M., Curtis C. and Gavalier, J (1987). Does oral enzyme replacement therapy reverse intestinal lactose malabsorption? *American Journal of Gastroenterology* **82**: 632–635.

Onwulata C.I., Rao D.R. and Vankineni C.P. (1989). Relative efficiency of yogurt, sweet acidophilus milk, hydrolyzed-lactose milk and a commercial lactase tablet in alleviating lactose maldigestion. *American Journal of Clinical Nutrition* **49**: 1233–1237.

Ramírez F., Lee K. and Graham D. (1994). All lactase preparations are not the same: Results of a prospective, randomized, placebo-controlled trial. *American Journal of Gastroenterology* **89**: 566–570.

Rand A.G., Jr. (1981). Enzyme technology and the development of lactose-hydrolyzed milk. In: Paige D.M. and Baylesa T.M. (eds), *Lactose digestion: Clinical and nutritional implications*. Baltimore: Johns Hopkins University. pp. 219–30.

Rao D.R., Pulusani S.R. and Chawan C.B. (1985). Role of fermented milk products in milk intolerance and other clinical conditions. *Advances in Nutrition Research* **7**: 203–219.

Rosado J.L., Solomons N.W., Lisker R. and Bourges, C.H. (1984). Enzyme replacement therapy for primary adult lactase deficiency: Effective reduction of lactose malabsorption and milk intolerance by direct addition of β-galactosidase at meal time. *Gastroenterology* **87**: 1072–1082.

Sahi T., (1994). Hypolactasia and lactase persistence: Historical review and the terminology. *Scandinavian Journal of Gastroenterology*, **29** (suppl, 202): 1–6.

Simoons F.J., (1970). Primary adult lactose intolerance and the milking habit: A problem in biological and cultural interrelations. II. A cultural historical hypothesis. *American Journal of Digestive Diseases* **15**: 695–710.

Solomons N.W., Guerrero A.M. and Torun B. (1982). *In vivo* intragastric hydrolysis of milk by a β-galactosidase: A potential approach to symptomatic milk intolerance in primary lactase deficiency (abstract). *Federal Proceedings* **41**: 750.

Solomons N.W., Guerrero A.M. and Torun B. (1985). Effective *in vivo* hydrolysis of lactose by beta-galactosidase in the presence of solid foods. *American Journal of Clinical Nutrition* **41**: 222–227.

Suarez F.L., Savaiano D.A. and Levitt M.D. (1995). A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *New England Journal of Medicine* **333**: 1–4.