Annu. Rev. Nutr. 1989. 9:161–86

SUGAR ALCOHOLS AS BULK SWEETENERS

William L. Dills, Jr.

Department of Chemistry, Southeastern Massachusetts University, North Dartmouth, Massachusetts 02747

CONTENTS

INTRODUCTION

Scope of this Review

This review considers polyols as bulk sweeteners, i.e. substances used to replace sucrose in food manufacture and in the household setting to provide sweetness and body or bulk to foods and beverages. Although numerous polyols have been examined, only the six in which commercial interest is the greatest are considered here in detail: the monosaccharide polyols sorbitol,

0199-9885/89/0715-0161$02.00

mannitol, and xylitol; the disaccharide polyols maltitol and lactitol; and an equimolar mixture of two disaccharide polyols, D-glucosyl-α(1-1)-D-mannitol and D-glucosyl-α-(1-6)-D-glucitol, that is denoted Palatinit®. Maltitol is the major component of two additional products discussed along with maltitol: Malbit® (79.9–88.4% maltitol) and Lycasin® (53.8% maltitol); these products also contain sorbitol, maltotriitol, and other minor components. The interest in alternatives to sucrose has resulted in extensive research on the polyols in recent years (9, 12–14, 53, 87, 101, 104, 107, 108, 148, 169, 180). For aspects covered in other appropriate reviews, the reader is referred to those reviews and given capsule summaries here. In general, clinical uses of the polyols are not discussed.

The reasons for the great interest in the polyol sweeteners follow:

1. Their intrinsic sweetness is of the same order of magnitude as that of sucrose. This point is discussed below.

2. They are easily manufactured, as discussed in earlier reviews.

3. Sugar consumption has a number of real and perceived side effects (see review 54). In this regard, three potential advantages of the polyols have been noted (e.g. 180):

a. For a large portion of the general population, the use of polyols may potentially reduce the incidence of dental caries. This topic has been reviewed in detail for xylitol (13, 104, 107, 108) and to a lesser extent for the other polyols (107, 180).

b. Some polyols have reduced caloric content, a quality of potential interest in the management of obesity. The basis of this reduced caloric content differs for various polyols and is discussed below. Also considered below is that this reduced caloric content may be more apparent than real when the relative sweetness is also considered.

c. The polyols in general yield glucose at a slower rate than dietary glucose or sucrose, which results in flattened blood glucose curves. This point is of interest and perhaps value to diabetics. The particular applications involving the use of polyols as sucrose substitutes for diabetics are not discussed in this review; interested readers are referred to reviews on this specific topic and to earlier reviews on the polyols.

Current Regulatory Status

Sorbitol is a direct food substance generally regarded as safe (GRAS). If consumption of a sorbitol-containing food is likely to result in a daily ingestion of more than 50 g, the label must contain the statement "Excess consumption may have a laxative effect." Mannitol is a food additive permitted on an interim basis pending further study. The same label noted above for sorbitol must be applied to any mannitol-containing food that could conceivably result in the ingestion of 20 g or more of mannitol in a single day. Both mannitol and sorbitol are widely used in food manufacture in the US.

Xylitol is a food additive permitted for special dietary or nutritional uses provided that the amount used is not in excess of that needed to produce the intended effect. A proposed revocation was never finalized and is still pending. A select panel of experts was recently convened by the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology under contract to the FDA to consider the scientific evidence regarding xylitol (see review 101). The present use of xylitol in the United States is limited.

Lactitol, maltitol, and the maltitol-containing product Lycasin are the subjects of GRAS petitions received and filed by the FDA. The same panel of experts noted above for xylitol also considered lactitol in their deliberations (101). A petition concerning Palatinit has also been received by the FDA but had not been filed as of winter, 1989.

National food laws and regulations differ from country to country and so, too, does the status and use of individual polyols (see 12 regarding xylitol for example). No attempt is made here to summarize the status of polyols as food additives in countries other than the US. It appears that each of the polyols discussed herein is either utilized or has at least been petitioned for specific commercial applications in some European nations.

Comparative Sweetness of the Polyols

The majority of simple sugars and polyols elicit a taste response characterized as "sweet." Because of the interest in sucrose substitutes, a wide variety of compounds have been subjected to tests of comparative sweetness. The values reported for the sweetness of all compounds, including sucrose and the polyols, are based on subjective assay methods, and results vary with assay conditions. Slopes of the sweetness-concentration lines differ for different sweeteners, and the relationships are not always linear as can be seen in the report by Hoppe & Gassmann (78) for a wide variety of sweeteners, including several polyols. Furthermore, sweetness values for different compounds are differentially influenced by temperature, as seen, for example, in the results of Hyvönen et al (82) in a detailed study of the sweetness of fructose, glucose, and xylitol. Nevertheless the results reported by different groups in comparative sweetness studies on the polyols are quite consistent (38, 78, 113, 180). On the basis of sweetness per gram, considered here is xylitol, which is generally reported as being "isosweet" with sucrose. Sorbitol, mannitol, and maltitol and the maltitol products were somewhat less sweet, with values ranging from 45 to 90% of the sweetness of sucrose. Lactitol and Palatinit were the least sweet, with sweetness values reported from 25 to 50%.

Of greater potential interest with regard to the use of polyols as bulk sweeteners are the sweetness values as expressed per kilocalorie of available metabolic energy. Values for kcal/g vary depending on the dosage and

experimental animal used, and few comparative studies are available. Results are probably best reviewed by Ziesenitz & Siebert (180). In humans, sorbitol and xylitol are reported as having caloric contents similar to that of sucrose, although high doses will most certainly result in decreased caloric values because these polyols are incompletely absorbed at higher dietary levels. Other polyols have reduced caloric values ranging from 40 to 70% of those reported for sucrose. For mannitol the reduced value probably reflects the incomplete metabolism of mannitol by L-iditol dehydrogenase and the incomplete reabsorption of mannitol by the kidney (for review see 169). For the disaccharide polyols, the low caloric values reflect slow rates of hydrolysis in the digestive tract and the involvement of intestinal microflora, as discussed below and in the review by Ziesenitz & Siebert (180). In any case, the polyols with reduced caloric contents tend to be those with reduced sweetness compared with sucrose, so that when sweetness is expressed per kcal, the six polyols are actually quite similar.

ABSORPTION AND METABOLISM OF THE POLYOLS

Monosaccharide Polyols

The absorption and metabolism of the monosaccharide polyols are thoroughly reviewed elsewhere and only summarized here. Sorbitol, mannitol, and xylitol are all absorbed from the digestive tract by passive diffusion and therefore enter the circulation less rapidly than do glucose or fructose. A portion of the ingested polyol, particularly at high doses, reaches the lower digestive tract, with the resulting involvement of the intestinal flora. In laboratory animals and humans, large doses result in diarrhea, although adaptation involving changes in intestinal flora frequently occurs over time. Some investigations have reported that xylitol is better tolerated than are the hexitols. In mice and rats, high levels of dietary monosaccharide polyol are associated with the cecal enlargement characteristic of any slowly absorbed carbohydrate, and in humans there are the increases in breath hydrogen or methane characteristic of colonic microfloral involvement.

The first step in the metabolism of all three monosaccharide polyols involves oxidation by the hepatic L-iditol dehydrogenase to the corresponding 2-ketose, D-fructose for sorbitol and mannitol and to D-xylulose for xylitol. For sorbitol and xylitol this oxidation is extensive, and only small quantities of polyol are excreted in the urine. Mannitol is a poor substrate for the enzyme, and significant portions of ingested mannitol are excreted. Most of the fructose and xylulose thus formed are phosphorylated by fructokinase and xylulokinase, respectively. The subsequent metabolism of the resulting phosphate esters by the fructose and pentose shunt pathways, respectively, is well documented. For xylitol a minor pathway has been proposed (19, 84) that

involves the phosphorylation of D-xylulose to xylulose-1-phosphate by fructokinase. This pathway does not play a major role in the overall metabolism of xylitol but may play a role in the relationship between xylitol and oxalate and is thus discussed below (see "Xylitol and Oxalate").

Disaccharide Polyols

Disaccharide polyols are mostly digested to hexoses and monosaccharide polyols, which are then absorbed. Traces of the intact disaccharide polyols are absorbed as evidenced by the small but measurable quantities of each recovered in the urine of rats and humans following ingestion (Table 1). In this regard Hosoya (79) demonstrated the transport of labelled maltitol in everted sacs of rat intestine.

Hydrolysis of the disaccharide polyols by the saccharidases of the intestine and other tissues has been studied extensively. Early studies performed with human salivary α-amylase and α-glucosidase from the small intestine of humans (172) and rats (173, 179) demonstrated that maltitol was a poor substrate and a weak inhibitor for these enzymes. Similar results were reported for the intestinal α-glucosidase and the two polyols of Palatinit (57). These results with maltitol have been confirmed and extended with highly purified preparations of the enzyme from rats (134). The relative maximal rates of hydrolysis for sucrose, maltose, maltitol, glucosyl-(1-1)mannitol, glucosyl-(1-6)glucitol, Palatinit, and Malbit were 280, 900, 112, 32, 67, 35, and 250–310 nmol/min/mg protein, respectively (57, 179). Tsuji et al (162) observed that the relative rates of hydrolysis of several of these compounds corresponded to their bioavailability as measured by the transmural potential differences produced by the Na^+-dependent glucose transport in rat everted jejunal sac preparations. Most recently the rates of hydrolysis of disaccharides and dissaccharide polyols were compared using human intestinal biopsies. Average rates of hydrolysis for maltose, sucrose, lactose, maltitol, Palatinit, and lactitol were 172, 42.9, 20.2, 19.1, 2.5, and 0.34 μmol/min/g respectively at 37°C. Furthermore, maltitol and Palatinit but not lactitol inhibited glucose release approximately 25% from maltose when present at the same concentration as the disaccharide (116).

The saccharidase hydrolysis products can be either absorbed directly or metabolized subsequently by the intestinal flora. Absorption of the hexitol products was discussed above and is apparent from the free hexitols measured in the urine (Table 1) and the blood (147) following disaccharide polyol ingestion. The glucose formed from maltitol or Palatinit and the galactose formed from lactitol are rapidly absorbed into the blood stream, as evidenced in the small but detectable rises in blood glucose in rats consuming Palatinit (114) and in humans consuming maltitol (94, 147) or Palatinit (150, 157) and by the rise in blood galactose in humans ingesting lactitol (175).

Table 1 Excretion of the disaccharide polyols in rats and humans

Polyol (Ref.)	Subject	Dose[a]	Polyol excreted in[b]			
			Urine		Feces	
			unchanged	hexitol	unchanged	hexitol
Palatinit (178)	rat	5% diet	0.11	0.09	6.0	8.3
	rat	10% diet	0.04	0.04	7.8	9.4
	rat, germ-free	5% diet	89	0.94	50	2.0
	rat, germ-free	10% diet	114	3.42	275	1.4
Palatinit (114)	rat	5% diet	n.r.	n.r.	18.7	21.3
Maltitol (94)	rat	1.0 g	~25	<5	~50	~15
	rat, germ-free	1.0 g	~210	~15	~90	~20
Maltitol (98)	rat	1.0 g	8	0.6	5	3
	rat	2.0 g	15	2	144	180
	rat	2.0 g	18.9	0.08	46.6	10.0
	rat, germ-free	2.0 g	211.6	10.4	86.5	13.1
Lactitol (95)	rat	2 mg	0.0	0.23	0.0	0.14
Palatinit (150)	human	50 g	n.r.	n.r.	n.r.	78
	human	100 g	n.r.	n.r.	n.r.	94
Maltitol (147)	human	3× 10 g	350–400	422	33	21
Lactitol (175)	human	50 g	n.r.	n.r.	n.r.	33 mg/dL

[a] Single doses were administered by stomach tube.
[b] In mg/24 h unless indicated. The notation n.r. indicates that data were not reported.

The importance of the intestinal flora in the metabolism of the disaccharide polyols is supported by several lines of evidence. First, the excretion patterns for disaccharide polyols and their hexitol products in normal and germ-free rats (Table 1) strongly support intestinal flora involvement. For maltitol and Palatinit, significantly more mono- and disaccharide polyol occurs in urine and feces of the germ-free animals than in comparable normal animals when fed the disaccharide polyols. Second, in rodents lactitol (135, 167), maltitol (79), and Palatinit (114, 178) cause cecal enlargement attributable to slowly absorbed carbohydrate. Third, the formation of hydrogen gas in humans has been studied with Palatinit (47) and with lactitol (56, 166). This gas formation is usually considered to indicate colonic involvement in metabolism. Fourth, a significant conversion of maltitol into fatty acids was observed in rat and human feces, which indicates that this polyol was fermented in the gastrointestinal tract (125). Last, the caloric values for lactitol (23, 45, 166), maltitol (79, 92, 125), and Palatinit (57, 94, 114, 157) were less than those for sucrose in animals and humans (see also 180 and references therein), probably a reflection of the microfloral utilization. In this regard Ziesenitz (177) has performed some interesting experiments with the carbohydrate-deficient diet assay system of Karimzadegan et al (89), which allows one to evaluate how a particular dietary component is available as carbohydrate. Mannitol, sorbitol, D-glucosyl-α(1-1)-D-mannitol, and D-glucosyl-α(1-6)-D-glucitol were metabolized to the extent of 6, 20, 39, and 42% as carbohydrate, respectively. The differences between these values and the percentage utilization values will ultimately be useful in evaluating the availability of fatty acids formed during cecal fermentation.

The major saccharide absorption products from the disaccharide polyols appear to be hexitol, hexose, and unchanged disaccharide polyol (Table 1). The metabolism of the hexitol portions was discussed briefly above, and the metabolic pathways for galactose (from lactitol) and glucose (from maltitol and Palatinit) are well known and need not be discussed here. The disaccharides are nearly inert as judged by their excretion in the urine following injection (92, 150) and by the fact that they are non- or poor substrates for L-iditol dehydrogenase (114) or aldose reductase (41).

POLYOL SWEETENERS AND DENTAL CARIES

Recent reviews describe the extensive work done on the relationship of polyols, especially xylitol, and dental caries (13, 104, 107, 108, 180). The most recent material is summarized below.

Dental caries is mediated by bacteria that accumulate in large masses and contribute to dental plaque. Accumulation of these bacteria is facilitated by the extracellular biosynthesis of insoluble glucans that increase cellular

adhesive properties and serve as a matrix for plaque formation. Fermentation of common dietary carbohydrate by plaque bacteria acidifies the plaque milieu, dissolves calcium and phosphate from the tooth enamel, and eventually forms a cavity. Dietary sucrose is believed to play a major role in caries formation (see reviews 54, 142). Polyol sweeteners can help prevent dental caries by inhibiting the fermentation of dietary carbohydrate and the formation of insoluble glucan. In general, all of the polyol sweeteners are significantly less cariogenic than sucrose, and xylitol may actually be cariostatic or anticariogenic.

Sorbitol and Mannitol

There is particular interest in sorbitol, as it has long been used as a humectant and binding agent to enhance the texture and shelf-life of dentifrice products (110). Sorbitol and mannitol are slowly fermented by oral microorganisms, and this decreases the acidification of the plaque. Long-term use of sorbitol may lead to metabolic adaptation by the oral microflora, and even traces of glucose have been reported to repress sorbitol metabolism. Formation of the soluble and insoluble polysaccharides of *Streptococcus mutans* was considerably less with sorbitol than with sucrose or fructose, and decreased adhesiveness of the microbial cells to glass surfaces has been observed.

In studies of rats under various conditions, dietary sorbitol and mannitol showed significantly less cariogenic activity than sucrose. In humans, the low cariogenicity of sorbitol appears to be supported by the beneficial results of good oral hygiene, which frequently involves a dentifrice containing sorbitol (e.g. 110).

Xylitol

Xylitol is fermented only very slowly by oral bacteria and is generally not catabolized into acid products. Oral microflora do not appear able to acquire the ability to utilize xylitol.

Animal studies have shown that rats fed xylitol had a low incidence of caries, significantly below that of rats fed other polyols, which was in turn below that of rats fed sucrose. The question as to whether xylitol was merely noncariogenic or was actively anticariogenic was studied in several laboratories. In general the results showed that under certain conditions xylitol significantly reduces the cariogenic potential of sucrose. In humans much work has been done with xylitol and is reported in the reviews cited earlier. In general the conclusions reached in the extensive Turku sugar studies (145) concerning xylitol's cariostatic or anticariogenic properties were confirmed in more recent studies in Thailand (16), Hungary (143, 144), and French Polynesia (16, 88).

MECHANISMS OF THE CARIOSTATIC EFFECTS OF XYLITOL The cariostatic or anticariogenic effects of xylitol are quite complex. It appears that more than one mechanism exists. It is not known at this time which of the effects noted below are clinically relevant. Much of this material can be found in the earlier review by Mäkinen & Scheinen (108) and other more recent reviews (13, 107).

On the microbial level, xylitol may produce its anticariogenic effects by several processes. In addition to being slowly fermented by oral bacteria, xylitol inhibits the acid formation from glucose in *S. mutans* much more effectively than any other polyol (180). In *S. mutans* and other oral bacteria the first metabolic step in the utilization of many polyols involves a phosphoenolpyruvate-dependent phosphorylation step linked to polyol or sugar uptake rather than a dehydrogenation reaction (124, 127). These phosphorylation-uptake systems involve several proteins, and the transport protein components are responsible for the substrate specificity of the process (124, 127). Quite probably, polyols exert some of their inhibitory effects on acid production in this phosphorylation-uptake process. In addition certain oral bacteria apparently may convert xylitol to a toxic metabolite, namely xylitol-5-phosphate (4, 73, 159, 161). Adaptation to xylitol leads to xylitol-resistant strains of bacteria, however (50, 160), even though cariostatic effects remain (20, 110).

Xylitol also inhibits the formation of the insoluble polysaccharides of *S. mutans,* although the synthesis of the soluble polysaccharides is increased by xylitol (154). The changes in polysaccharide synthesis in the presence of xylitol resulted in a decrease in the adhesive properties of the bacteria. The synthesis of the insoluble polysaccharides by *S. mutans* appears to involve multiple extracellular glucosyl transferases (59). Some of these enzymes are inhibited by polyols (G. Siebert and F. Frosthuber, unpublished observations cited in 180), although xylitol exerted only slight inhibitory effects in their system (G. Siebert, personal communication).

Most recently, Beckers (20) studied the growth and metabolism of xylitol-sensitive and xylitol-resistant mutants of *S. mutans*. While differences in colony establishment time in vivo and growth rate in vitro could be observed, the formation of fissure caries lesions was inhibited by xylitol regardless of whether the xylitol-resistant or xylitol-sensitive strain was used. This result suggests that some of the anticariogenic properties of xylitol may be independent of oral microflora. Specific changes in salivary parameters occur in response to xylitol and may play a role in the natural defenses against dental caries. Many were observed during the original Turku sugar studies (145) and are noted extensively in review articles (13, 104, 107, 108). Among the changes observed in saliva are increases (*a*) in volume produced by sweeteners and more specifically in glycine and the basic amino acids, (*b*) in total

salivary protein, (*c*) in the activities of saccharidases and other enzymes, and (*d*) in the level of thiocyanate ion—all of which may play a role in the natural defense against caries. More recently an increase in ammonia has also been noted to occur concomitantly with the decrease in lactic acid formation (105, 155).

Last, the physical chemical properties of xylitol may be involved. Polyols in general protect proteins from denaturation (see review in 105), a factor that may play a role in changes in the salivary environment noted above. Xylitol and other polyols also form strong calcium complexes (105, 109) that prevent the precipitation of calcium phosphate. Xylitol did not enhance the rehardening of surface-softened enamel under conditions favoring rehardening (152). On the other hand, high xylitol concentrations prevented the demineralization of enamel in vitro (2). In vivo the same effect was observed on surface enamel but not in fissures (153). This latter effect was attributed to the absence of plaque on the enamel surface.

Disaccharide Polyols

Only recently have the disaccharide polyols been considered sweeteners; as a result they have not been subject to the same scrutiny as have the monosaccharide polyols. The disaccharide polyols all appear to be less cariogenic than sucrose and possibly also less than the hexitols (see reviews 107, 180). In bacterial studies they are fermented slowly by oral microflora (22, 43, 52, 163). They reduced the incidence of caries in laboratory animals (51, 52, 55, 74, 90, 91, 164, 165) and, in the few studies performed thus far, in humans (24). With regard to the mechanisms of their effects, the disaccharide polyols, besides being slowly fermented by oral bacteria, appear to inhibit acid production from glucose (180 and references therein).

PHYSIOLOGIC AND TOXICOLOGIC EFFECTS OF THE POLYOLS

Numerous studies have been performed with the polyols in animals and humans. The sections below discuss new information obtained in certain areas and recent work on the reported occurrence of tumors in laboratory animals consuming polyol-containing diets. For the purpose of discussion, the effects are divided into those reported for many if not all of the polyols in question and those unique to individual polyols. Note that in general polyols have low toxicities and mutagenicities as discussed in earlier reviews.

Effects Common to Many of the Polyols

EFFECTS OF POLYOLS ON MINERAL METABOLISM When 20% dietary xylitol, mannitol, or galactitol are included in rat diets, urinary calcium

excretion increases (46, 65, 140). Similarly, the presence of 10% sorbitol in mouse diets results in an increase in the levels of blood calcium and in calcium excretion (103). This increased calcium excretion stemmed from increased dietary calcium absorption and not loss of skeletal calcium (67). Similar effects were observed with lactitol (1, 9, 101). Earlier investigations had reported that other slowly absorbed carbohydrates such as lactose (21, 42, 77, 96) and the modified starches (37, 77, 93; see review 100), but not the nonabsorbable carbohydrates found in fiber (see review 99), also increased calcium absorption in rats. The effects of lactose on calcium absorption have also been noted in humans (34, 176), although the effects are considerably smaller than in rats.

The absorption of other minerals is enhanced by polyols in the diet. In rats fed diets with high polyol levels, an increase in iron absorption has been observed (62, 63, 65, 75). With sorbitol, a similar effect was reported in humans (58, 102). In the rat the increase in iron absorption was accompanied by an increase in duodenal xanthine oxidase and ferroxidase (64). Also, dietary xylitol increases the absorption of dietary lead in female mice but not in male mice or cockerels (115). Last, in mice but not rats, dietary xylitol increased the intestinal absorption and urinary excretion of oral oxalate (136, 139).

For purposes of discussion the effects are treated here as if similar mechanisms operate for each of the metal ions and as if the effects produced by lactose, starches, and the polyols are the same. Most of the mechanistic work has been performed with calcium, for which there are two independent uptake processes: a physiologically regulated, vitamin-D-regulated transcellular process and a nonsaturable, vitamin-D-independent process (30, 171). A variety of evidence supports the statement that slowly absorbed carbohydrates affect the nonsaturable process. First, the lactose effect was observed to occur in the ileum (96), where calcium is absorbed only by the nonsaturable process (122). Second, the xylitol (67) and lactose (112) effects are vitamin D independent. Third, the levels of carbohydrate needed to produce the effect are high enough to cause the cecal enlargement in rodents that occurs when unabsorbed carbohydrate is present in the lower intestine (see references above and 121).

Outside of this conclusion, the mechanisms by which the polyol-lactose effects are produced are not clear. Several possible mechanisms for the effects of polyols and lactose on mineral absorption have been reviewed (101, 128–130); they include complex formation involving the mineral in question and the polyol or sugar (32, 61, 109), the removal of an energy barrier to calcium movement (70), changes in the transport potential of the intestine (111), changes in luminal calcium concentrations due to water absorption (117, 174), the mechanical extension of the intestine by the hyperosmolar

polyol solution in the intestinal lumen (101), and the acidification of the intestinal contents (1). Any and all of these mechanisms may eventually be found to play a role in the polyol-induced increases in mineral uptake. Any discussion of mechanism must ultimately consider the following information, some of which was discussed above.

First, the effect requires absorbable carbohydrate or polyol in the intestine. Glucose, which normally does not reach the lower gastrointestinal tract, does enhance calcium absorption in ligated loops (123) and in vivo if introduced by perfusion (174). Non- or poorly metabolized but absorbable substances like xylose (123) and mannitol (65, 117) were also effective. Note that these latter substances are metabolized by intestinal flora and absorbed from the intestine.

Second, the lactose effect's dependence on lactase (34) suggests that the carbohydrate needs to be in monosaccharide form or in the form in which it will be absorbed.

Third, those minerals that formed complexes of intermediate strength with the polyols were those with enhanced absorption, while those with stronger or weaker interactions were unaffected (28, 61). There is no evidence for cotransport, however, and the lactose effect in rat gut sacs required only preincubation with lactose and was not produced by the simultaneous presence of lactose (3).

POLYOLS AND THE RAT ADRENAL GLAND One of the observations of the so-called Huntingdon studies was the incidence of adrenal medullary hyperplasias associated with xylitol feeding in rats (48, 49, 80). More recently, long-term feeding studies have noted an increased incidence of adrenal medullary hyperplasia and pheochromocytoma in rats fed polyol-containing diets (5, 9, 128–130, 151). These lesions have not been seen in any other species.

The mechanisms linking the hyperplastic changes observed in rats to the polyols in their diets are not known but appear to be linked to the changes in calcium metabolism discussed above. In general, high levels of dietary polyol or lactose are associated with increased catecholamine levels (14, 25, 26, 66, 106), but controversy exists as to the effect on actual catecholamine synthesis and as to whether the effects observed are primary or secondary to other homeostatic changes. Bär has reported that decreasing the concentration of calcium in the diets of rats fed 20% xylitol reverses the increases in calcium excretion noted above and simultaneously decreases the catecholamine levels in adrenal glands of rats and the incidence of proliferative changes (5, 14; also see review 101). Whether the polyol- or lactose-produced effects on the adrenal medulla are mediated by calcium itself or are mediated by accompanying changes in the calcium homeostatic hormones is not known. Indirect evidence linking calcium to adrenal function in rats has been reported

(see review 14). Vitamin D deficiency reportedly lowers catecholamine levels (8, 29), and hypercalcemia has been observed to increase blood catecholamine levels (156).

Also, high levels of dietary xylitol resulted in changes in the adrenal cortex as reflected in reduced aldosterone levels (66). This effect was suggested to be secondary to changes in the electrolyte or acid-base balance.

With regard to the possible significance of this lesion to humans, several factors must be considered: First, rats are more susceptible to adrenal medullary hyperplasia than are other species, including humans, and some scientists consider the lesion in rats to be irrelevant to humans (14, 27, 33, 101, 128–130). Second, the effects observed in the adrenal medulla in rats appear to be related in some way to the changes in calcium homeostasis. This link has not been observed in any other species, notably not in mice or humans. Third, the enhancing effects of slowly absorbed carbohydrates on calcium absorption are much more pronounced in rodents than in humans although, as noted above, the effects are observed in humans.

As a result the consensus is that the adrenal tumors in rats fed diets high in polyol or lactose have little or no significance for humans. Nevertheless, until the mechanism linking the polyol diets to adrenal medullary hyperplasia has been elucidated, the mechanism cannot definitively be ruled out in other species (see reviews 101). It should be noted, however, that the lesion has not been reported in any other species (including humans) at this time.

Effects Unique to One Polyol

EFFECT OF XYLITOL ON GASTRIC EMPTYING Several investigations have considered the effects of xylitol on gastric emptying and intestinal motility with regard to possible beneficial effects of xylitol on food intake. Whether other polyol sweeteners share these effects has not been determined, although the slowly absorbed sugar lactose has been noted to have similar effects (86, 97).

Salminen et al (141) showed that oral xylitol produced no change in the secretion of the gastric inhibitory polypeptide in rats, whether or not the animals had been adapted to xylitol. This effect was also observed in humans (141). Another study with rats showed that adaptation to xylitol resulted in a decrease in the rate of gastric emptying but that no change in the levels of the gastric inhibitory polypeptide was involved (137). Subsequently Shafer et al (149) observed that ingestion of 25 g of xylitol by humans led to decreased rates of gastric emptying and food intake during a subsequent meal, an effect not observed with glucose or fructose. Salminen et al (138) have since reported an increase in motilin secretion accompanying the increase in intestinal transit and the delay in gastric emptying.

XYLITOL AND OXALATE Interest in the metabolic interrelationships between xylitol and oxalate arises from clinical observations of oxalate deposition in certain tissues of some patients infused with xylitol (36, 44, 146, 158) and reports of oxalate stones in laboratory rodents fed diets with high levels of xylitol (48, 49, 81). Subsequent investigations have noted oxalate formation during infusions or injections of xylitol in rats (68, 72, 131, 133) and humans (36, 118). The effect was not observed in similar studies with rabbits (120, 168) nor in all studies with humans (31, 36, 71, 169) or rats (70), although in some instances increases in other two-carbon acids were observed (31, 68, 70, 71, 133). Feeding studies have also given variable results. Some studies in rats (60, 140) and mice (17) showed no increases in oxalate. On the other hand, Bär showed increases in oxalate and glycolate excretion in mice fed xylitol-containing diets (10). In humans, slight increases in urinary glycolate but only occasional marginally significant increases in urinary oxalate occurred in response to xylitol (17); both compounds were labelled in the urine of individuals consuming labelled xylitol but not labelled glucose (15). The synthesis of oxalate in isolated liver cells (119, 132, 133) and liver tissue (69) was also observed, although the effect was not always specific for xylitol, and oxalate was also formed from other carbohydrates or polyols (119, 132). The most interesting observations in this regard were reported by Hauschildt & Brand (69), who did not observe oxalate synthesis from either glucose or xylitol under normal conditions but did observe oxalate formation in liver homogenates from both when substrate oxidation was enhanced. Under these conditions xylitol was 1.6 times as effective as glucose.

Initially, investigators of the metabolic relationship between xylitol and oxalate proposed the formation of glycolaldehyde, an oxalate precursor, by the release of "active glycolaldehyde" from the transketolase reaction (31, 72, 158). More recently, a direct pathway for the formation of oxalate from xylitol was proposed and investigated simultaneously by two independent laboratories (19, 84). This pathway involves the phosphorylation of the first metabolic product of xylitol oxidation, D-xylulose, by fructokinase to give xylulose-1-phosphate rather than by xylulokinase to give xylulose-5-phosphate. The xylulose-1-phosphate is subsequently cleaved by aldolase to give dihydroxyacetone-phosphate and oxalate precursor glycolaldehyde. Glycolaldehyde is converted to oxalate by way of glycolate and glyoxalate sequentially. Barngrover et al (19) devised enzymatic assays for xylulose-1-phosphate and glycolaldehyde and demonstrated the formation of both compounds in rat hepatocytes treated with D-xylulose. At the same time James et al (84) demonstrated the formation of xylulose-1-phosphate and glycolaldehyde in a reconstructed system using human liver fructokinase and aldolase.

Subsequent studies in both laboratories have been aimed at quantifying this pathway and evaluating what factors might influence the formation and subsequent metabolism of the glycolaldehyde produced. Barngrover & Dills substantiated the role of fructokinase in the formation of xylulose-1-phosphate and glycolaldehyde in xylulose-treated hepatocytes but could not measure the formation of either compound in xylitol-treated hepatocytes, probably because of the insensitivity of the assay method devised (18). Similar difficulties were encountered in similar studies with labelled xylitols of high specific activities (40), although the authors did postulate an upper limit to the flux through the xylulose-1-phosphate pathway. They proposed that under their incubation conditions the flux of xylitol through the minor pathway as outlined could not exceed 5% of that of the overall rate of xylitol metabolism, corresponding to a conversion of less than 2% of the xylitol-carbon to two-carbon fragments (40).

James et al (85) extended their earlier studies to include fructokinase and aldolase from various tissues in several species and commented on the potentialities of the xylulose-1-phosphate pathway in several animal models. Bais et al (6) purified thc human liver fructokinase to homogeneity and discussed its relationship to oxalate formation in human liver. They concluded that the flux through this pathway is generally minor but that it may contribute to oxalate formation. They subsequently reported extensive studies on inhibitory effects of various substances, including intermediates of oxalate metabolism on aldolase and fructokinase (7).

Dills & Audet (39) recently used a kinetic computer model to simulate flux through the metabolic pathways involving the two xylulose phosphates. To this end they purified and studied the xylulokinase from bovine liver to determine the kinetic parameters of its interaction with D-xylulose. Using these and other literature kinetic and enzyme level data concerning L-iditol dehydrogenase, fructokinase, xylulokinase, and aldolase, they calculated the potential fluxes and evaluated the factors influencing these fluxes. The formation of both xylulose-1-phosphate and glycolaldehyde was found to be potentiated by factors that increase the flux through the dehydrogenase step, notably any increase in the NAD^+/NADH ratio, and by any decrease in xylulokinase activity or any increase in fructokinase activity (39). The increase in the potential for glycolaldehyde formation with regard to an increase in xylitol oxidation is particularly interesting when considered with the previously mentioned differential stimulation of oxalate formation from xylitol by substrate oxidation increases reported by Hauschildt & Brand (69).

The significance of the minor pathway in humans remains unclear. Evidence for its existence is indirect and consists of the observation that urinary glycolate and oxalate excretion increase in volunteers consuming xylitol (11)

and that labelled xylitol but not labelled glucose is converted to labelled glycolate and oxalate (15). At the most, the net conversion of xylitol carbon to oxalate appears to be about 0.5% experimentally (36) and less than 5% in the most unfavorable circumstances, i.e. when low levels of xylulokinase are assumed for humans, predicted by the kinetic computer model (39). The major metabolic precursors of oxalate, glycolate, and glyoxalate are known to have several metabolic precursors besides xylitol and several metabolic fates besides oxalate (see reviews 7, 76, 126). It has been suggested that the conversion of xylitol to oxalate is regulated primarily at the level of glyoxalate or glycolate metabolism (7, 15). Further work on the kinetics of the conversion of xylitol carbon to oxalate are needed, particularly with regard to the kinetics of human xylulokinase and alternative metabolic fates of glycolaldehyde, glycolate, and glyoxalate.

BLADDER STONES, BLADDER TUMORS, AND XYLITOL Mice consuming diets with high levels of xylitol exhibited an increased incidence of bladder calculi and an increased incidence of hyperplastic and neoplastic changes in the bladder (47, 48, 81). Evidence indicates that urinary stone formation is a reasonable explanation for the occurrence of bladder tumors in mice fed xylitol (see review 101). In mice (10, 101 and references therein) but not rats (140), xylitol increases oxalate excretion as noted above, whether by way of xylitol metabolism, increased oxalate absorption, or both, and it increases excretion of calcium in rodents. In mice, the consumption of xylitol therefore increases two of the urinary parameters that are linked to possible stone formation.

As noted above humans fed xylitol do show slightly higher-than-average oxalate excretions (10, 15); far greater changes are noted in glycolate excretion, however (10). In this regard, Conyers et al (35) examined the kinetics of oxalate formation from xylitol using a one-compartment model; they concluded that even small conversions, 0.5% in their model, may at times be significant during infusions. Their model can be extended to dietary xylitol if one assumes that the highest doses of xylitol consumed during the Turku sugar studies (145) were consumed over a 12-hour period in any given day. The largest long-term dosage of 100 g/day for 100 days and the largest one-time dosage of 400 g would be the equivalent of infusions of 0.80 and 3.20 mmol/h/kg body wt for an average subject weighing 70 kg. These levels would not raise levels of oxalate above the 0.10 mM level suggested to be the threshold for crystallization (35). This model does not, however, take into account any differences in enzyme or effector levels or any other sources of oxalate besides xylitol, whether they be metabolic or dietary. The polyol-induced increases in calcium absorption in humans (34, 176) are also not considered. With regard to the significance of the lesions noted in mice to

humans, it should be noted that the occurrence of bladder or kidney stones in humans consuming xylitol has not been reported, despite numerous closely monitored, long-term studies (see previous sections and reviews). Nevertheless, certain subgroups still may exist within the general population, individuals susceptible to calcium oxalate stone formation for instance, who may be at risk if consuming large amounts of xylitol.

LACTITOL AND LEYDIG CELL TUMORS IN RATS Male rats fed diets containing high levels of lactitol or lactose were reported to have an increased incidence of Leydig cell tumors (151). These tumors are fairly common in the rat unlike in mice or humans (see review 101). In contrast, many earlier studies with lactose and a few with lactitol never demonstrated an increase in rat Leydig cell tumors. There is no ready mechanistic explanation as to why both lactose and lactitol would result in such tumors. A mechanism would almost certainly have to involve a common metabolite, galactose for instance, or a common physiologic change, such as the calcium absorption discussed previously. Neither of these has been reported associated with Leydig cell tumors. Considering the high consumption of lactose by humans and the extremely low incidence of human Leydig cell tumors, the results, even if reproducible, are of questionable significance for humans.

SUMMARY AND CONCLUSIONS

The polyols are a family of bulk sweeteners, some of which are currently used in the United States and in other nations. The use of these compounds is likely to increase in the future.

The greatest advantage of polyols as sweeteners is their reduced cariogenicity compared with sucrose, fructose, or glucose. This reduced cariogenicity has been observed with all of the polyols considered in this review. Furthermore, evidence suggests that one of these polyols, xylitol, may have cariostatic properties. More research is needed to clarify the mechanism of this cariostatic effect.

Evidence suggests that moderate usage of the polyols in human diets over long periods is not likely to produce many toxic effects. This conclusion is supported by the facts that (*a*) both sorbitol and mannitol have been used as sweeteners for some time without apparent side effects, and (*b*) extensive long-term studies with dietary xylitol in Europe have not yielded any reports of toxicity. At this point there is no reason to believe that the disaccharide polyols differ significantly in a qualitative sense from sorbitol or mannitol with regard to their effects in humans.

There are some research needs with regard to the inclusion of the polyol sweeteners in human diets:

1. All of the polyols can cause osmotic diarrhea in humans if higher levels are consumed. This fact is noted in the labelling of products containing mannitol and sorbitol in the United States (see "Current Regulatory Status"). If the disaccharide polyols are to be used as bulk sweeteners, further studies of the dose levels that can cause diarrhea may be needed.

2. The polyols, like other slowly absorbed carbohydrates, enhance the absorption of certain minerals, particularly divalent cations. More comparative and mechanistic studies of this effect are needed.

3. All of the polyols, lactose, and other slowly absorbed carbohydrates appear to cause adrenal medullary hyperplasia at high doses in laboratory rats. Evidence suggests that these lesions are linked in some way to the lactose or polyol-induced changes in calcium homeostasis. Despite long-term use of lactose, sorbitol, and mannitol in human diets, similar lesions in humans have not been reported and some investigators have concluded that the lesion in rats has no relevance to humans. Nevertheless further studies are needed to elucidate the mechanisms of the dietary lactose and polyol-induced adrenal hyperplasias in rats to ascertain definitively if they also operate in other species.

4. For xylitol alone among the polyols, the occurrence of calcium oxalate bladder stones and accompanying neoplastic lesions was noted in mice. While the available evidence strongly suggests that dietary xylitol will not be a major risk factor for stone formation in the general population, certain questions remain. A minor metabolic pathway exists that can give rise to the metabolic production of oxalate from xylitol. Further work is needed on this pathway and on the metabolism of oxalate precursors in general. In addition the possibility that subpopulations of humans might face an increased risk of calcium oxalate stone formation by high levels of dietary xylitol needs to be addressed.

5. A single study that reported an increased incidence of Leydig cell tumors in male rats fed high levels of lactitol or lactose needs to be repeated. If the effect were reproduced, additional studies on the mechanism would be in order. The probable significance of the effect with respect to humans is unknown but is likely to be important.

ACKNOWLEDGMENTS

The author thanks Dr. Kate Stygall, Dr. Donald McCormick, and Dr. J. Donald Smith for reviewing portions of this manuscript; Anna Giuliano and Dr. Gregory Miller for helpful discussions regarding calcium absorption; S.M.U. students Michael Garant and Jane Klinger for assistance with the literature search during the preparation of this manuscript; and the following scientists who generously supplied reprints and preprints of their studies with

the polyols: Dr. Albert Bär, Dr. Urs A. Boelsterli, Dr. Robert A. J. Conyers, Dr. Faye M. Dong, Dr. Mauri M. Hämäläinen, Dr. Kauko K. Mäkinen, Dr. Vincent Marks, Dr. Yoshide Ogawa, Drs. Seppo and Eeva Salminen, and Dr. Günther Siebert.

Literature Cited

1. Amman, P., Rizzoli, R., Fleisch, H. 1988. Influence of the disaccharide lactitol on intestinal absorption and body retention of calcium in rats. *J. Nutr.* 118:793–95
2. Arends, J., Christofferson, J., Schuthof, J., Smits, M. T. 1984. Influence of xylitol on the demineralization of enamel. *Caries Res.* 18:296–301
3. Armbrecht, H. J., Wasserman, R. H. 1976. Enhancement of Ca^{++} uptake by lactose in the rat small intestine. *J. Nutr.* 106:1265–71
4. Assev, S., Rölla, G. 1984. Evidence for presence of a xylitol phosphotransferase system in *Streptococcus mutans* OMZ 176. *Acta Pathol. Microbiol. Immunol. Scand. B* 92:89–92
5. Baer, A. 1988. Sugars and adrenomedullary proliferative lesions: the effects of lactose and various polyalcohols. *J. Am. Coll. Toxicol.* 7:71–81
6. Bais, R., James, H. M., Rofe, A. M., Conyers, R. A. J. 1985. The purification and properties of human liver ketohexokinase. *Biochem. J.* 230:53–60
7. Bais, R., Nairn, J. M., Rofe, A. M., Conyers, R. A. J. 1987. Enzymology of endogenous oxalate formation. *Adv. Clin. Enzymol.* 5:43–52
8. Baksi, S. N., Hughes, M. J. 1984. Alteration of adrenal catecholamine levels in the rat after dietary calcium and vitamin D deficiencies. *J. Auton. Nerv. Syst.* 11:393–96
9. Bär, A. 1985. Safety assessment of polyol sweeteners—some aspects of toxicity. *Food Chem.* 16:231-41
10. Bär, A. 1985. Urolithiasis and nephrocalcinosis in xylitol- and sorbitol-fed male mice of two different strains. *Int. J. Vitam. Nutr. Res. Suppl.* 28:69–89
11. Bär, A. 1985. Effect of high oral doses of xylitol versus sucrose on urinary risk factors of urolithiasis in man. *Int. J. Vitam. Nutr. Res. Suppl.* 28:91–118
12. Bär, A. 1986. Xylitol. In *Alternative Sweeteners,* ed. L. O. Nabors, R. C. Gelardi, pp. 185–216. New York: Dekker
13. Bär, A. 1988. Caries prevention with xylitol, a review of the scientific evidence. *World Rev. Nutr. Diet.* 55:183–209
14. Bär, A. 1987. Toxicological evaluation of sugar alcohols. In *Low Digestibility Carbohydrates,* D. C. Leegwater, V. J. Feron, R. J. J. Hermus, pp. 42–50. Zeist, The Netherlands: Pudoc Wageningen
15. Bär, A., Oesterhelt, G. 1985. Conversion of [U-^{13}C]xylitol and D-[U^{13}C]glucose into urinary [1,2-^{13}C]glycollate and [1,2-^{13}C]oxalate in man. *Int. J. Vitam. Nutr. Res. Suppl.* 28:119–33
16. Barmes, D., Barnaud, J., Khambonanda, S., Infirri, J. S. 1985. Field trials of preventative regimes in Thailand and French Polynesia. *Int. Dent. J.* 35:66–72
17. Barngrover, D. A. 1982. *Xylitol metabolism: an alternative pathway.* PhD thesis. Cornell Univ. 108 pp.
18. Barngrover, D. A., Dills, W. L. Jr. 1983. The involvement of liver fructokinase in the metabolism of D-xylulose and xylitol in isolated rat hepatocytes. *J. Nutr.* 113:522–30
19. Barngrover, D. A., Stevens, H. C., Dills, W. L. Jr. 1981. D-Xylulose-1-phosphate: enzymatic assay and production in isolated rat hepatocytes. *Biochem. Biophys. Res. Commun.* 102:75–80
20. Beckers, H. J. A. 1988. Influence of xylitol on the growth, establishment, and cariogenicity of *Streptococcus mutans* in dental plaque of rats. *Caries Res.* 22:166–73
21. Bergeim, O. 1926. Intestinal chemistry. V. Carbohydrates and calcium and phosphorus absorption. *J. Biol. Chem.* 70: 35–45
22. Bibby, B. G., Fu, J. 1985. Changes in plaque pH in vitro by sweeteners. *J. Dent. Res.* 64:1130–33
23. Bird, S. P., Hewit, D., Gurr, M. I. 1985. Digestible and metabolizable energy values of lactitol for the rat and miniature pig. *Proc. Nutr. Soc.* 44:40A (Abstr.)

24. Birkhed, D., Edwardsson, S., Ahlden, M.-L., Frostell, G. 1979. Effects of 3-months frequent consumption of hydrogenated starch hydrolysate (Lycasin®), maltitol, sorbitol and xylitol on human dental plaque. I. Biochemical investigations. *Acta Odontol. Scand.* 37:103–15
25. Boelsterli, U. A., Zbinden, G. 1985. Early biochemical and morphological changes in the rat adrenal medulla induced by xylitol. *Arch. Toxicol.* 57:25–30
26. Boelsterli, U. A., Zbinden, G. 1986. Hypothetical mechanism of adrenal medullary hyperplasia in xylitol fed rats. *Arch. Toxicol.* 59:194
27. Bosland, M. C., Bär, A. 1984. Some functional characteristics of adrenal medullary tumors in aged male Wistar rats. *Vet. Pathol.* 21:129–40
28. Briggs, J., Finch, P., Matulewicz, M. C., Weigel, H. 1981. Complexes of copper(II), calcium, and other metal ions with carbohydrates: thin-layer ligand-exchange chromatography and determination of relative stabilities of complexes. *Carbohydr. Res.* 97:181–88
29. Brion, F., Dupuis, Y. 1980. Calcium and monamine regulation: role of vitamin D nutrition. *Can. J. Physiol. Pharmacol.* 58:1431–34
30. Bronner, F., Pansu, D., Stein, W. D. 1986. An analysis of intestinal calcium transport across rat intestine. *Am. J. Physiol.* 250:G561–69
31. Chalmers, R. A., Lawson, A. M., Hauschildt, S., Watts, R. W. E. 1979. The urinary excretion of glycollic acid and threonic acid by xylitol-infused patients and their relationship to the possible role of 'active glycolaldehyde' in the transketolase reaction *in vivo*. *Biochem. Soc. Trans.* 3:518–21
32. Charley, P., Saltman, P. 1963. Chelation of calcium by lactose: its role in transport mechanisms. *Science* 139: 1205–6
33. Cheng, L. 1980. Pheochromocytoma in rats: incidence, etiology, morphology and functional activity. *J. Environ. Pathol. Toxicol.* 4:219–28
34. Cochet, B., Jung, A., Griessen, M., Bartholdi, P., Schaller, P., Donath, A. 1983. Effects of lactose on intestinal calcium absorption in normal and lactase deficient subjects. *Gastroenterology* 84:935-40
35. Conyers, R. A. J., Huber, T. W., Thomas, D. W., Rofe, A. M., Bais, R., Edwards, R. G. 1985. A one-compartment model for calcium oxalate tissue deposition during xylitol infusions in humans. *Int. J. Vitam. Nutr. Res. Suppl.* 28:47–57
36. Conyers, R. A. J., Rofe, A. M., Bais, R., James, H. M., Edwards, J. B., et al. 1985. The metabolic production of oxalate from xylitol. *Int. J. Vitam. Nutr. Res. Suppl.* 28:9–28
37. DeGroot, A. P., Til, H. P., Feron, V. J., Dreef-vanderMeulen, H. C., Willems, M. I. 1974. Two-year feeding and multigeneration studies in rats on five chemically modified starches. *Food Chem. Toxicol.* 12:651–63
38. Dermer, O. 1946. The science of taste. *Proc. Okla. Acad. Sci.* 27:9–20
39. Dills, W. L. Jr., Audet, N. J. 1988. Computer model for the prediction of the rates of hepatic formation of the xylulose phosphates and oxalate precursors from xylitol. *FASEB J.* 2:A1362 (Abstr.)
40. Dills, W. L. Jr., Barngrover, D. A., Covey, T. R. 1985. Metabolism of 1-^{3}H-D-xylitol and 5-^{3}H-D-xylitol in isolated rat hepatocytes. *Int. J. Vitam. Nutr. Res. Suppl.* 28:59–64
41. Dills, W. L., Garant, M. S., Collins, P. G. 1989. Activity of bovine brain aldose reductase towards maltose and lactose. *FASEB J.* 3:In press (Abstr.)
42. Dupuis, Y., Fournier, P. L. 1964. Etude comparée de l'action de la vitamine D et du lactose sur les échanges calciques durant la vie du rat. *CR Acad. Sci. Ser. D* 258:2906–9
43. Edwardsson, S., Birkhed, D., Mejare, B. 1977. Acid production from Lycasin®, maltitol, sorbitol and xylitol by oral streptococci and lactobacilli. *Acta Odontol. Scand.* 35:257–63
44. Evans, G. W., Phillips, G., Mukherjee, T. M., Snow, M. R., Lawrence, J. R., Thomas, D. W. 1973. Identification of crystals deposited in brain and kidney after xylitol administration by biochemical, histochemical, and electron diffraction methods. *J. Clin. Pathol.* 26:32–36
45. Figdor, S. K., Allingham, R. P., Kita, D. A., Hobbs, D. C. 1987. Caloric utilization of sorbitol and isomalt in the rat. *J. Agric. Food Chem.* 35:996–1001
46. Fournier, P. L., Gambier, J., Fontaine, N. 1967. Effets d'une ingestion prolongée de sorbitol sur l'utilisation du calcium et sur l'ossification du rat. *CR Acad. Sci. Ser. D* 264:1301–4
47. Fritz, M., Siebert, G., Kasper, H. 1985. Dose dependence of breath hydrogen and methane in healthy volunteers after ingestion of a commercial disaccharide

mixture, Palatinit®. *Br. J. Nutr.* 54: 389–400
48. Gatti, G. L., Salvatore, G. 1978. L'impiego dello xilitolo e riflessi tossicologici. Parte I. *Riv. Soc. Ital. Sci. Aliment.* 7:329–36
49. Gatti, G. L., Salvatore, G. 1978. L'impiego dello xilitolo e riflessi tossicologici. Parte II. *Riv. Soc. Ital. Sci. Aliment.* 7:387–94
50. Gauthier, L., Vadeboncouer, C., Mayrand, D. 1984. Loss of sensitivity to xylitol by *Streptococcus mutans* LG-1. *Caries Res.* 18:289–95
51. Gehring, F. 1973. Über die Säuerbildung kariesätologisch wichtiger Streptokokken aus Zuckern und Zuckeralkoholen unter besonderer Berücksichtigung von Isomaltit und Isomaltulose. *Z. Ernährungswiss. Suppl.* 15:16–21
52. Gehring, F., Karle, E. J. 1981. Der saccharoseaustauschstoff Palatinit® unter besonderer Berücksichtigung mikrobiologischer und kariesprophylaktischer Aspekte. *Z. Ernährungswiss.* 20:96–106
53. Georgieff, M., Moldawer, L. L., Bistrian, B. R., Blackburn, G. L. 1985. Xylitol, an energy source for intravenous nutrition after trauma. *J. Parenteral Enteral Nutr.* 9:199–209
54. Glinsmann, W. H., Irasquin, H., Park, Y. K. 1986. Evaluation of health aspects of sugars in carbohydrate sweeteners. *J. Nutr.* 116(11S):S1–S216
55. Grenby, T. H. 1985. Dental and lipogenic effects of polyols and Lycasins replacing sucrose in the diet of laboratory rats. In *Advances in Dietetics and Nutrition* (1st Int. Congr. 1983), ed. C. Horwitz, pp. 86–89. London: Libbey
56. Griessen, M., Bergoz, R., Balant, L., Loizeau, E. 1986. Effet du lactitol sur la producyion d'hydrogène expiré chez l'homme normal. *Schweiz. Med. Wochenschr.* 116:469–72
57. Grupp, U., Siebert, G. 1978. Metabolism of hydrogenated palatinose, an equimolar mixture of a-D-glucopyranosido-1,6-sorbitol and a-D-glucopyranosido-1,6-mannitol. *Res. Exp. Med. (Berlin)* 173:261–78
58. Hallberg, L., Sövell, L., Brise, H. 1966. Search for substances promoting the absorption of iron. *Acta Med. Scand. Suppl.* 459:11–21
59. Hamada, S., Slade, H. D. 1980. Biology, immunology, and cariogenicity of *Streptococcus mutans*. *Microbiol. Rev.* 44:331–84
60. Hämäläinen, M. M. 1987. Organic aciduria in rats fed high amounts of xylitol or sorbitol. *Toxicol. Appl. Pharmacol.* 90:217–20
61. Hämäläinen, M. M. 1988. *Sugar alcohols and mineral metabolism*. Doctoral thesis. Univ. Turku. 226 pp.
62. Hämäläinen, M. M., Mäkinen, K. K. 1983. Effect of peroral xylitol on the concentration levels of lipids and electrolytes in rat tissues. *Nutr. Res.* 3:497–510
63. Hämäläinen, M. M., Mäkinen, K. K. 1983. Peroral xylitol increases concentration levels of tissue iron in the rat. *Br. J. Nutr.* 50:109–12
64. Hämäläinen, M. M., Mäkinen, K. K. 1985. Duodenal xanthine oxidase (EC 1.2.3.2) and ferroxidase activities in the rat in relation to the increased iron absorption caused by peroral xylitol. *Br. J. Nutr.* 54:493–98
65. Hämäläinen, M. M., Mäkinen, K. K. 1986. Alterations in electrolyte and iron metabolism in the rat in relation the peroral administration of galactitol, mannitol and xylitol. *J. Nutr.* 116:599–609
66. Hämäläinen, M. M., Mäkinen, K. K. 1987. Adrenal function of the rat in relation to peroral administration of xylitol: depression of aldosterone. *Acta Physiol. Scand.* 130:687–94
67. Hämäläinen, M. M., Mäkinen, K. K., Parvianen, M. T., Koshinen, T. 1985. Peroral xylitol increases intestinal calcium absorption in the rat independently of vitamin D action. *Mineral Electrolyte Metab.* 11:178–81
68. Hannett, B., Thomas, D. W., Chalmers, A. H., Rofe, A. M., Edwards, J. B., Edwards, R. G. 1977. Formation of oxalate in pyridoxine or thiamine deficient rats during intravenous xylitol infusions. *J. Nutr.* 107:458–65
69. Hauschildt, S., Brand, K. 1979. [^{14}C]Oxalate formation from [U-^{14}C]glucose and [U-^{14}C]xylitol in rat liver homogenate. *Biochem. Med.* 21:55–61
70. Hauschildt, S., Chalmers, R. A., Lawson, A. M., Brand, K. 1981. In-vivo studies on C_2 organic acids in the tissues of rats injected with xylitol and glucose. *Z. Ernährungswiss.* 20:69–75
71. Hauschildt, S., Chalmers, R. A., Lawson, A. M., Schultis, K., Watts, R. W. E. 1976. Metabolic investigations after xylitol infusion in human subjects. *Am. J. Clin. Nutr.* 29:258–73
72. Hauschildt, S., Watts, R. W. E. 1976. Studies on the effect of xylitol on oxalate formation. *Biochem. Pharmacol.* 25:27–29

73. Hausman, S. Z., Thompson, J., London, J. 1984. Futile xylitol cycle in lactobacillus casei. *J. Bacteriol.* 160:211–15
74. Havenaar, R., Huis in't Veld, J. H. J., deStoppelaar, J. D., Dirks, O. B. 1983. A purified cariogenic diet for rats to test sugar substitutes with special emphasis on general health. *Caries Res.* 17:340–52
75. Herndon, J. F., Rice, E. G., Tucker, R. G., Van Loon, E. J., Greenberg, S. M. 1958. Iron absorption and metabolism. III. The enhancement of iron absorption in rats by D-sorbitol. *J. Nutr.* 64:615–23
76. Hodgkinson, A. 1977. *Oxalic Acid in Biology and Medicine.* New York: Academic
77. Hodgkinson, A., Davis, D., Fourmar, J., Robertson, W. G., Roe, F. J. C. 1982. A comparison of the effects of lactose and of two chemically modified waxy maize starches on mineral metabolism in the rat. *Food Chem. Toxicol.* 20:371–82
78. Hoppe, K., Gassmann, B. 1985. Vergleichstabellen zur Süssintensität von 16 Süssungsmitteln. *Lebensmitteilindustrie* 32:227–31
79. Hosoya, N. 1975. Effect of sugar alcohol on the intestine. In *Malabsorption due to Carbohydrate Intolerance,* ed. A. Chávez, H. Bourges, S. Basta, pp. 164–68. Basel: Karger
80. Hunter, B., Colley, J., Street, A. E., Heywood, R., Prentice D. E., Magnusson, G. 1978. *Xylitol tumorigenicity and toxicity study in long-term dietary administration to rats,* Vol. I, Report of the Huntingdon Res. Cent., Huntingdon, Cambridgeshire, England. In *Xylitol,* Vol. 11. Switzerland: Hoffmann-LaRoche
81. Hunter, B., Graham, C., Heywood, R., Prentice, D. E., Roe, F. J. C., Nookes, D. N. 1978. *Tumorigenicity and carcinogenicity study with xylitol in long term dietary administration to mice.* See Ref. 80. Vol. 20
82. Hyvönen, L., Kurkela, R., Koivistoinen, P., Merimaa, P. 1977. Effects of temperature and concentration on the relative sweetness of fructose, glucose and xylitol. *Lebensm. Wiss. Technol.* 10:316–20
83. Deleted in proof
84. James, H. M., Bais, R., Edwards, J. B., Rofe, A. M., Conyers, R. A. J. 1982. Models for the metabolic production of oxalate from xylitol in humans: a role for fructokinase and aldolase. *Aust. J. Exp. Biol. Med. Sci.* 60:117–22
85. James, H. M., Williams, S. G., Bais, R., Rofe, A. M., Edwards, J. B., Conyers, R. A. J. 1985. The metabolic production of oxalate from xylitol: activities of transketolase, transaldolase, fructokinase and aldolase in liver, kidney, brain, heart and muscle in the rat, mouse, guinea pig, rabbit and human. *Int. J. Vitam. Nutr. Res. Suppl.* 28:29–46
86. James, W. P. T. 1970. Sugar absorption and intestinal motility in children when malnourished and after treatment. *Clin. Sci.* 39:305–18
87. Joint FAO/WHO Expert Committee on Food Additives. 1983. Xylitol. In *Toxicological Evaluation of Certain Food Additives and Food Contaminants. WHO Food Additives Ser.,* 18:161–74. Geneva: WHO
88. Kandelman, D., Bär, A., Hefti, A., 1986. Collaborative WHO xylitol field study in French Polynesia. I. Baseline prevalence and three year caries increment. *Caries Res.* 22:55–62
89. Karimzadegan, E., Clifford, A. J., Hill, F. W. 1979. A rat bioassay for measuring the comparative availability of carbohydrates and its application to legume foods, pure carbohydrates and polyols. *J. Nutr.* 109:2247–59
90. Karle, E. J., Gehring, F. 1978. Palatinit®---ein neuer Zuckeraustauschstoff und seine kariesprophylaktische Beurteilung. *Dtsch. Zahnärztl. Z.* 33:189–91
91. Karle, E. J., Gehring, F. 1979. Kariogenitütsunteruschungen von Zuckeraustauschstoffen an xerostomierten Ratten. *Dtsch. Zahnärztl. Z.* 33:551–54
92. Kearsley, M. W., Birch, G. G., Lian-Loh, R. H. P. 1982. The metabolic fate of hydrogenated glucose syrups. *Stärke* 34:279–83
93. Kelly, S. E., Chawla-Singh, K., Sellin, J. H., Yasillo, N. J., Rosenberg, I. H. 1984. Effect of meal composition on calcium absorption: enhancing effect of carbohydrate polymers. *Gastroenterology* 87:596–600
94. Kirchgessner, M., Zinner, P. M., Roth, H.-P. 1983. Inergiestoffwechsel und Insulinaktivität bei Ratten nach Palatinitfütterung. *Int. J. Vitam. Nutr. Res.* 53:86–93
95. Leegwater, D. C. 1978. *Studies on the metabolic fate of intravenously administered [^{14}C] lactitol in the rat.* Rep. No. R5657 of the Central Inst. for Nutr. Food Res. Zeist, The Netherlands: TNO. 4 pp.
96. Lengemann, F. W. 1959. The site of action of lactose in the enhancement of calcium utilization. *J. Nutr.* 69:23–27

97. Lengemann, F. W., Wasserman, R. H., Comar, C. L. 1959. Studies on the enhancement of radiocalcium and radiostrontium absorption by lactose in the rat. *J. Nutr.* 68:443–45
98. Lian-Loh, R., Birch, G. G., Coates, M. E. 1982. The metabolism of maltitol in the rat. *Br. J. Nutr.* 48:477–81
99. Life Sci. Res. Off. Fed. Am. Soc. Exp. Biol. 1977. *The Nutritional Significance of Dietary Fiber,* ed. K. K. Kimura. Bethesda: FASEB. 68 pp.
100. Life Sciences Research Office, Federation of American Societies for Experimental Biology. 1979. *Evaluation of the Health Aspects of Starch and Modified Starches as Food Ingredients.* Bethesda: FASEB. 99 pp.
101. Life Sciences Research Office, Federation of American Societies for Experimental Biology. 1986. *Health Aspects of Sugar Alcohols and Lactose,* ed. F. R. Senti. Bethesda: FASEB. 85 pp.
102. Loria, A., Medal, S., Elizondo, J. 1962. Effect of sorbitol on iron absorption in man. *Am. J. Clin. Nutr.* 10:124–27
103. MacKenzie, K. M., Hauck, W. N., Wheeler, A. G., Roe, F. J. C. 1986. Three-generation reproductive study of rats ingesting up to 10% sorbitol in the diet—and a brief review of the toxicological status of sorbitol. *Food Chem. Toxicol.* 24:191–200
104. Mäkinen, K. K. 1981. Xylitol. In *Foods, Nutrition, and Dental Health,* ed. J. J. Hefferren, H. M. Koehler, 1:83–96. Park Forest South, Ill: Pathotex
105. Mäkinen, K. K. 1985. New biochemical aspects of sweeteners. *Int. Dent. J.* 35:23–35
106. Mäkinen, K. K., Hämäläinen, M. M. 1986. Biochemical and morphological changes of the rat adrenal medulla induced by peroral xylitol. *Arch. Toxicol.* 59:192–93
107. Mäkinen, K. K., Isokangas, P. 1988. Relationship between carbohydrate sweeteners and oral diseases. *Prog. Food Nutr.* 12:37–73
108. Mäkinen, K. K., Scheinin, A. 1982. Xylitol and dental caries. *Annu. Rev. Nutr.* 2:133–50
109. Mäkinen, K. K., Söderling, E. 1984. Solubility of calcium salts, enamel and hydroxyapatite in aqueous solutions of simple carbohydrates. *Calcif. Tissue Int.* 36:64–71
110. Mäkinen, K. K., Soderling, E., Hurttia, H., Lehtonen, O.-P., Luukkala, E. 1985. Biochemical, microbiologic, and clinical comparisons between two dentifrices that contain different mixtures of sugar alcohols. *J. Am. Dent. Assoc.* 111:745–51
111. Martin, D. L., DeLuca, H. F. 1969. Influence of sodium on calcium transport by the rat small intestine. *Am. J. Physiol.* 216:1351–59
112. Miller, S. C., Miller, M. A., Omura, T. H. 1988. Dietary lactose improves endochondrial growth and bone development and mineralization in rats fed a vitamin D–deficient diet. *J. Nutr.* 118:72–77
113. Moskowitz, H. R. 1974. The psychology of sweetness. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 37–64. New York: Academic
114. Musch, K., Siebert, G., Schiweck, H., Steinle, G. 1973. Ernährungsphysiologische Untersuchen mit Isomaltit an der Ratte. *Z. Ernährungswiss. Suppl.* 15:3–16
115. Mykkänen, H. M., Salminen, S. J. 1986. Effects of xylitol on the absorption of ^{203}Pb in mice and cockerels. *Bull. Environ. Contam. Toxicol.* 37:77–80
116. Nilsson, U., Jägerstad, M. 1987. Hydrolysis of lactitol, maltitol and Palatinit® by human intestinal biopsies. *Br. J. Nutr.* 58:199–206
117. Norman, D. A., Morawski, S. G., Fordtran, J. S. 1980. Influence of glucose, fructose, and water movement on calcium absorption in the jejunum. *Gastroenterology* 78:22–25
118. Ogawa, Y. 1981. Studies on oxalate in urolithiasis. III. Effect of xylitol infusion on plasma and urinary oxalate. *Jpn. J. Urol.* 72:1553–58
119. Ogawa, Y., Takahashi, S., Kitagawa, R. 1983. [^{14}C]Oxalate formation from [U-^{14}C]glucose and [U-^{14}C]xylitol in isolated rat hepatocytes. *Jpn. J. Nephrol.* 25:1079–82
120. Oshinsky, R. J., Wang, Y.-M., Van Eys, J. 1977. Xylitol infusion and oxalate formation in rabbits. *J. Nutr.* 107:792–804
121. Pansu, D., Bellaton, C., Bronner, F. 1979. Effect of lactose on duodenal calcium-binding protein and calcium absorption. *J. Nutr.* 109:508–12
122. Pansu, D., Bellaton, C., Roche, C., Bronner, F. 1983. Duodenal and ileal calcium absorption in the rat and the effects of vitamin D. *Am. J. Physiol.* 244:G695–G700
123. Pansu, D., Chapuy, M. C., Milani, M., Bellaton, C. 1975. Transepithelial calcium transport enhanced by xylose and glucose in the rat jejunal ligated loop. *Calcif. Tissue Res.* 21:45–52

124. Postma, P. W., Lengeler, J. W. 1985. Phosphoenolpyruvate: carbohydrate phosphotransferase system of bacteria. *Microbiol. Rev.* 49:232–69
125. Rennhard, H. H., Bianchine, J. R. 1976. Metabolism and caloric utilization of orally administered maltitol-^{14}C in rat, dog, and man. *J. Agric. Food Chem.* 24:287–91
126. Richardson, K. E., Farinelli, M. P. 1980. The pathways of oxalate biosynthesis. In *Urolithiasis*, ed. L. Smith, W. G. Robertson, B. Finlayson, pp. 855–63. New York: Plenum
127. Robillard, G. T. 1982. The enzymology of the bacterial phosphoenolpyruvate-dependent sugar transport systems. *Mol. Cell. Biochem.* 46:3–24
128. Roe, F. J. C. 1984. Perspectives in carbohydrate toxicology with special reference to carcinogenicity. *Swed. Dent. J.* 8:99–111
129. Roe, F. J. C. 1987. Pathology of polyols. In *Proc. 2nd Joint Meet. Netherlands Soc. Toxicol. Br. Toxicol. Soc.* pp. S12–S15. Leiden, Netherlands: Univ. Leiden
130. Roe, F. J. C., Bär, A. 1985. Enzootic and epizootic adrenal medullary proliferative disease of rats: influence of dietary factors which affect calcium absorption. *Hum. Toxicol.* 4:27–52
131. Rofe, A. M., Conyers, R. A. J., Bais, R., Edwards, J. B. 1979. Oxalate excretion in rats injected with xylitol or glycollate: stimulation by phenobarbitone pre-treatment. *Aust. J. Exp. Biol. Med. Sci.* 57:171–76
132. Rofe, A. M., James, H. M., Bais, R., Edwards, J. B., Conyers, R. A. J. 1980. The production of [^{14}C]oxalate during the metabolism of [^{14}C]carbohydrates in isolated rat hepatocytes. *Aust. J. Exp. Biol. Med. Sci.* 58:103–16
133. Rofe, A. M., Thomas, D. W., Edwards, R. G., Edwards, J. B. 1977. [^{14}C]Oxalate synthesis from [U-^{14}C]xylitol: In vivo and in vitro studies. *Biochem. Med.* 18:440–51
134. Rosiers, C., Verwaerde, F., Dupas, H., Bouguelet, S. 1985. New approach to the metabolism of hydrogenated starch hydrolysate: hydrolysis by the maltase/glucoamylase complex of the rat intestinal mucosa. *Ann. Nutr. Metab.* 29:76–82
135. Salminen, E., Salminen, S. 1986. Lactulose and lactitol induced enlargement and microflora changes in mice. *Proc. Eur. Food Toxicol.* 2:313–17
136. Salminen, E., Salminen, S., Marks, V., Bridges, J. W. 1983. Urinary excretion of orally administered oxalic acid in xylitol fed mice. In *Developments in the Science and Practice of Toxicology*, ed. A. W. Hayes, R. C. Schnell, T. S. Miya, pp. 333–36. Amsterdam: Elsevier Sci.
137. Salminen, E., Salminen, S., Porkka, L., Koivistoinen, P. 1984. The effects of xylitol on gastric emptying and secretion of gastric inhibitory polypeptide in the rat. *J. Nutr.* 114:2201–3
138. Salminen, E. K., Salminen, S., Porkka, L., Kwasowski, P., Marks, V., Koivistoinen, P. 1989. Effect of xylitol on the rate of gastric emptying and motilin, insulin and GIP release: comparison with glucose. *Am. J. Clin. Nutr.* In press
139. Salminen, S., Salminen, E., Bridges, J., Marks, V. 1989. Intestinal absorption of oxalate by xylitol treated rats and mice. *Toxicol. Lett.* In press
140. Salminen, S., Salminen, E., Koivistoinen, P. 1985. Urinary excretion of calcium and oxalate in xylitol-related rats—a short communication. *Int. J. Vitam. Nutr. Res. Suppl.* 28:65–68
141. Salminen, S., Salminen, E., Marks, V. 1982. The effects of xylitol on the secretion of insulin and gastric inhibitory polypeptide in man and rats. *Diabetology* 22:480–82
142. Scheinen, A. 1987. Dietary carbohydrates and dental disorders. *Am. J. Clin. Nutr.* 45:1218–25
143. Scheinen, A., Banoczy, J. 1985. Xylitol and caries: the collaborative WHO oral disease preventative programme in Hungary. *Int. Dent. J.* 35:50–57
144. Scheinin, A., Banoczy, J., Szöke, J., Esztari, I., Pienhäkkinen, K., et al. 1985. Collaborative WHO xylitol field studies in Hungary. I. Three-year caries activity in institutionalized children. *Acta Odontol. Scand.* 43:327–47
145. Scheinin, A., Mäkinen, K. K., 1975. Turku sugar studies I-XXI. *Acta Odontol. Scand.* 33(Suppl. 70):1–348
146. Schröder, R. 1980. Storungen im Oxalsäurestuffwechsel bei Parentenalen Ernährung mit Xylit. *Dtsch. Med. Wochenschr.* 105:997–1001
147. Secchi, A., Pontiroli, A. E., Cammelli, L., Bizzi, A., Cini, M., Pozza, G. 1986. Effects of oral administration of maltitol on plasma glucose, plasma sorbitol, and serum insulin levels in man. *Klin. Wochenschr.* 64:265–69
148. Sestoft, L. 1985. An evaluation of biochemical aspects of intravenous fructose, sorbitol and xylitol administration in man. *Acta Anaesthesiol. Scand.* 29:19–29

149. Shafer, R. B., Levine, A. S., Marlette, J. M, Morley, J. E. 1987. Effects of xylitol on gastric emptying and food intake. *Am. J. Clin. Nutr.* 45:744–47
150. Siebert, G., Grupp, U., Heinkel, K. 1975. Studies on isomaltitol. *Nutr. Metab.* 18(Suppl. 1):191–96
151. Sinkeldam, E. J., van Garderen-Hoetner, A., Wouterson, R. A. 1983. *Life-span oral toxicity study and lactitol in rats, pretreated in utero (final report).* Rep. CIVO Inst., TNO, Zeist, The Netherlands. 232 pp.
152. Smits, M. T., Arends, J. 1985. Influence of xylitol and/or fluoride containing toothpastes on the remineralization of surface softened enamel defects in vivo. *Caries Res.* 19:528–35
153. Smits, M. T., Arends, J. 1988. Influence of extraoral xylitol and sucrose drippings on enamel demineralization in vivo. *Caries Res.* 22:160–65
154. Söderling, E., Älaräisänen, L., Scheinin, A., Mäkinen, K. K. 1987. Effect of xylitol and sorbitol on polysaccharide production by and adhesive properties of *Streptococcus mutans*. *Caries Res.* 21:109–16
155. Söderling, E., Talonpoika, J., Mäkinen, K. K. 1987. Effect of xylitol-containing carbohydrate mixtures on acid and ammonia production in suspensions of salivary sediment. *Scand. J. Dent. Res.* 95:405–10
156. Sowers, J. R., Barrett, J. D. 1982. Hormonal changes associated with hypertension in neoplasia-induced hypercalcemia. *Am. J. Physiol.* 242:E330–34
157. Thiébaud, D., Jacot, E., Schmitz, H., Spengler, M., Felber, J. P. 1984. Comparative study of isomalt and sucrose by means of continuous indirect calorimetry. *Metabolism* 33:808–13
158. Thomas, D. W., Edwards, J. B., Gilligan, J. E., Lawrence, J. R., Edwards, R. G. 1972. Complications following intravenous administration of solutions containing xylitol. *Med. J. Aust.* 1:1238–46
159. Trahan, L., Bareil, M., Gauthier, L., Vadeboncoeur, C. 1985. Transport and phosphorylation of xylitol by a fructose phosphotransferase system of *Streptococcus mutans*. *Caries Res.* 19:53–63
160. Trahan, L., Mouton, C. 1987. Selection for *Streptococcus mutans* with an altered xylitol transport capacity in chronic xylitol consumers. *J. Dent. Res.* 66:982–88
161. Trahan, L., Néron, S., Bareil, M. 1988. Preparation and purification of xylitol-5-phosphate from a cell extract of *Lactobacillus casei* C1-16. *Appl. Environ. Microbiol.* 54:570–73
162. Tsuji, Y., Yamada, K., Hosoya, N., Moriuchi, S. 1986. Digestion and absorption of sugars and sugar substitutes in rat small intestine. *J. Nutr. Sci. Vitaminol.* 32:93–100
163. Van der Hoeven, J. S. 1979. Influence of disaccharide alcohols on the oral microflora. *Caries Res.* 13:301–6
164. Van der Hoeven, J. S. 1980. Cariogenicity of disaccharide alcohols in rats. *Caries Res.* 14:61–66
165. Van der Hoeven, J. S. 1986. Cariogenicity of lactitol in program fed rats. *Caries Res.* 20:441–43
166. VanEs, A. J. H., DeGroot, L., Vogt, J. E. 1986. Energy balances of eight volunteers fed on diets supplemented with either lactitol or saccharose. *Br. J. Nutr.* 56:545–54
167. Van Velthuijsen, J. A. 1979. Food additives derived from lactose: lactitol and lactitol palmitate. *J. Agric. Food Chem.* 27:680–86
168. Wang, Y. M., Oshinsky, R. J., Klantin, E., Ukab, W., Van Eys, J. 1977. Zur Frage der Toxizität von Xylitinfusionen bei Kaninchen. *Infusiontherapie* 4:251–57
169. Wang, Y.-M., Van Eys, J. 1981. Nutritional significance of fructose and sugar alcohols. *Annu. Rev. Nutr.* 1:437–75
170. Wasserman, R. H. 1964. Lactose-stimulated intestinal absorption of calcium: a theory. *Nature* 201:997–99
171. Wasserman, R. H., Taylor, A. N. 1969. Some aspects of the intestinal absorption of calcium, with special reference to vitamin D. In *Mineral Metabolism: An Advanced Treatise,* Vol. III, *Calcium Physiology,* ed. C. L. Comar, F. Bronner, pp. 321–403. New York: Academic
172. Würsch, P., DelVedovo, S. 1981. Inhibition of human digestive enzymes by hydrogenated malto-oligosaccharides. *Int. J. Vitam. Nutr. Res.* 51:161–65
173. Yoshizawa, S., Moriuchi, S., Hosoya, N. 1975. The effects of maltitol on rat intestinal disaccharidases. *J. Nutr. Sci. Vitam.* 21:31–37
174. Younoszai, M. K., Nathan, R. 1985. Intestinal calcium absorption is enhanced by D-glucose in diabetic and control rats. *Gastroenterology* 88:933–38
175. Zaal, J., Ottenhof, A. 1977. *Influence of lactitol in blood sugar levels after sucrose intake.* Rep. CIVO Inst., TNO, Zeist, The Netherlands. 9 pp.
176. Zeigler, E. E., Fomon, S. J. 1983. Lactose enhances mineral absorption in in-

fancy. *J. Pediatr. Gastroenterol. Nutr.* 2:288–94
177. Ziesenitz, S. C. 1983. Bioavailability of glucose from Palatinit®. *Z. Ernährungswiss.* 22:185–94
178. Ziesenitz, S. C. 1986. Zur Verwertung des Zuckeraustauschstoffes Palatinit® in Stoffwechsel. *Beitr. Infusionstherapie Klin. Ernähr.* 16:120–32
179. Ziesenitz, S. 1986. Stufenweises Prüfschema für Zuckeraustauschstoffe Vorprüfung mittels Enzymen. 3. Carbohydrasen aus Jejunalmucosa des Menschen. *Z. Ernährungswiss.* 25:253–58
180. Ziesenitz, S. C., Siebert, G. 1987. The metabolism and utilization of polyols and other bulk sweeteners compared with sugar. In *Developments in Sweeteners*, ed. T. H. Grenby, 3:109–49. London: Elsevier Appl. Sci.