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NUTRITIONAL SIGNIFICANCE OF FRUCTOSE AND SUGAR ALCOHOLS

Yeu-Ming Wang and Jan van Eys

The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030

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INTRODUCTION

Four dilemmas have surfaced in recent years in dealing with sugar and other related sweeteners: (*a*) the undesirable effects of sugar (sucrose and

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glucose) to humans, particularly in dental health, and to selected populations with genetic or metabolic defects, most prominently diabetes; (*b*) the chronic toxicity of a number of noncaloric sweeteners, some of which were removed from markets because of existing rules and regulations; (*c*) the explosion in knowledge of human carbohydrate metabolism—even though we are adapted to glucose as the major source of carbohydrate energy, we are or may be able to utilize chronically other monosaccharides or polyalcohols as the primary carbohydrates source; and (*d*) the pressure generated by the improved technology for inexpensive production of D-fructose, D-sorbitol, D-mannitol, and xylitol or their related products.

Primarily because of these recent and current pressures, efforts at research and development for scientific or industrial/commercial application of these glucose analogues have soared. In the past two decades in Europe and Japan, research in the clinical use of the nonglucose carbohydrates D-fructose, D-sorbitol, and xylitol has been very active. Their use has been evaluated in diabetes, as advocated by K. Lang, K. H. Bässler, and H. Förster in Germany, and in dental health by A. Scheinin and K. K. Mäkinen in Finland. This research, along with the propensity of people to consume sweets, encouraged commercial institutions to produce and use nonglucose carbohydrate products. However, these fragmented, though positive, findings required North American clinicians and scientists to await a systematic confirmation of the results obtained by their European colleagues. On the other hand, the food and related industries are tantalized by the potential and are anxious to use these nonglucose carbohydrates on a large scale in their products. The recent ban of a number of noncaloric sweeteners, because of their confirmed genotoxicity in animals, has made the problem more acute.

Because of these problems, the Life Science Research Office of the Federation of American Societies for Experimental Biology, under a contract with the Food and Drug Administration, has recently gathered the current information available on D-fructose (105), xylitol (51), D-sorbitol (4), and D-mannitol (5). An effort was also made to evaluate the need for special foods and sugar substitutes by people with diabetes (178). In addition, xylitol was also the focus of a recent symposium in London (40).

In this review, we summarize briefly the state of our understanding on the nutritional significance of D-fructose, D-sorbitol, D-mannitol, and xylitol, mainly in humans. However, the discussion includes pertinent results in animals. The chemical formulas of these compounds are shown in Figure 1. Results on other nonglucose carbohydrate sweeteners were discussed in a few symposia (107, 164, 167), and glycerol has been reviewed recently (116). We inject our own views on this subject, to formulate suggestions on future research needs.

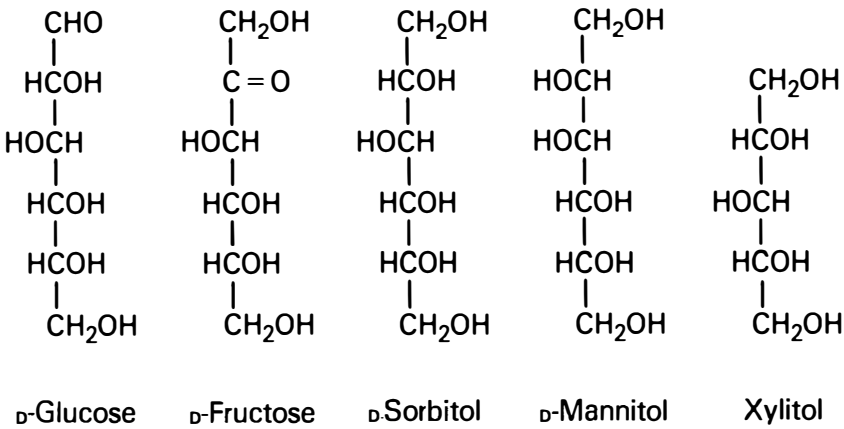

Figure 1 The structural formulas of D-glucose, D-sorbitol, D-mannitol, and xylitol.

FRUCTOSE

Occurrence and Manufacture

Fructose is a major dietary ingredient because of the extensive use of sucrose, of which it is a component, as a sweetener. Fructose was first isolated from cane sugar in 1847. It is somewhat sweeter than sucrose (132). Free fructose is consumed in substantial quantities in edible fruits, vegetables, and honey. Honey contains 37% fructose (166); cherries, pears, bananas, apples, grapes, and oranges contain from 2–3% (46, 80, 107, 161). The total world consumption of fructose per year is approximately 13,000 metric tons.

About a decade ago, separation of glucose and fructose from invert sugar solutions was achieved by ion-exchange chromatography. The adoption of this method increased the production of pure fructose and drastically lowered the price. At about the same time, the isolation of isomerases capable of isomerizing D-glucose to D-fructose led to the commercial introduction of a fructose-containing starch-derived syrup.

Metabolism

Fructose is believed to be absorbed slower in the gastrointestinal tract but is utilized faster in tissues than is glucose. There is a minimal conversion of D-fructose to L-lactic acid and D-glucose during absorption in human intestinal mucosa cells (88). The mechanism of D-fructose transport is controversial, partly due to species differences in the transport system. The metabolism of D-fructose in the rat is similar to that in humans. The cellular uptake of fructose in rat small intestines appears to be a highly specific and energy-dependent process that may be Na^+ dependent and inhibited by

L-sorbose. The absorbed fructose does not enter the liver cell freely. However, it is difficult to characterize the nature of the hepatic fructose transport because of the instant intracellular phosphorylation of the ketose. Sestoft & Fleron (160) have estimated the carrier-mediated transport of D-fructose in isolated perfused rat liver by building a mathematical model to separate the kinetic process of transport and phosphorylation. They reported that hepatic fructose transport has an apparent Km of 67 mM and a V_{max} equal to 30 μmol per min per g of wet tissue. This analysis suggested that carrier-mediated transport has an affinity of two orders of magnitude higher than phosphorylation and is the limiting step in fructose metabolism. Rapid accumulation of fructose-1-phosphate occurs in any tissue that possesses ketohexokinase. The enzyme is not specific for fructose, and it also catalyzes the phosphorylation of L-sorbose, D-tagatose, D-xylulose, and L-galactohepatulose. The hepatic accumulation of fructose-1-phosphate has been seen in laboratory animals as well as in humans, but the exact mechanism is not known. The finding that accumulation of the fructose-1-phosphate precedes the increase of inosine 5'-monophosphate (IMP) in vitro (189) makes it unlikely that this fructose-1-phosphate aldolase inhibitor is the cause of the initial build-up of the sugar metabolite. D-Fructose-1-phosphate is cleaved to D-glyceraldehyde and 1,3-dihydroxyacetone phosphate (DHAP) by the fructose-1-phosphate aldolase. DHAP enters the glycolytic pathway to become L-lactate, glucose, or glycogen. D-Glyceraldehyde is metabolized in three ways: to glyceraldehyde-3-phosphate, to glyceric acid, and to glycerol. It appears that glyceraldehyde-3-phosphate formation is the major route in liver and glycerol formation is the major route in kidney for the catabolism of glyceraldehyde.

Fructose, in contrast to glucose, is not an adequate energy source for isolated guinea pig heart (32). However, fructose metabolism has a significant role in supplying energy for spermatozoa motility. There is a significant correlation between the rate of fructolysis and the quantity of mobile spermatozoa. Seminal D-fructose concentration is an indicator of the size and secretory capacity of the seminal vesicle. The metabolism of D-fructose in sperm is via Embden-Meyerhof glycolysis. Ketohexokinase, phosphofructokinase, and pyruvate kinase activities are responsible for the regulation of fructolysis. Seminal D-fructose originates from blood D-glucose either via the phosphorylated intermediates or by enzymic reactions of aldehyde reductase and polyol dehydrogenase. The importance of D-fructose in testis and spermatozoa and the metabolism of fructose has been discussed in a recent review (35).

The most striking biochemical difference between the infusion or ingestion of substantial quantities of fructose and glucose is the degree of hyperuricemia. Glucose usually does not result in excessive uric acid pro-

duction. However, depending upon the dose and the infusion rate, fructose does often result in an increase in the catabolism of purine nucleotides. In 1967, Perheentupa & Raivio (143) and Förster et al (57) independently reported that oral or intravenous administration of fructose at a dose of 0.5 g/kg (body weight) provoked hyperuricemia and hyperuricosuria in normal individuals and in children with hereditary fructose intolerance. This observation has since been confirmed (24, 25). At least two mechanisms can account for the pathological effects: increased synthesis or degradation of purine nucleotides, and decreased renal or extrarenal disposal of uric acid, mainly through competition with lactic acid from fructose-induced lactic acidosis. An increase of de novo synthesis of purines has been demonstrated elegantly by the enhancement of [1-^{14}C]-labeled glycine incorporation into uric acid under fructose loading (148). The increased depletion of ATP by fructose loading is also accompanied by an increase of hepatic IMP concentration and urinary inosine-hypoxanthine excretion. In addition, there is a reduced production of cAMP. However, the level of cAMP is adequate for its intracellular function (96). The short-lived ATP depletion appears to be a self-limiting phenomenon. The decrease of hepatic ATP ends when it decreases to 30% (1 mM) of the original level. This appears to result from the deregulation of hepatic AMP deaminase activity. The activity of this enzyme is usually controlled by the concentrations of ATP, GTP, and P_i. The enzyme activity can be enormously increased after fructose loading, apparently because of sudden concentration changes of intracellular ATP and P_i.

The metabolism of D-fructose, along with the metabolic routes of D-sorbitol, D-mannitol, and xylitol, are shown in Figure 2.

Safety

Fructose administration has been recommended in a number of clinically adverse conditions in which the rapid utilization of D-fructose appears to be advantageous. The beneficial effect of fructose infusion is thought to be lack of dependence on insulin for its initial metabolism, a reduced risk of hypoglycemia after abrupt cessation of parenteral alimentation, and potential protein-sparing effect.

Recent biochemical findings have demonstrated that fructose utilization bypasses the enzyme regulation of phosphofructokinase. A rapid infusion or injection of D-fructose may result in the accumulation of fructose-1-phosphate in liver, kidney, and gastrointestinal tract with concomitant intracellular depletion of ATP, total adenine nucleotides, and intracellular inorganic phosphate. These sequential changes are dose- and infusion-rate-related toxicities. Although the decrease of ATP is not lethal to cellular function and integrity, it reduces RNA and protein biosynthesis and inhib-

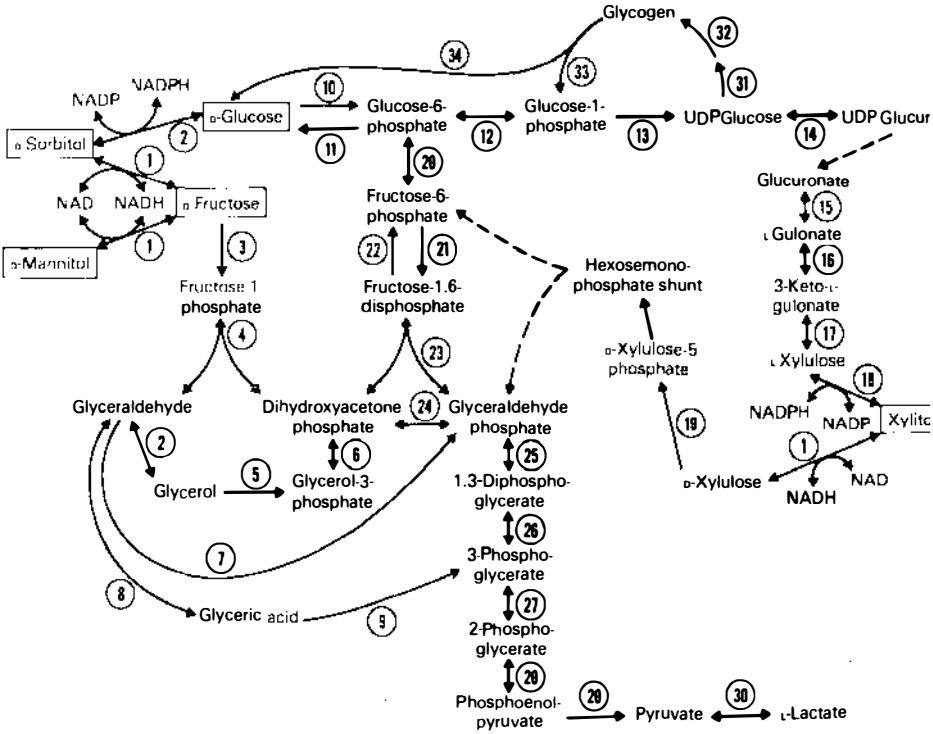

Figure 2 The metabolism of D-fructose, D-sorbitol, D-mannitol and xylitol in liver. 1, L-Iditol dehydrogenase (E C 1.1.1.14), NAD-dependent polyoldehydrogenase (E C 1.1.1.10); 2, aldose reductase (1.1.1.21); 3, ketohexokinase (2.7.1.3); 4, aldolase B (4.1.2.13); 5, glycerol kinase (2.7.1.30); 6. glycerol-3-phosphate dehydrogenase (1.1.1.94); 7, triosekinase (2.7.1.28); 8, aldehyde dehydrogenase (1.2.1.3); 9, glycerate kinase (2.7.1.31); 10, glucokinase (2.7.1.2); 11, glucose-6-phosphatase (3.1.3.9); 12, phosphogluocomutase (2.7.5.1); 13, glucose-1-phosphate uridylytransferase (2.7.7.9); 14, UDPG dehydrogenase (1.1.1.22); 15, glucuronate reductase (1.1.1.19); 16, L-gulonate dehydrogenase (1.1.1.45); 17, keto-L-gulonate decarboxylase (4.-1.1.34); 18, NADP-dependent xylitol dehydrogenase (1.1.1.9); 19, D-xylulokinase (2.7.1.17); 20, glucose phosphate isomearase (5.3.1.9); 21, phosphofructokinase (2.7.1.11); 22, fructosebisphosphatase (3.1.3.11); 23, fruxtose bisphosphate aldolase (4.1.2.13); 24, triose phosphate isomerase (5.3.1.1); 25, glyceralehyde-3-phosphate dehydrogenade (1.2.1.12); 26, phosphoglycerate kinase (2.7.2.3); 27, phosphoglycerate mutase (2.7.5.3); 28, enolase (4.2.1.11); 29, pyruvate kinase (2.7.1.40); 30, L-lactate dehydrogenase (1.1.1.27); 31, glycogen synthase (2.-4.1.11); 32, amylo-1-4,1-6-transglucosylase (2.4.1.18); 33, phosphorylase (2.4.1.1.); 34, oligo,1-6-glucosidase (3.2.1.10).

its the production of triglycerides. Therefore, the high-dose infusion of fructose is toxic. Förster et al (55) advocated an infusion rate of 0.5 g of fructose/kg (body weight)/h, which appeared to be safe and well tolerated for 48 to 72 h in normal and intensive-care patients.

The rapid phosphorylation of fructose poses a significant and potential danger. The accumulation of AMP and IMP during fructose infusion could

further aggravate fructose-1-phosphate accumulation through the inhibition of fructose-1-phosphate aldolase by the nucleotides (208). These biochemical changes, including hypophosphatemia, have been confirmed in humans through hepatic biopsy following acute fructose administration. The total adenine nucleotide content in a liver biopsy sample after 10 days of fructose infusion was subnormal but without significant difference from that in patients infused with glucose. This raised the question of whether or not the type of nucleotide disturbance could be different in acute and chronic administration of D-fructose.

ATP depletion by very rapid administration of a metabolite or its analogues was first recognized with infusion of 2-deoxyglucose (171, 212). More recently, the depletion of liver adenine nucleotides and inorganic phosphates was also reported for glycerol and xylitol, as well as for D-fructose. In a study of fructose infusion, the intracellular concentration of inorganic phosphate and ATP fell to about one third to one fourth normal level (120). The minimum effective dose of fructose corresponded to a mean initial concentration of 4.5 mM in the medium (80 mg per 100 ml of medium). In perfusion experiments, the loss of rat liver adenine nucleotides was of a similar order of magnitude as the amount of allantoin produced (149). The severity of depletion of inorganic phosphate and not the magnitude of fructose-1-phosphate accumulation determines the reduction of intracellular ATP (130). The same effects of large doses of fructose on liver adenine nucleotide have been observed in humans by Bode and his co-workers (24). Similarly, Wood & Krebs (209) observed a depletion of adenine nucleotides and inorganic phosphate after xylitol loading of isolated perfused liver. However, at lower doses of fructose or xylitol, liver ATP and inorganic phosphate levels seemed to be maintained well (149, 209). Even high doses of glucose depleted inorganic phosphate significantly. An increase of serum bilirubin was also reported after fructose infusion. The increase of bilirubin was identical regardless of whether glucose, fructose, sorbitol, or xylitol was used (58). The bilirubin increase resulting from glucose infusion was first reported in 1961 (see 54). Some ultrastructural changes have been reported to occur in the liver after fructose administration (69, 144). Similar structural alterations can also be found in rat liver cells after glucose injection (69). It has been reported, however, that maintenance of severely depressed levels of ATP and other adenine nucleotides, as low as 20–25% of normal, for as long as 36–48 h does not compromise the viability of the liver parenchymal cells (165). A number of investigators have indicated that D-fructose increases the α-glycerophosphate concentration in livers. Exton & Park (50) reported that 20 mM D-fructose increases the α-glycerophosphate concentration in the perfused rat liver up to 4 μ mol/g of dry tissue in 1 h. Wieland & Matchinsky (201) found only up to 0.15 μmol of α-glycerophosphate/g of wet tissue in 2 h after D-fructose

infusion. Oral intake of large amounts of D-fructose did not increase hepatic phosphate concentration over that produced by D-glucose (215, 216).

The results of oral D-fructose-induced hyperlipidemia in man and in animals are controversial. MacDonald (118) reported that the specific activity of the serum triglycerides in healthy men was greater after the oral ingestion of ^{14}C-labeled fructose than after that of ^{14}C-labeled glucose. This was also observed in humans fed sucrose. The fructose portion of the sugar appear to be responsible for the increase of triglyceride. In baboons, a cause and effect relationship between fructose tolerance and triglyceride-specific activity was demonstrated with a high, ^{14}C-labeled sucrose diet (39). Heinz et al (87) showed in biopsy materials that fructose is converted in human livers to glycerophosphate faster than in glucose. Fructose added to rat liver perfusates increases the secretion of very low density lipoprotein (VLDL)-triglycerides into the medium (183). On the other hand, the sucrose-induced hyperlipidemia, which does not occur by feeding an isocaloric equimolar mixture of glucose and fructose, was thought to be a dissacharide effect (105). Consumption of moderate amounts of fructose (72 g/day) in 35 study subjects for a 2-year period had no discernable effect on the fasting serum triglycerides or cholesterol (99). Similar findings were seen in controlled juvenile diabetics (3) and patients with other pathological states (139). There is ample evidence to suggest that the fructose-induced hyperlipidemia might be species related, with rats being more susceptible to the fructose-mediated anomaly. The mechanism of this difference is unknown. Therefore, the implication for man of results obtained from rats concerning fructose-mediated elevation of serum triglycerides has to be cautiously interpreted.

Fructose and Dental Caries

Current concepts hold that dental caries is an infectious disease of multifactorial etiology. A heterogenous population of facultative and anerobic gram-negative and gram-positive bacteria has been identified in plaque, but recent attention has been directed to the acid-and-polysaccharide-forming *Streptococcus mutans* in the oral cavity (30, 52, 105). This is further influenced by the anatomical peculiarities of the different sites, the substrate availability, and thus the colonization potential of the organism. Long-chain polysaccharides (polyglucans or dextrans) assist in entrapping the bacteria in plaque and force close contact between the cariogenic organism and the tooth surface (67, 81). However, the low pH of the plaque/tooth interface is apparently the ultimate cause of enamel breakdown at the tooth surface. This process of transformation is, in fact, influenced or modulated to a large degree by the quantity and frequency of sugar consumption. Thus, individuals with hereditary fructose intolerance who learn to avoid all forms

of sweets to omit dietary fructose have fewer dental cavities than does the general population (137). Numerous investigators have reported that sucrose is the most cariogenic sugar in animal experiments. There is evidence from a number of laboratories that a variety of sugar substitutes may provide an ecosystem that reduces plaque formation and dental caries in animals and humans. Fructose has been reported to be a good substrate for oral bacterial growth and cavity production in laboratory animals (72, 73, 136, 175). In a number of comparative studies carried out on the cariogenicity of sucrose, glucose, and fructose in the hamster (62, 77, 158), however, the observations have generally shown fructose and glucose to be clearly less cariogenic than is sucrose. The difference was evident when the animals were infected with *S. mutans.* Frostell et al (62) showed in a double-blind test that D-fructose produces fewer cavities than does sucrose. In recent years, however, it was clearly demonstrated that polyols, xylitol, sorbitol, and mannitol are generally superior to D-fructose in preclinical trials for dental care. This is discussed further in the sections on xylitol and D-sorbitol.

Fructose and Diabetes

Fructose first attracted attention in medicine over 100 years ago when it was claimed that fructose was assimilated better than glucose by patients with diabetes mellitus. Minkowsky (126) first observed in 1893 that the pancreatectomized dog could synthesize glycogen in liver from D-fructose but not from D-glucose. This and clinical studies over many decades have encouraged the widespread belief that fructose (93, 127), as well as xylitol and sorbitol, are beneficial in the diet for diabetic patients.

Those favoring the argument have the following views: (*a*) Transport and distribution of fructose, sorbitol, and xylitol at the initial step are independent of insulin; (*b*) the absorption of oral fructose, sorbitol, and xylitol is much slower (20–30%) than that of glucose and, therefore, (*c*) it results in minimal or transient increase of plasma glucose, which at least gives a slight edge to fructose, sorbitol, and xylitol over either glucose or sucrose; (*d*) it appears that there is adequate glycogen synthesis activities in diabetic animals, including humans, after administration of these nonglucose carbohydrates and this glycogen formation is independent of plasma glucose levels; and (*e*) there is definitely an antiketogenic effect of these sugar substitutes. Those who have opposed the use of fructose, sorbitol, and xylitol as a sugar substitute or as a treatment regimen for diabetes have held the following views: (*a*) Up to 80% of these compounds are metabolized in liver and almost always exclusively metabolized to glucose or its polymer form, glycogen; (*b*) the antiketogenic effect of xylitol, fructose, or sorbitol decreases proportionally to the severity of diabetic acidosis and the tendency

toward gluconeogenesis; and (*c*) therapy with insulin and proper hydration is a necessary and far more reasonable approach than infusion of sugar substitutes such as fructose or polyols, which may further aggravate the hyperglycemic condition and osmotic stress.

Since D-fructose is readily available in many countries, it is of considerable interest to know whether or not it can be used by patients with impaired sucrose utilization. Nikkilä (139) reported that sucrose in daily amounts close to average intake in various populations increases serum triglyceride levels in subjects with primary hypertriglyceridemia. Fructose seems to be less active. Diabetics with either uncontrolled disease or treated with insulin can consume 75 g of fructose daily without any evidence of adverse effects or metabolic signs of their disease. Åkerblom et al (3) fed diabetic children fructose daily at either 1 g/kg (body weight) or 1.5 g/kg with no toxic symptoms. Recently, Crapo et al (41) studied the acute effects of oral ingestion of 50-g loads of glucose, sucrose, and fructose in 36 subjects, including 9 normal ones, 10 with impaired glucose tolerance, and 17 non-insulin-dependent diabetic ones with fasting hyperglycemia (>140 mg/dliter). They concluded that fructose ingestion resulted in lower serum glucose, decreased insulin response, and less glycosuria than glucose or sucrose. However, the serum glucose response to fructose was increased the more glucose intolerant the subject was.

Froesch and his colleagues injected ^{14}C-labeled fructose, sorbitol, xylitol, and glucose in the presence or absence of insulin in normal, fasted, and streptozotocin-treated rats (60, 104). There was no incorporation into the diaphragm glycogen of radioactivity from fructose, xylitol, and sorbitol in the absence of insulin. All three glucose substitutes were rapidly converted to glucose by the liver. Adipose tissue took up fructose in greater quantities than did either xylitol or sorbitol. Fructose transport in adipose tissue was not enhanced by the presence of insulin in streptozotocin-treated rats. However, it appeared that fructose intake by adipose tissue is slightly insulin dependent in the absence of glucose (59). Insulin significantly stimulated liver glycogen synthesis from fructose in the animals (104), but this transformation was inferior to that found in normal livers. Keller & Froesch (104) suggested that the antiketogenic effect of fructose decreased proportionally to the severity of diabetic acidosis and the degree of relying on gluconeogenesis for energy production. They observed a more rapid utilization of fructose in the liver of humans with diabetes compared to that of glucose and a higher rate of glycogen, lactate, and pyruvate formation. Furthermore, Arvidsson Lenner (6, 7) reported that blood sugar levels and urinary glucose excretion did not differ in nine adult diabetics compared with three normal control subjects when they all consumed breakfast with isocaloric quantities of sucrose, fructose, or sorbitol. She further suggested

(7) that it is unnecessary to use special sweeteners in foods prepared for diabetics. Another consideration that tends to diminish enthusiasm for substitution of fructose for sucrose or starch is the demonstration that carbohydrate restriction may not play an important role in disease control (200). The important determinant appears to be the total energy consumption rather than qualitative features of the diet. This view was echoed by Bierman & Nelson (22). However, Talbot (178) recently concluded from his literature research that individuals with diabetes mellitus have a potential need for special dietary foods and sugar substitutes. This summary can be condensed to three points: (*a*) Data are insufficient to determine whether or not fructose, sorbitol, and xylitol have beneficial properties as sucrose substitutes for the long-term management of diabetes; (*b*) the use of fructose, sorbitol, and xylitol is accepted by reputable European diabetologists and these compounds may provide some minor advantages in dietary management of diabetes mellitus; and (*c*) the inherent preference for sweets is a major cause of rejection of the usual carbohydrate-restricted diet by diabetics.

SORBITOL

Sorbitol crystalizes with one half or one molecule of water at melting points of 110–112°C or 75°C, respectively (198). It is 35–60% as sweet as sucrose at equal weight (210). Food-grade sorbitol occurs as white, hygroscopic powder, flakes, or granules. The absence of aldehyde or keto groups, which could participate in Maillard reactions and affect color and flavor during processing and storage, contributes to the stability of polyols in food products.

Sorbitol is produced commercially from aqueous glucose solution at 120-160°C and hydrogen pressures of 70–140 atm in the presence of Ni or Raney nickel catalysts (4). Fructose treated with a similar procedure may yield equal amounts of sorbitol and mannitol, and the products can be separated by recrystallization because of their solubility differences.

Sorbitol has been used as food additive, as starting material in the production of ascorbic acid or sorbose, as a humectant, as a flavoring agent, etc. The per capita daily consumption of sorbitol as a food ingredient is about 200 mg. Sorbitol, like xylitol, is widely distributed in plants and animals. It is present in pears, peaches, plums, cherries, apples, and berries, as well as in various seaweeds (74, 196). The content of sorbitol as well as mannitol and xylitol in some fruits, vegetables, and related products is summarized in Table 1. Oral sorbitol as well as xylitol is absorbed slowly by rat intestine. The rate of absorption of sorbitol appears to be one third that of glucose. This is definitely a factor in the laxative effect reported for excessive doses

of sorbitol in animal and man. Excessive consumption of sorbitol-containing chewing gum reportedly induces diarrhea (68).

There is no biochemical evidence to suggest that D-sorbitol can be further oxidized intracellularly without prior conversion to D-fructose and D-glucose (Figure 2). Blakley (23) first demonstrated the metabolic pathways of sorbitol to glucose via fructose and phosphorylated fructose intermediates. Hers isolated an enzyme aldolase reductase, which catalyzes the conversion of sorbitol to glucose in liver, muscle (89), and seminal vesicles (90). Subsequent work by Hers (91) and others (36) showed that the fructose → sorbitol → glucose route is responsible for the formation of sorbitol in the placenta and that sorbitol is then metabolized to fructose in the fetal liver. Aldose reductase has a broad substrate specificty (23). In human erythrocyte, the enzyme has a low affinity for D-glyceraldehyde, with a *Km* of 8.3×10^{-1} M, and for glucose, with a *Km* of 6.7×10^{-1} M (Y.-M. Wang and J. van Eys, unpublished data). The enzyme appears to be highly localized in certain cell types within each tissue, such as the epithelium of lens, Schwann cell in peripheral nerve, islets of Langerhans in the pancreas, and kidney papilla (63). The conversion of sorbitol to fructose is catalyzed by an NAD-dependent polyol dehydrogenase or L-iditol dehydrogenase. This enzyme activity also has a broad specificity toward a number of polyols mostly with low affinity. In human erythrocytes, the Michaelis-Menten constants are 1.7×10^{-3}, 2.2×10^{-3}, 2.8×10^{-2}, 1.0×10^{-2}, and 1.1×10^{-1} M for xylitol, sorbitol, ribitol, galactitol, and D-mannitol, respectively (Y.-M. Wang and J. van Eys, unpublished data). Because of the unique distribution of aldolase reductase and the subsequent low affinity of the NAD-dependent polyol dehydrogenase for a number of polyols, the sugar alcohols can be expected to accumulate in lens, sciatic nerve, and renal papilla. Particularly, a number of types of cells are not readily permeable to the sugar alcohols. The consequence of these reactions leads to toxicity, specifically in certain pathological states in which blood precursor levels are high, as in diabetes mellitus. Intracellular conversion of glucose to sorbitol and fructose has been demonstrated (115).

Most studies suggest that sorbitol in normal man is converted into fructose primarily and only a small portion is metabolized directly to glucose. As discussed in the previous section, in man most fructose is metabolized by liver, with minor contributions by peripheral adipose tissue and muscle. The fate of fructose metabolism in liver, again, is mainly the immediate formation of glyceraldehyde and DHAP through ketohexokinase and aldolase B. Therefore, sorbitol metabolism eventually leads to the formation of glucose, glycogen through gluconeogenesis, and L-lactate by the glycolytic pathway. Lactic acidosis has been reported after intravenous infusion of sorbitol (18).

Table 1 Sugar alcohols content in some fruits, vegetables, and related products[a]

Products	Sorbitol	Mannitol	Xylitol
Apple Wine	220[b]	—	120
Artichokes (*Cynara scolymus* L.)	—	183	—
Asparagus (*Asparagus officinalis* L.)	—	170	—
Beetroot (*Beta vulgaris* L. var. *cruenta alef*)	77	192	—
Carrots, fresh (*Daucus carota* L.)	—	—	86.5
Cauliflower (*Brassica oleracea* L. var. *botrytis*)	—	—	300
Celery (*Apium graveolens* var. *dulce miller*)	—	4,050	—
Chanterelles (*Cantharellus cibarium* Fries)	—	374	—
Cherry preserve	645	—	—
Eggplant (*Solanum Melon gena* L.)	—	270	180
Endives (*Cichorium endivis* L.)	—	334	258
Hawthorn juice	664	—	—
Lam's lettuce (*Valerianella olitoria* L.)	—	190	273
Lettuce (*Lactura sativa*)	—	—	131
Manna of pine	—	17,000	—
Onions (*Allium cepa* L.)	—	47.5	89
Parasol mushrooms (*Macrolepiota procera* Sing)	—	1,390	—
Parsley (*Petroselinum crisoum* (Mill) Nym.)	—	334	—
Peaches (*Prunus Persica* Stokes)	960	—	—
Pears (*Pyrus communis* L.)	4,600	—	—
Plums (*Prunus domestica* subsp. *italia*)	935	—	935
Prunes, dried (*Prunus domestica* L.)	2,420	—	—
Pumpkins (*Cucurbita pepo* L.)	—	200	96.5
Raspberries (*Rubus idaeus* L.)	—	—	268
Red cherry jam	1,100	—	56
Strawberries (*Fragaria* var.)	—	—	362
Spinach (*Spinacia oleracea* L.)	—	—	107
White mushrooms (*Boletus edulis* Bull.)	—	476	128

[a] Modified from Ref. 196.
[b] All numbers are as mg per 100 g of dry material, or as mg per 100 g of liquid.

Sorbitol appears to be an adequate energy source for the maintenance and the growth of human skin fibroblasts and arterial smooth-muscle cells in culture (187).

Oral Sorbitol and Dental Caries

About one of every three packs of gum sold in the world contains sorbitol as the sweetener. In view of the considerable success of this commercial use, the sale of sorbitol per annum has risen to an estimated 30,000,000 pounds (119). The dental aspects of the use of sorbitol have been summarized recently in a symposium held in Washington (138). It appears that gum base containing sorbitol/mannitol or sorbitol/mannitol/xylitol could indeed maintain physiological pH in a 3-day-old interdental plaque in tested sub-

jects. In contrast to sucrose, all sugar substitutes contained in the chewing gum were not fermented (101). However, sorbitol dehydrogenase activity can be demonstrated in oral enterococci and *S. mutans.* In addition, sorbitol dehydrogenase activity was identified in saliva, but xylitol dehydrogenase activity was absent (76). An increased capacity to ferment both sorbitol and xylitol by these oral organisms (121, 152) could be demonstrated in vitro. Therefore, one could conclude that neither sorbitol nor xylitol are truly noncariogenic; however, in the Turku sugar studies (124, 152), the xylitol-catabolizing enzyme did not increase significantly in saliva and plaque after more than 2 years of xylitol consumption. The polyol dehydrogenase in oral organisms has yet to be characterized. Frostell (61) studied 22 subjects for 3 months. The study subjects were given 1-g patilles containing 50% sorbitol, xylitol, mannitol, or Lycasin (Swedish quality, Luckeby Starch Refining Company). He found that moderate acid production in suspensions of dental plaque material occurred in all sorbitol test subjects. An adaptation to increased sorbitol fermentation and increased pH changes in dental plaque in vivo was documented. The risks of adaptive changes seem to be greater with sorbitol than with xylitol. Xylitol was inert in dental plaque. Söldering et al (170) reported that xylitol and sorbitol increased salivary HCO_3^- more than did sucrose.

In an earlier clinical trial, Slack et al (168), using sorbitol-containing (84.5%) tablets, studied salivary flow in 200 subjects over a 2-year period. After the first study year, a 48% caries reduction was observed in comparison to an untreated control group. However, a mere 12–27% reduction was found after the completion of the 2-year study. There was no control of sucrose intake in this investigation. In addition, an investigation of 174 children (8–12 years) who chewed sorbitol-containing gum three times daily showed a 10% caries reduction, again over a 2-year span. The most striking effect of sorbitol on dental caries was obtained by Bánóczy et al (13). A reduction of 54% in decayed, missed, and filled teeth surfaces was measured when 20 g of sorbitol chocolate (containing 8 g of sorbitol) was used in comparison to an equal intake of sucrose chocolate. This study involved 404 children age 3–12 years for over a 1-year period.

Sorbitol in Parenteral Nutrition

Sorbitol has been used in parenteral alimentation in recent years (33, 113). Because of similar reasoning to that for the use of fructose, it is less insulin dependent, less ketogenic, and better utilized in glucose intolerance or in liver or renal damage (95); it also enhances protein sparing (71) and produces a lower frequency of venous thrombosis during infusion. Clinical trials and use have almost exclusively occurred in European countries. Meng (125) studied the long-term intravenous administration of sorbitol in

dogs in combination with amino acids, vitamins, and minerals. The dose of sorbitol was 8–16.75 g/kg/day at an infusion rate of 0.35–0.7 g/kg/h. His results showed that this amount of sorbitol can be effectively utilized without diuresis and histopathological changes. The infusion, however, induced transient elevation of serum alkaline phosphatase and serum glutamic-pyruvic transaminase. Up to 10% sorbitol can be recovered from urine. This was in agreement with observations in humans (33, 113). In normal volunteers, Lee and his co-workers (113) found severe side effects of epigastric pain, tachycardia, nausea, and faintness after rapid infusion of sorbitol at a total dose of 150 g (30%) in 5 h (0.5 g/min.). The urinary excretion of sorbitol was 15%. Sorbitol was well utilized and tolerated otherwise. However, in patients with hepatic or renal disease, the rate of sorbitol utilization was impaired and compared poorly with that of glucose. In this study the reduced incidence of thrombosis (113) could not be confirmed.

In continental Europe, sorbitol has been used often in comparisons with xylitol, fructose, and glucose in carbohydrate feeding or infusion studies in humans. Sorbital infusions result in an increase of serum uric acid and bilirubin similar to that of fructose. Förster (54) concluded in his animal studies that sorbitol properly infused was without adverse effects, though its protein-sparing effect was not substantial compared with that of xylitol and fructose. The safe infusion rate of sorbitol has been suggested as being 0.25 g/kg/h by Berg et al (20).

The Vitamin-Sparing Action of Sorbitol and Other Polyols

In the course of experiments on dietary adaptation, Morgan & Yudkin (128) discovered that rats fed a diet of 10–20% sorbitol as sole source of carbohydrate lost their dietary requirement for thiamin. Additional sugars tested at that time included varying levels of glycerol, glucose, fructose, sorbose, sorbic acid, ascorbic acid, and mannitol. A sucrose diet served as control. Only sorbose gave an effect equivalent to sorbitol, and glycerol produced a small effect. A similar sparing action of sorbitol could be shown for riboflavin requirements (86, 129). A sparing effect or increased excretion was also found for other vitamins after sorbitol feeding (129). Mice showed the same response to sorbitol feeding (128). In man, the excretion of thiamin was increased after sorbitol administration (197).

The most likely explanation for the effect is an increased intestinal synthesis of thiamin. There are no obvious qualitative changes in the intestinal microflora, but there is probably a quantitative change, since the cecum is enlarged in rats and mice. In rats, coprophagy is the mechanism whereby thiamin is made available, and prevention of coprophagy precludes thiamin sparing. However, the increased excretion of thiamin after sorbitol administration in human points to an increased absorption as well (129).

These data were recently again confirmed and were extended to xylitol in rats (27). Xylitol spares riboflavin and pyridoxine as well (28). There was a quantitative change in microflora in the rats that did not adapt to high xylitol loads (199).

MANNITOL

D-Mannitol is the hexitol chemically related to mannose. It is widely distributed in nature and occurs in the exudates of many plants. It can be found in onions, grasses, the Jerusalem artichoke, and most varieties of mushrooms (Table 1). It is especially high in the exudate of olive trees (26). In marine algae, especially brown algae, mannitol is a major product of photosynthesis.

Mannitol has a sweet taste, its sweetness being 45–57% that of sucrose (132). The sugar is assumed to be nonabsorbable. The data for the lack of absorption came from studies of intestinal and renal physiology (53, 102). In addition, it is generally assumed that the substance is not metabolized (176). However, there are conflicting data in the literature. Nasrallah & Iber (135) evaluated the oral administration of uniformly labeled ^{14}C-labeled mannitol in doses of 28–100 g to five normal subjects and five subjects with cirrhosis. They recovered up to 50% of the mannitol in urine and stool after 48 h and as much as 18% was recovered as expired CO_2. However, after intravenous administration little was metabolized. An attempt to explain this discrepancy by bacterial flora metabolism was considered, but incubation of mannitol in stool samples showed very little breakdown (135). Earlier experiments in rats suggested the same findings. In 12 h 50% of an oral mannitol dose was recovered as CO_2, whereas intraperitoneal injection resulted in only 2.3% recovery expired CO_2. The investigators attempted to explain the discrepancy by exclusive liver metabolism, since they found extensive oxidation after intrasplenic injection (202). Based on the results in humans to whom a 5% solution of mannitol was given, the availability of energy from mannitol was estimated to be 2.0 kcal per g. Staub (174) estimated that on the basis of growth rate of rats fed 3–24% mannitol in their diet, 2.7 kcal per g was the energy available in mannitol.

Recently, two long-term feeding studies of mannitol in rats were concluded (see 5). The first study used Wistar rats who received 1.5, 4, or 10% mannitol in their diet and revealed an apparent mannitol-related incidence of benign thymic tumors in female rats but not in males. Subsequently, three strains of female rats, Sprague-Dawley, Fischer, and Wistar (which came from a different supplier), were again fed similarly. No mannitol-related adverse effects were revealed. However, the combined incidence of focal medullary hyperplasia and medullary pheochromocytoma was significantly

higher in Fischer rats fed the 10% mannitol diet than in the comparable control group.

The concept that mannitol is poorly absorbed persists. For this reason the polyol is extensively used for irrigation and gastrointestinal perfusion in patients with impaired renal function (214). Data on the absorption of mannitol in uremic patients seem to suggest that 7.2% of ingested mannitol is absorbed. The absorbed mannitol is excreted by the kidney and also is eliminated by an extrarenal route, possibly by metabolism. The extrarenal clearance was estimated to be 1.95 ml/min, which is insufficient to remove absorbed mannitol in anuric patients.

When mannitol is fed to rats, it results in a decrease in food intake. In one study, it was thought to be through a reduction of the meal size (37), whereas in another it seemed that the addition of mannitol to the diet delayed the next feeding (21). The mechanism was not thought to be learned food aversion but an actual limitation of intake (37). The explanation given is the distention of the small intestine by the nonabsorbable carbohydrate. When mannitol is infused in a pouch preparation, it does not affect the secretion of the endogenous gastric inhibitory polypeptide, but it does inhibit gastric acid secretion (140).

Currently, the greatest use of mannitol is as an osmotic diuretic. Mannitol is cleared by the kidney like inulin (169). When injected in high concentration, it shows no entry into tissues. Only after prolonged maintenance of very high concentrations is any appreciable metabolism noted (31, 176). Mannitol is also added to foods principally as a formulating aid in candies, chewing gum, and other items in which its sweet taste is useful. Extensive use of mannitol is not practical because of its absorption in humans. The estimated usage as a food additive was between 1.5–2.5 X 10^6 kg by 1975.

Mannitol is endogenously formed. It can be detected as a normal urinary constituent (29, 110). Polyol dehydrogenase in the tissues can metabolize mannitol (Figure 2). It is possible, therefore, that mannitol is derived from reduction of endogenous or dietary D-fructose (190). Increased cerebrospinal fluid mannitol concentration recently has been linked to chronic renal failure or uremia (145, 159). Mannitol is metabolized by dental plaque and is about as cariogenic as sorbitol (30) or sucrose (136). However, a number of investigators (75, 162, 163) have provided evidence that mannitol is less cariogenic than is glucose, sucrose, or fructose.

The discrepancy between the data on utilization of oral mannitol by the tracer methodology and the physiological experiments is not resolved. It is likely that bacterial flora plays a major role in this seeming absorption and metabolism. The experience from the current medicinal use of mannitol as an osmotic diuretic and irrigating solution seems to provide ample evidence that utilization, intestinal absorption, and renal reabsorption are minimal.

XYLITOL

Chemical Properties

Xylitol is a five-carbon polyol whose existence has been known for over 90 years. It was crystallized in a metastable form (mp 61–61.5°C) 50 years after its discovery. The stable modification (mp 93–94.5°C) was reported shortly thereafter. Xylitol can be obtained through the chemical reduction of D-xylose, accomplished over nickel under pressure or through the classic method of using a sodium amalgam. Crystalline xylitol is the sweetest of all known polyols. It is stable at room temperature and withstands autoclaving.

Occurrence and Manufacture

Xylitol is widely distributed in the plant kingdom (Table 1). Onishi & Suzuki (141) studied over 100 species of yeast for their ability to produce xylitol directly from glucose. They also observed that most wines contain xylitol as a fermentation product. Significant quantities of xylitol have been detected in plums, strawberries, cauliflower, raspberries, etc. (196). In plums, approximately 1% of the dry weight is xylitol. Xylose is believed to be the precursor. Xylitol currently is mainly produced from xylan derived from birchwood chips. The total production is estimated to be 1000 tons per year. There are other suitable starting materials for commercial production, including larch, beech, other hardwood chips, sugar cane, bagasse, cottonseed hulls, cornstalks, corn, and shells of coconut, almond, and pecan (48). Commercial production of xylitol from corncobs has been considered by a few United States manufacturers. However, products containing added xylitol for public dietary use were not available in the United States. One brand of gum contained 10% xylitol and was sold in this country. In Germany, Switzerland, and the Scandinavian countries, xylitol has been used as a sweetener in chewing gum, chocolate, bakery products, and other food products (40, 107).

Nutritional Values

Isotonic solutions of xylitol and sucrose have approximately equal sweetness (131). Xylitol yields 4.06 kcal per g, and a 4.56% solution of xylitol is physiological isotonic. It has been estimated that 1 mol of xylitol yields 35 mol of ATP compared with 38 mol of ATP by glucose in cellular oxidation (15). Studies in mice, rats, and humans showed that over 90% of xylitol can be assimilated, which is closer to the 100% assimilation of glucose by these species. This indicated equal net carbohydrate utilization between xylitol and glucose in an open system. Because of this similarity, rats fed regular diets containing 35% xylitol or glucose gained weight

steadily and equally (111, 172). There are at least four studies indicating that xylitol can be used as a sole carbohydrate source to maintain growth and physiological functions. In a culture system of human fibroblast, xylitol could be used as the sole carbohydrate source and could produce 70% of ATP compared to glucose and thus maintain fibroblast growth (44). Meng (125) showed that there was no detectable difference between two groups of dogs, one of which received daily infusion of xylitol at no more than 10 g/kg/day for 14–20 days and the other received glucose as the sole carbohydrate source. In a feeding trial of approximately 2 years performed at Huntington Research Center, 1000 28-day-old CFLP male and female mice were fed 0, 2, 10, or 20% xylitol or 20% sucrose in the diet, with 100 mice of each sex in each group, for 102 to 106 weeks (98). The mean intakes of the three xylitol concentrations and one sucrose concentration were 1.3, 8.5, 17.4, and 11.3 g/kg/day, respectively, for males and 1.9, 9.8, 19.6, and 16.5 g/kg/day, respectively, for female mice. Except for those animals fed 20% xylitol, growth and gain of body weight for these mice were comparable to those in control mice. The statistical analysis of this particular study may be marred by the increased mortality of all animals in the latter part of this study.

A similar study was performed (97) in 350 male and 350 female rats. The rats were fed for 98–107 weeks a diet containing 0, 2, 5, 10, and 20% xylitol, 20% sorbitol, and 20% sucrose. A statistically significant reduction in body weight gain was recorded during the first 26 weeks of treatment for males receiving 20% sucrose. A lower than normal body weight gain was recorded throughout the first 78 weeks of the study for males and females receiving 5, 10, or 20% xylitol or 20% sorbitol. However, these differences did not consistently attain a statistical significance from control animals.

In the Turku sugar studies, a 2-year total dietary sugar substitution with xylitol, D-fructose, or sucrose was tested in 117 human subjects of whom 8 were pregnant. The average consumption of xylitol was 1.6 kg per month. The consumption of xylitol did not cause a significant change in the weight of the tested persons. No untoward effect was seen on this group (121–124, 152).

Metabolism

The metabolism of xylitol varies by the origin or route of administration. Approximately 5–15 g of xylitol are formed per day in the human body, based upon the observation that similar amounts of L-xylulose are excreted daily in urine in patients with essential pentosuria (94). Xylitol fed orally, depending on dosage, may not be totally absorbed. However, adaptation appears to occur in humans. This adaptation is most likely due to the transition of intestinal flora contents (199) rather than to other biochemical

mechanisms. Unlike glucose, xylitol is most likely absorbed by intestinal mucosa through passive or facilitated diffusion (14, 112). Therefore, the rate of xylitol absorption is far slower than that of glucose. Although the exact rate of absorption is unknown, 20 g or less of xylitol given as a single oral dose can be completely absorbed in healthy adult humans (Y.-M. Wang and J. van Eys, unpublished data). Higher oral xylitol intake will induce osmotic diarrhea, as do most sugars when given in excessive amounts. A slower increment of daily xylitol intake can boost the intestinal and colon tolerance of xylitol. The adaptation of oral xylitol feeding is demonstrated in Table 2. Up to 400 g of xylitol can be given orally per day without side effects in some subjects (123). The adaptation once established can be retained even by intermittent xylitol feedings (14). Further, through intravenous administration xylitol can also be adapted (14, 190). This is likely due to inducible hepatic xylitol dehydrogenase(s). Enzyme activity in the adapted rat was found to be twice that of nonadapted animals. Liver is the major site for removal of either oral or intravenous xylitol. The liver appears to be responsible for 50–80% of xylitol metabolism in normal conditions. Some 15–20% of the remaining amount of parenterally administered xylitol can be used extrahepatically (134) in the kidney, lung, erythrocyte, fat stores, and myocardium. The distribution of xylitol in eviscerated rats was found to be insulin independent. The xylitol space is approximately 40% with or without the administration of insulin (17). The removal of xylitol from blood appeared to be first-order kinetic process with a half-life of 19–23 min for nonadapted human adults (14). Xylitol excretion is by simple glomerular filtration, and there is no readsorptive mechanism for it (111).

A metabolic pathway of glucuronic acid and xylitol (Figure 2) was first formulated by Touster (184). L-Xylulose was also found to be significantly increased in starved and alloxan diabetic rats, a pathological state reversible by insulin administration (205). Touster (185) suggested recently that this pathway may well be the major biochemical route for the synthesis of D-glucuronic acid, which plays a significant role in detoxification processes. Studies in vivo with radioactive intermediates in humans strongly indicated the existence of the pathway, which leads to an oxidation of the C_6 of glucose. Most of the intermediates are unphosphorylated. A radioisotopic study by Hiatt (92) demonstrated the formation of ribose from glucuronolactone, which produced a labeling pattern that was expected from the operation of the cycle. Using ^{13}C-labeled glucuronic acid, Touster et al (186) demonstrated the formation of xylulose from glucuronic acid in a pentosuric subject. Hankes et al (78) showed the conversion of myoinositol to L-xylulose in humans. Intracellularly, xylitol is mainly metabolized either by a nonspecific NAD-dependent polyol dehydrogenase (EC 1.1.1.10) or by a more specific NADP-dependent xylitol dehydrogenase (EC 1.1.1.9). Both enzymes are largely in the cytosol fractions. The normal metabolism

of xylitol always favors the production of D-xylulose (1). Although no allosteric regulation of the NAD-dependent polyol dehydrogenase affects the metabolism of xylitol, this enzyme shows substrate inhibitory effects with xylitol or sorbitol as substrates (193). The optimal xylitol concentration for the liver enzyme in both rabbits and humans was found to be below 5×10^{-2} M and for partially purified erthrocytic enzyme it was below 10^{-2} M. Therefore, a steady-state concentration of 25 mg per 100 ml of plasma, which results from 8 mg of xylitol/kg/min of infusion (193) or ingestion of 0.5 g of xylitol per kg (body weight) (188), will give an estimate 50% saturation of liver NAD-dependent polyol dehydrogenase and a concentration that exceeds that needed to completely saturate the erythrocytic enzyme. The saturation of the NAD-dependent polyol dehydrogenase will favor L-xylulose production in xylitol metabolism because of the nature of substrate inhibition of the NAD-dependent enzyme.

The final products of xylitol metabolism in mammals are glucose, glycogen, L-lactic acid, and in certain pathological states L-xylulose. Although oxalate was claimed to be a metabolite of infused xylitol, solid evidence refutes this assertion. Recently, in a single hepatocyte preparation from rats, 0.015 M xylitol generated more methylglyoxal than the comparable concentration of glucose (151). The significance of this finding has yet to be determined, but it could be due to the characteristic accumulation of triosephosphate following the infusion of xylitol in the isolated rat liver (208). The accumulation of α-glycerophosphate results from the change of NADH/NAD ratio after xylitol infusion. This has been confirmed by the simultaneous ingestion of ethanol and xylitol by healthy humans (213). Recent evidence, however, suggests the secondary importance of the α-glycerophosphate shuttle to translocate the xylitol-induced imbalance of NADH/NAD ratio (147).

The Toxicity and Safety of Xylitol

Xylitol-induced dose-dependent abnormalities are of three types. First, oral xylitol induced osmotic diarrhea. A second type of abnormality is intravenous xylitol-induced hyperosmolar effect. This has been shown by an in-

Table 2 Frequency of diarrhea-like conditions and flatulance during three continuous 8 month periods in Turku sugar studies[a]

8 Month period	Frequency per subject per month		
	Sucrose	Fructose	Xylitol
1st	0.38	0.38	2.25
2nd	0.38	0.25	0.88
3rd	0.38	0.38	0.50

[a] Adapted from Ref. 152. Average daily intake of sucrose was 72 g, Fructose was 70 g, and xylitol was 50 g.

crease in serum osmolality, an increase in 24-h urine output, and an elevation of packed cell volume. This toxicity is lethal and has been clearly demonstrated in animals (192). The third type of xylitol-induced abnormality is caused by the imbalance of tissue metabolites and cofactors. This can result in an alteration of liver cytosol NADH/NAD ratio (203) and a depletion of hepatic ATP and inorganic phosphate, but it does not disturb the ATP/ADP+P_i ratio or the rate of oxygen consumption (147). These immediate metabolic changes further result in hyperuricemia and occasionally lactic acidosis. Hyperosmolar infusions also induce metabolic acidosis (2, 206). This third type of abnormality can occur after either oral or intravenous administration. However, the metabolic impact is usually more profound after intravenous xylitol. The rate of infusion is definitely a factor in the determination of toxicity, provided the xylitol dose is the same (125, 192). Except for its laxative effect when ingested as an excessive single dose, xylitol apparently induces no undesirable side effects. Oral xylitol produces usually no lactic acidosis (213), no ketosis, and little hyperglycemic and negligible insulin response. However, it can induce a transient increase of serum uric acid.

Tolerance studies on oral xylitol have been performed in children (56) and adults. Xylitol was given to healthy adults at doses varying from 30–220 g per day. Most of the tested subjects tolerated these doses well and weight and fasting blood sugars were normal (47). The absorption of oral xylitol appeared to range from 49–95%. Chronic administration of 30 g per day did not alter the rate of xylitol absorption (10). Transient increase in plasma lactate and urate were observed in some subjects. A small transient rise in serum xylitol (47) was observed along with a minimal rise in plasma insulin (109). By using continuous indirect calorimetry, Dubach et al (47) concluded that the total increase in carbohydrate oxidation after oral xylitol amounted to one fourth that caused by glucose. In the Turku sugar studies, Huttunen et al (99) observed no significant increases in serum or urinary uric acid levels in subjects who consumed foods containing xylitol, fructose, or sucrose for a 2-year period. This was also found in subjects who consumed over 100 g per day of these carbohydrates in more than 100 days of the study period (99). Transient diarrhea occurred in half of the subjects, but adaptation developed within 1–3 weeks.

There is no evidence that exogenous xylitol has any effect on the lens. Mäkinen (121) reported that the human subjects participating in the 2-year chronic xylitol intake studies did not develop any eye abnormalities, even though the eye absorbs aldoses. The crystalline lens (106) does not absorb polyols.

There were no significant changes in serum calcium, magnesium, potassium, phosphatase, amylase, glutamic-oxalacetic transaminase, glutamic-

pyruvic transaminase, and lactate dehydrogenase. Most importantly, clinical chemical derminations in pregnant subjects were normal. There were eight pregnancies in the xylitol group, and all newborns appeared to be normal (121). Förster et al (56) gave 10 g of xylitol three times daily in aqueous solution to 24 insulin-treated diabetic children (5–15 years) over a period of 4 weeks. All subjects tolerated xylitol well except one child, who because of diarrhea discontinued the trial prior to the end of the study. A significant but small increase of serum uric acid (1 mg/100 ml) was observed as compared to the sugar-free control period. Fourteen healthy children ages 7–16 years were given increasing amounts of xylitol in chewing gums, chocolate bars, waffles, meringue candies, yogurt, ice cream, or crystalline xylitol for tea or coffee. The daily dose was given from 10–85 g/day in a 50-day period. Flatulence was the most common side-effect during the daily intake of 45 g or higher of xylitol. Of 13 children, 4 had symptoms of diarrhea at a daily dose of 65 g. A number of children experienced occasional mild abdominal pain with or without ingestion of xylitol.

The safety of intravenous xylitol has been a controversy in the early part of 1970 because of the adverse effect reported in Australia (179) and subsequently in Chicago (45, 157). However, these unsuspected incidents stimulated the re-evaluation of the safety of xylitol given intravenously. The clinical reports of Thomas et al (180–182) have been widely publicized. In Australia, aqueous solutions containing 10, 20, 40, or 50% xylitol were infused to 22 patients (17–74 years). Ten had serious pre-existing disease and 17 were on intensive care. Ten patients developed various reactions, including azotemia, oliguria, diuresis, hyperuricemia, and calcium oxalate deposition in kidney. The identity of the oxalate crystals were confirmed by X-ray crystallography (49). Only one patient, with a renal transplant, presented all these adverse reactions. D. W. Thomas et al (180) noted that it is difficult to attribute these abnormalities to the infusion of xylitol. A number of questions have been raised about this study with regard to specifics of patient conditions, xylitol dosage, infusion rate, and the quality of infusion solution (29, 54). The induction of calcium oxalosis has not proved to be related to xylitol infusion (83). Biochemical evidence has not yet been found to support the claim made by Edwards and his colleagues (84, 142, 193) except in some of their own studies in rats (74). Recently, the same group further suggested that the phenobarbitone may predispose patients to form increased amounts of oxalate from glycolate and xylitol. Again, control experiments with glucose were not included (15). Secondary oxalosis is seen in patients with renal insufficiency who do not receive xylitol infusion (12). Berg and his associates (20) established the safe infusion rate in a human to be 0.25 g/kg/h. With this rate of infusion, xylitol does not cause significant side effects, except transient hyperuricemia. However, a number of

investigators regard the increase of blood uric acid concentration as a toxic symptom of xylitol administration. Förster (54) and his collaborators believe that this is without pathophysiological significance. He suggests that the increase of serum uric acid might occur in persons consuming the standard North American diet or after ingestion of meat. He further suggested that a xylitol infusion rate of 0.25 g/kg/h up to 100 g total dose can be infused per day. The German Drug Commission has recommended a limit to the dosage of all intravenously infused glucose substitutes of 0.25 g/kg (body weight) per h.

Carcinogenicity and Mutagenicity of Xylitol

Large-scale chronic toxicity trials of xylitol were performed by Huntingdon Research Center, Huntingdon, England. This work was under contract from Hoffmann-La Roche, Inc., Basel, Switzerland. These studies included a 2-year feeding experiment with mice, a 2-year feeding trial with a small number of beagle dogs, 1-year feeding and multigeneration reproduction studies with rats, teratogenicity and reproduction testing in rabbits, and other ancillary studies, including mutagenicity studied with xylitol by using the Ames test, host-mediated assay, micronucleus test, and human lymphocytes chromosomal analysis. These studies suggested that xylitol has no adverse effect on the reproduction of rats nor was it teratogenic (see 51). Unexpected observations were found in male mice fed 10 and 20% xylitol diet throughout their life-times. These mice had more crystalline calculi in their bladder than control male mice or male mice fed with 2% xylitol or 20% sucrose diets. Histological studies revealed increased hyperplasia, metaplasia, and neoplasia of the transitional epithelium of the bladder associated with urinary calculi. However, in those male animals fed with 10 or 20% xylitol, there was a reduction in the incidence of hepatocellular carcinomas. Further, female mice fed a 20% sucrose diet exhibited an increased incidence of hepatocellular tumors without anomalies in bladder (17).

Two questions are unanswered about these experiments: the comparative purity of the sugar and sugar alcohol and the health of these animals. In addition, feeding experiments in Sprague-Dawley (CD strain) rats for 26–52 weeks and in beagle dogs for 2 years showed no evidence of increased frequency of urinary calculi formation, nor hepatocellular tumors at autopsy. However, rats fed 5, 10, or 20% xylitol or 20% sorbitol exhibited an increased incidence of adrenal medullar pheochromocytosis (98). Sorbitol-induced chromophobe cell hyperplasia in rat pituitary has also been reported previously (cited in 4). Batzinger et al (19) reported that neither 200–500 μg of xylitol per petri dish nor urinary extracts from mice fed with 2.5 g of xylitol/kg (body weight) were mutagenic by either the Ames test

or the mouse host-mediated assay system. Similar negative results for varying doses of xylitol were obtained by Gallandre (64) with the Ames test, the host-mediated assay, the micronucleus test, or chromosomal analyses of cultured human lymphocytes.

Xylitol and Dental Caries

The prime interest in xylitol in recent years has focused on its potential for prevention of dental caries. This interest is largely based upon the observation made in the Turku sugar studies. This was an ambitious, thorough, and successful 2-year comparison of sucrose, fructose, and xylitol in human dental health (121, 122, 124, 152).

Mühlemann et al (133) were the first to suggest the noncariogenicity of xylitol in a rat model. In their experiment, the addition of xylitol, fed at 10, 20, or 30%, to a low-cariogenic wheat flour diet did not change the cariogenicity. In comparison, the addition of sorbitol resulted in a significant increase in caries. This finding was confirmed by other investigators (65, 103). Grunnberg et al (75) indicated that approximately similar incidence of dental caries was observed in rats fed either 10% glucose or 10% sucrose. Mannitol or sorbitol induced a lower incidence and xylitol induced the lowest incidence of dental caries. They further suggested that the caries-producing strains of streptococci were unable to utilize xylitol. However, it appeared that substituting small quantities of sucrose for polyols destroyed any protection in animal model systems (136). Laboratory results (see 121) have suggested several possibilities: that the consumption of xylitol lessens the activity of glucosyl transferase, invertase, and sucrose permease activities in saliva and plaque; that the consumption of a xylitol diet was associated with an increase in the concentration of basic amino acids in saliva; that xylitol reduces the adhesive interactions of *S. mutans* by increasing the proportion of soluble polysaccharides in plaque; and that xylitol increases salivary flow rates and maintains a higher and more advantageous pH at 7.2–7.8. The critical pH value (approximately 5.5) will not be readily reached (at a pH of lower than 5.5, dental enamel—hydroxyapatite, calcium, and phosphate—will be dissolved). It appears that more HCO_3^- was in saliva when xylitol was consumed as a sugar substrate. This is likely a consequence of the inability of oral bacteria to metabolize xylitol effectively, and thus negligible acid production occurs. The results also suggested that xylitol can stimulate the synthesis of glycoprotein and the activity of lactoperoxidase. In addition, the inhibition of *S. mutans* OMZ 176 growth by xylitol was reported (11).

The striking finding of Scheinin & Mäkinen (152) and their collaborators that xylitol may have therapeutic and remineralization effects in human teeth in addition to its noncariogenic properties deserves to be discussed.

They reported after 1, 2, and 4.5 years from the start of this 2-year Turku sugar study (124, 152). The 2-year clinical trial was designed to investigate the comparative effect of the chronic consumption of fructose, xylitol, and sucrose as an additive in diet to the oral and dental health in general. The human tolerance of chronic intake of xylitol and fructose thus was analyzed in comparison to that of sucrose. Initially, the study included 125 volunteers with a mean age of 27.6 years. Eight of them withdrew during the trial, and two more in the xylitol group were exclusively used for survey of the metabolic effect of the polyol. The fructose group had 35 study subjects, sucrose had 33, and xylitol had 49. The final results were based on the analysis of 115 subjects, 39 males and 76 females. The mean individual monthly intake of fructose, sucrose, and xylitol was 2.1, 2.2 and 1.6 kg, respectively. To enhance the cooperation of the participants, a variety of sugar products were developed solely for this clinical trial. The total assortment comprised 100 products (154). During the 2-year span the dental condition of the study subjects was evaluated eight times. After the completion of the trial, the mean increment of decayed, missed, and filled (DMF) teeth surfaces was 7.2 in the sucrose group, 3.8 in the fructose group, and 0 in the xylitol group (155). Furthermore, in the analysis of all qualitative changes in lesion size and the numerical development of all secondary caries reversals, in addition to the quantitative increment of DMF tooth surface, the differences between xylitol and sucrose, and fructose, were found highly significant ($P < 0.005$). However, the difference was not significant between the groups of sucrose and fructose ($P = 0.0522$).

A longitudinal study was then carried out, again by the Finnish group, to evaluate whether the partial substitution of dietary sucrose by xylitol in chewing gum would result in a finding similar to that in the total dietary substitution of sucrose (153). In this 1-year study, the effects of sucrose- and xylitol-containing chewing gum was compared in 102 subjects (28 males and 74 females, mean age 22.2 years). These dental or medical student volunteers in the sucrose and xylitol groups consumed an average of 4.0 and 4.5 pieces of chewing gum per day, respectively. The results were similar to those in the dietary investigation. The caries incidence expressed as the mean increment of DMF tooth surface was 2.92 in the sucrose chewing-gum group and –1.04 in the xylitol chewing-gum group. The negative score suggested the therapeutic and remineralization potential of xylitol in human teeth. No extensive adaptation of the plaque flora to xylitol use occurred, even during the 4.5-year continuous ingestion of this carbohydrate (124). However, when a decreased score in DMF index occurs, the results are usually attributed to unintentional changes in diagnostic criteria (177). Further, it should be noted that Ainamo et al (1) reported no reduction in plaque formation, either in numbers or in size, in subjects who chewed

xylitol-containing gum 2.5 h per day for 21 days, nor did a 3-day experiment with xylitol-containing gum show significant impact on plaque growth. It was reported that the partial substitution of xylitol for sucrose did not appear to reduce the biochemical effect or the degradation of sucrose (177).

Xylitol in Diabetics

In the past 20 years, xylitol has been constantly suggested for and tested in the clinical treatment of diabetic ketoacidosis. The structural configuration of xylitol suggested that tissue transport of xylitol might not be facilitated by insulin. This hypothesis was proved by Bässler & Prellwitz (17), who found that the distribution of xylitol was the same in both normal and eviscerated diabetic rats. Of interest are the reports that intravenous injection of a high dose of xylitol stimulates insulin release in dogs and men. However, Geser et al (66) could not demonstrate a significant increase of insulin in plasma upon administration of doses of 0.8 g of xylitol per kg (body weight) fed intravenously to young healthy persons. The observations in humans was confirmed by a number of investigators.

There are at least two groups of investigators who have opposite views on the use of xylitol as a potential substitute for sucrose for diabetic subjects. The reasons were similar to those described in the discussion of D-fructose.

There is evidence that 95% of pancreatectomized rats are able to metabolize all exogenous xylitol when fed a 6% xylitol diet. Over a period of 1 month there was no difference in the assimilation of xylitol in pancreatectomized and non-pancreatectomized rats (see 121). This proves that xylitol entered the metabolic machinery normally in diabetic animals without the help of insulin.

Based on these experimental observations, xylitol has been used for the clinical treatment of diabetes (211). Xylitol possesses a strong antiketogenic action and is believed to improve the retarded metabolism in diabetic ketosis (85). Haydon (85) observed that the antiketogenic effect of xylitol was more striking than most other polyalcohols such as sorbitol, mannitol, and glactitol. Bässler & Dreiss (16) found that xylitol decreased the urinary ketone bodies about 50–80% as compared to that of 35% with sorbitol in alloxan-diabetic rats. Administration of xylitol to diabetic rats increased glycogen synthesis and restored glycolytic function. Xylitol infusion (0.25–0.5 g/kg) in normal, prediabetic, and diabetic individuals as well as in patients with insulinomas exerted antiketogenic effect. The plasma disappearance rate of xylitol is about the same in normal and diabetic subjects. However, the rate of glucose clearance was much suppressed in diabetic patients.

A remarkable decrease of acetoacetate in blood was observed in patients with acetonemic reactions and diabetic mellitus after xylitol infusion. The decrease was paralleled by β-hydroxybutyrate. An initial drop of serum

phosphate following the injection of xylitol solution was seen in patients with liver cirrhosis and fatty liver and in normal subjects (173, 207). There are a number of favorable reports on the use of intravenous xylitol for the treatment of diabetic ketoacidosis (42, 112, 211), mostly from Europe and Japan. Recently, De Kalbermatten et al (43) demonstrated again that fructose, sorbitol, and xylitol are oxidized at a higher rate than is glucose during suppression of endogenous insulin secretion. They suggested that the apparent contradiction of their results in humans with those of others (19, 59, 104), in which most of the injected ^{14}C-labeled substrates were rapidly transformed into glucose in rats with further needs for insulin, was likely due to the faster infusion rate. They believe that a higher infusion rate does not allow these sugar substitutes to be directly oxidized along their particular metabolic pathway.

Other Potential Uses of Xylitol

Since the clinical trials of xylitol in the treatment of diabetes, xylitol has been investigated in patients with bile duct and liver diseases, renal diseases, ketonemia, and pulmonary tuberculosis and for parenteral nutrition during and after surgery. The use of xylitol has also been suggested in the treatment of erythrocytic glucose-6-phosphate dehydrogenase (G6PD) deficiency anemia and as a potential carbohydrate source for blood storage. Recently, investigation of the differential utilization of carbohydrate in tumor and host has been initiated. Xylitol may also have significant clinical applications.

Among these applications, three areas deserve further discussion because of their scientific rationale. Trauma or physiological insult in man or animals elicits predictable negative nitrogen balance and changes in energy expenditure. It is generally agreed that an increase in tissue oxidation heavily relying on protein consumption occurs and is usually associated with body heat production. Additional substantial losses of body nitrogen and secondary metabolic responses occur, such as increased synthesis of enzymes, particularly in hepatic cells, responsible for the catabolism of amino acids. Trauma-related glucose intolerance is consistent with inhibited insulin release and an enhanced glucagon secretion known to be related to pituitary function during trauma. In humans, following stress, the fasting glucose level is higher than normal. Fructose, sorbitol, and xylitol have been compared with glucose in their nitrogen-sparing effect as exogenous energy sources (156). It appears that xylitol has an anticatabolic effect. The blood glucose level is enhanced after infusion of fructose or sorbitol, but not of xylitol, during the post-traumatic period. After the infusion of xylitol, very little glucose is lost in the urine. Recently in Finland, 30 middle-aged women were infused with 100 g of xylitol as postoperative fluid therapy after

laparotomy and general anesthesia. An infusion rate of 0.25 or 0.5 g/kg/h significantly increased lactic acid, pyruvic acid, uric acid, and bilirubin levels. Unfortunately, only 50 g of glucose was given to the control group (108).

Xylitol can be effectively metabolized in human erythrocytes in vitro (8, 9) and in vivo (134). The polyol can be metabolized to D-xylulose or L-xylulose, as in the liver tissue. Because of the generation of NADPH from NADP through the enzymic reaction of the NADP-dependent xylitol dehydrogenase, xylitol was proposed as a therapeutic biochemical tool in the treatment of erythrocytic G6PD deficiency anemia (195), in which the chemical consequence of the genetic anomaly is a deficiency of intracellular NADPH and concomitant depletion of reduced glutathione. The normal levels of NADPH and of reduced glutathione were apparently quite essential to the integrity of human erythrocyte. No effective treatment is known for this disease, although some rational investigative therapies have been suggested (191), including the use of high-doses of vitamin E (38). Previously in the G6PD-deficient human erythrocytes, the addition of xylitol in vitro could maintain or increase glutathione levels more effectively than that of glucose. Xylitol was then evaluated in other centers for the clinical treatment of drug-induced hemolysis secondary to G6PD deficiency with mixed results (34, 100).

Recently, the potential use of xylitol as an alternative source of energy was suggested for tumor-bearing hosts if the tumor is unable to metabolize exogenous xylitol (J. Sato, unpublished data). The acute administration of a single dose of xylitol to AS3OD tumor-bearing rats proved that xylitol was converted primarily into glucose in the liver, whereas in the tumor 80–90% remained unchanged. It appears that this animal tumor has negligible NAD-dependent xylitol dehydrogenase activity. However, the advantages of xylitol in this animal model need to be confirmed either by chronic xylitol feeding or by chronic infusion.

SUMMARY

Human metabolism of D-fructose, D-sorbitol, D-mannitol, and xylitol has been documented. In humans, sorbitol and xylitol at a single oral dose of 20 g or less and fructose at 70 g or less most likely can be fully absorbed. These three sugars can maintain, either independently or nearly independently, the integrity or the carbohydrate requirement for the growth of cells and animals. The absorption of D-mannitol is no more than 80% and is more laxative. In general, there is no adverse effect other than osmotic diarrhea after oral administration of these sugars. Transient hyperuricemia was seen in some humans. The chronic toxicity of life-long usage of these

sugars in humans or other primates is not known. However, a 2-year Turku sugar studies suggested the safety of fructose and xylitol. Two-year feeding experiments in mice and rats indicated possible carcinogenicity of a high-percentage xylitol diet. Abnormalities of cellular growth were also documented in animals fed high percentages of sorbitol and sucrose. Long-term mannitol feeding experiments also revealed an increased incidence of benign thymic tumors in rats.

Intravenous feeding of fructose, xylitol, and sorbitol causes major concern. The toxicity is total-dose and infusion-rate dependent. The physical toxicity induced by hyperosmolar effect of the concentrated infusion solutions can be lethal. The primary metabolic toxicities, mainly lactic acidosis and hyperuricemia, are reversible. The suggested safe infusion rate of these sugars is 0.25 g/kg/h; sporadic toxic observations have been reported at this or lower doses (0.125 g/kg/h). The combination of glucose, fructose, xylitol, and sorbitol mixture intravenously is in use in Europe due to the critical threshold of each element. There are positive findings from the use of the combination in human illness (114).

The beneficial effect of xylitol, mannitol, sorbitol, and fructose in decreasing order has been well documented in the prevention of dental caries in animals and in humans. Oral organisms do not appear to metabolically adapt to xylitol even after 4 years of in vivo exposure. This was based on the quantitation of xylitol dehydrogenase activity in saliva and oral organisms. In addition, a therapeutic and preventive effect for xylitol in human and animal dental caries has been demonstrated. There appears to be at least a theoretical edge in the dietary use of fructose, xylitol, and sorbitol in diabetics. The published results obtained mostly in Europe favored the use of these sugars as a sweetener in special diets for patients with insulin insufficiency. A number of reports, however, challenged the validity of the claims of a benefit.

The use of fructose, sorbitol, xylitol, and mannitol has been suggested in a number of other areas. Most of these proposals either need theoretical bases or confirmation in human studies.

FUTURE NEEDS

Further studies would benefit a number of future needs: to truly establish the human tolerance of oral fructose, xylitol, sorbitol, and mannitol (a prior study in primates may be necessary, particularly in long-term feeding experiments); to thoroughly investigate each individual tissue capacity to utilize and metabolize these nonglucose carbohydrates; to study chronic toxicities, particularly the carcinogenicity, of these polyalcohols in comparison with those of glucose, fructose, and their dimer sucrose; and to conduct random-

ized clinical trials to confirm the striking results of xylitol obtained by Scheinin and Mäkinen and other colleagues in the preventive and therapeutic effect of xylitol in dental health, to compare the effect and side effects among xylitol, sorbitol, and mannitol in this regard, to study the objective utility of oral fructose, xylitol, sorbitol, and mannitol or their combination as sweeteners in special diets for diabetics (these studies do not need to await the results of preclinical trials of chronic toxicity of these polyols), and to investigate the utility of intravenous glucose, fructose, and xylitol combinations as compared to glucose in certain clinical settings.

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Literature Cited

1. Ainamo, J., Asikainen, S., Ainamo, A., Laktinen, A., Sjoblom, M. 1979. Plaque growth while chewing sorbitol or xylitol with sucrose flavoured gum. *J. Clin. Periodontol.* 6:397–406
2. Ainsworth, S. K., Allison, F. J. Jr. 1971. Effects of hypertonic solutions infused intravenously in rabbits. 1. Metabolic acidosis and lactic acidemia. *J. Lab. Clin. Med.* 78:619–32
3. Åkerblom, H. K., Siltanen, I., Kallio, A.-K. 1972. Does dietary fructose affect the control of diabetes in children. *Acta Med. Scand. Suppl.* 542:195–202
4. Allison, R. G. 1979. *Dietary Sugars in Health and Disease. III. Sorbitol.* Bethesda, Md: Life Sci. Res. Off., Fed. Am. Soc. Exp. Biol.
5. Allison, R. G. 1979. *Dietary Sugars in Health and Disease. IV. Mannitol.* Bethesda, Md: Life Sci. Res. Off., Fed. Am. Soc. Exp. Biol.
6. Arvidsson Lenner, R. 1976. Studies of glycemia and glucosuria in diabetics after breakfast meals of different composition. *Am. J. Clin. Nutr.* 29:716–25
7. Arvidsson Lenner, R. 1976. Specially designed sweeteners and food for diabetics—a real need? *Am. J. Clin. Nutr.* 29:726–33
8. Asakura, T., Adachi, K., Minakami, S., Yoshikawa, H. 1967. Nonglycolytic sugar metabolism in human erythrocytes. I. Xylitol metabolism. *J. Biochem.* 62:184–93
9. Asakura, T., Ninomiya, H., Minakami, S., Yoshikawa, H. 1969. Utilization of xylitol in human erythrocytes. In *Pentose and Pentitol,* ed. M. L. Horecker, K. Lang, Y. Takagi, pp. 158–73. Berlin: Springer-Verlag. 408 pp.
10. Asano, T., Levitt, M. D., Goetz, F. C. 1973. Xylitol absorption in healthy man. *Diabetes* 22:279–81
11. Assev, S., Vegarud, G., Rölla, G. 1980. Growth inhibitions of Streptococcus mutans strain OMZ 176 by xylitol. *Acta Pathol. Microbiol. Scand. Sect. B* 88:61–63
12. Balcke, P., Schmidt, P., Zazgornik, J., Kopsa, H., Deutsch, E. 1980. Secondary oxalosis in chronic renal insufficiency. *N. Engl. J. Med.* 303:944
13. Bánóczy, J., Esztari, I., Hadas, E., Marosi, I., Fözy, L., Szantó, S. 1978. Einjährige Erfahrungen mit Sorbit in Klinischem Längsschnitt-Versuch. *Dtsch. Zahnärztl. Z.* 33:701–5
14. Bässler, K. H. 1969. Adaptive processes concerned with absorption and metabolism of xylitol. See Ref. 9, pp. 190–96
15. Bässler, K. H. 1978. Biochemistry of xylitol. In *Xylitol,* ed. J. N. Counsell, 4:35–41. London: Appl. Sci. Publ. Ltd. 191 pp.
16. Bässler, K. H., Dreiss, G. 1963. Antiketogene Wirkung von Xylit bei alloxandiabetischen Ratten. *Klin. Wschr.* 41:593–95
17. Bässler, K. H., Prellwitz, W. 1964. Insulin und der Verteilungsraum von Xylit bei eviscerierten Ratten. *Klin. Wschr.* 42:94–95
18. Batstone, G. F., Alberti, K. G. M. M., Dewar, A. K. 1977. Reversible lactic acidosis associated with repeated intravenous infusions of sorbitol and ethanol. *Postgrad. Med. J.* 53:567–69

19. Batzinger, R. P., Ou, S. Y. L., Bueding, E. 1977. Saccharin and other sweetener mutagenic properties. *Science* 198: 944–46
20. Berg, G., Matzkies, F., Bickel, H. 1974. Dosierungsgrenzen bei der Infusion von Glucose, Sorbit, Fructose, Xylit und deren Mischungen. *Dtsch. Med. Wschr.* 99:633–38
21. Bernstein, I. L., Vitiello, M. V. 1978. The small intestine and the control of meal patterns of the rat. *Physiol. Behav.* 24:417–22
22. Bierman, E. L., Nelson, R. 1975. Carbohydrates, diabetes, and blood lipids. *World Rev. Nutr. Diet.* 22:280–87
23. Blakley, R. L. 1951. The metabolism and antiketogenic effects of sorbitol. Sorbitol dehydrogenase. *Biochem. J.* 49:257–70
24. Bode, C., Schumacher, H., Goebell, H., Zelder, O., Pelzel, H. 1971. Fructose induced depletion of liver adenine nucleotides in man. *Horm. Metab. Res.* 3:289–90
25. Bode, J. C., Zelder, O., Rumpelt, H. J., Wittkamp, U. 1973. Depletion of liver adenosine phosphates and metabolic effects of intravenous infusion of fructose or sorbitol in man and in the rat. *Eur. J. Clin. Invest.* 3:436–41
26. Brimacombe, J. S., Webber, J. M. 1972. Alditols and derivatives. In *The Carbohydrates. Chemistry and Biochemistry,* ed. W. Pigman, D. Horton, 14:479–518. New York: Academic. 642 pp. 2nd ed.
27. Brin, M., Gabriel, E., Machlin, L. T. 1977. Effect of xylitol on growth of thiamine deficient rats. *Fed. Proc.* 36:1173 (Abstr.)
28. Brin, M., Machlin, L. T., Osadca, M., Gabriel, E. 1978. The sparing effect of dietary xylitol on thiamin (B_1), riboflavin (B_2) and pyridoxine (B_6). *Fed. Proc.* 37:448 (Abstr.)
29. Brin, M., Miller, O. N. 1974. The safety of oral xylitol. *Sugars in Nutrition,* ed. H. L. Sipple, K. M. McNutt, pp. 591–606. New York: Academic. 768 pp.
30. Brown, A. T. 1974. Carbohydrate metabolism in caries-conducive, oral streptococci. *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 689–719. New York: Academic, 768 pp.
31. Buckell, M. 1964. Blood changes on intravenous administration of mannitol or urea for reduction of intracranial pressure in neurosurgical patients. *Clin. Sci.* 27:223–27
32. Bünger, R., Sommer, O., Walter, G., Scholz, R. 1978. Fructose, a substrate for energy-yielding metabolism in the heart? *Hoppe-Seylers Z. Physiol. Chem.* 359:819–24
33. Bye, P. A. 1969. The utilization and metabolism of intravenous sorbitol. *Br. J. Surg.* 56:653–56
34. Chan, T. K., Todd, D. 1975. *Can xylitol infusion prevent oxidative haemolysis in G6PD deficiency?* Presented at 3rd Meet. Eur. Afr. Div. Int. Soc. Haematol., London, Aug. 24–28
35. Chen, M., Whistler, R. L. 1977. Metabolism of D-fructose. *Adv. Carbohydr. Chem. Biochem.* 34:285–343
36. Clements, R. S. Jr., Winegrad, A. I. 1972. Purification of alditol: NADP oxidoreductase from human placenta. *Biochem. Biophys. Res. Commun.* 47: 1473–79
37. Collins, B. J., David, J. D. 1978. Long term inhibition of intake by mannitol. *Physiol. Behav.* 21:957–65
38. Corash, L., Spielberg, S., Bartsocas, C., Boxer, L., Steinherz, R., Sheetz, M., Egan, M., Schlessleman, J., Schulman, J. D. 1980. Reduced chronic hemolysis during high-dose vitamin E administration in mediterranean-type glucose-6-phosphate dehydrogenase deficiency. *N. Engl. J. Med.* 303:416–20
39. Cortart, T. M., Crossley, J. N. 1970. Influence of dietary sucrose on glucose and fructose tolerance and triglyceride synthesis in the baboon. *Clin. Sci.* 38:427–37
40. Counsell, J. N., ed. 1978. *Xylitol.* London: Appl. Sci. Publ. Ltd. 191 pp.
41. Crapo, P. A., Kotterman, O. G., Olefsky, J. M. 1980. Effects of oral fructose in normal, diabetic, and impaired glucose tolerance subjects. *Diabetes Care* 3:575–81
42. Davis, J. D., Collins, B. J. 1978. Distension of the small intestine, satiety and the control of food intake. *Am. J. Clin. Nutr.* 31:S255–58
43. De Kalbermatten, N., Ravussin, E., Maeder, E., Geser, C., Jequier, E., Felber, J. P. 1980. Comparison of glucose, fructose, sorbitol and xylitol utilization in humans during insulin suppression. *Metabolism* 29:62–67
44. Demetrakopoulos, E. G., Amos, H. 1976. D-Xylose and xylitol: Previously unrecognized sole carbon and energy sources for chick and mammalian cells. *Biochem. Biophys. Res. Commun.* 72: 1169–78
45. Donahoe, J. F., Powers, R. J. 1974. Xylitol-clinical pharmacology in normal adult volunteers. *J. Clin. Pharmacol.* 14:255–60

46. Doty, T. E., Vanninen, E. 1975. Crystalline fructose: use as a food ingredient expected to increase. *Food Technol.* 29(11):34–38
47. Dubach, U. C., Feiner, E., Forgo, I. 1969. Orale Verträglichkeit von Xylit bei-stoffwechselgesunden Probanden. *Schweiz Med. Wochenshr.* 99:190–94
48. Emodi, A. 1978. Xylitol its properties and food applications. *Food Technol.* 32(1):28–32
49. Evans, G. W., Phillips, G., Mukherjee, T. M., Snow, M. R., Lawrence, J. R., Thomas, D. W. 1973. Identification of crystal deposited in brain and kidney after xylitol administration by biochemical, histochemical and electron diffraction methods. *J. Clin. Pathol.* 26:32–36
50. Exton, J. H., Park, C. R. 1965. Control of gluconeogenesis in the perfused liver of normal and adrenalectomized rats. *J. Biol. Chem.* 240:955–56
51. Fisher, K. D. 1978. *Dietary Sugars in Health and Disease. II. Xylitol.* Bethesda, Md: Life Sci. Res. Off., Fed. Am. Soc. Exp. Biol.
52. Fitzgerald, R. J., Jordan, H. V. 1968. Polysaccharide-producing bacteria and caries. In *Art and Science of Dental Caries Research,* ed. R. S. Harris, 8:79–86. New York: Academic. 428 pp.
53. Fordtran, J. S., Rector, F. C. Jr., Ewton, M. F., Soter, N., Kinney, J. 1965. Permeability characteristics of human small intestines. *J. Clin. Invest.* 44: 1935–44
54. Förster, H. 1974. Comparative metabolism of xylitol, sorbitol and fructose. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 259–80. New York: Academic. 768 pp.
55. Förster, H., Boecker, S., Dudziak, R., Steuer, A. 1977. Long-term parenteral nutrition with fructose in intensive care patients. *Nutr. Metab.* 21: Suppl. 1, pp. 124–27
56. Förster, H., Boecker, S., Walther, A. 1977. Verwendung von Xylit als Zuckeraustauschstoff bei diabetischen Kindern. *Fortschr. Med.* 95:99–102
57. Förster, H., Mehnert, H., Alhoug, I. 1967. Anstieg der Serumharnsäure nach Verabreiehung von Fructose. *Klin. Wschr.* 45:436
58. Förster, H., Meyer, E., Ziege, M. 1970. Erhöhung von Serumharnsäure únd Serumbilirubin nach hochdosierten Infusionen von Sorbit, Xylit und Fructose. *Klin. Wschr.* 48:878–78
59. Foresch, E. R., Jacob, A. 1974. The metabolism of xylitol. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 241–58. New York Academic. 768 pp.
60. Froesch, E. R., Zapti, J., Keller, V., Oelz, O. 1971. Comparative study of the metabolism of U-^{14}C-fructose, U-^{14}C-sorbitol, and U-^{14}C-xylitol in the normal and in the streptozotocin-diabetic rat. *Eur. J. Clin. Invest.* 2:8–14
61. Frostell, G. 1978. Biochemical effects of and bacteriological response to sugar substitutes in the oral environment. *Pharmacol. Therapeut. Dent.* 3:75–84
62. Frostell, G., Keyes, P. H., Larson, R. H. 1967. Effect of various sugars and sugar substitutes on dental caries in hamsters and rats. *J. Nutr.* 93:65–76
63. Gabby, K. H. 1974. The sorbitol pathway in the nervous system. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 469–82. New York: Academic. 768 pp.
64. Gallandre, F. 1978. Mutagenicity studies with xylitol using various methods. In *Xylitol* p. 19. Basel: Hoffmann LaRoche Company, Ltd.
65. Gehring, F., Karle, E. J. 1975. Der Zuckeraustauschstoff Xylitol and seine Bedentung in der Kariesprophylaxe. *Süsswaren* 19:330–40
66. Geser, K. A., Förster, H., Pröls, H., Mehnert, H. 1967. Zur Frage Einer Wirkung von Xylit au die Insulinsekretion des Menschen. *Klin. Wschr.* 45:851–52
67. Glickman, I. 1971. Medical progress: peridontal disease. *N. Engl. J. Med.* 284:1071–77
68. Goldberg, L. D., Ditchek, N. T. 1978. Chewing gum diarrhea. *Am. J. Dig. Dis.* 23:568
69. Goldblatt, P. J., Witschi, H., Friedman, M. A., Sullivan, R. J., Shull, K. H. 1970. Some structural and functional consequences of hepatic adenosine triphosphate deficiency induced by intraperitoneal D-fructose administration. *Lab. Invest.* 23:378–85
70. Deleted in proof
71. Green, W., Lang, K. 1960. Versuche zur Parenteralen Ernährung mit Aminosäuren-Sorbit-Losüngen. *Klin. Wschr.* 38:336–37
72. Grenby, T. H. 1967. Investigations in experimental animals on the cariogenicity of diets containing sucrose and/or starch. *Caries Res.* 1:208–21
73. Grenby, T. H., Hutchison, J. B. 1969. The effect of diets containing sucrose, glucose, or fructose on experimental dental caries in two strains of rats. *Arch. Oral. Biol.* 14:373–80

74. Griffin, W. C., Lynch, M. J. 1972. Polyhydric alcohol. In *Handbook of Food Additives,* ed. T. E. Furia, pp. 431–55. West Palm Beach, Fla: CRC Press
75. Grunberg, E., Beskid, G., Brin, M. 1973. Xylitol and dental caries: Efficacy of xylitol in reducing dental caries in rats. *Int. J. Vit. Nutr. Res.* 43:227–32
76. Gülzow, H.-J. 1974. Vergleichende Untersuchungen über den abbau von xylit im menschlichen Speichel. *Dtsch Zahnärztl. Z.* 29:772–75
77. Gustafson, G., Stelling, E., Abramson, E., Brunius, E. 1955. Cariogenic effect of different carbohydrates in dry and moist diets. Experimental dental caries in golden hamsters. *V. Odont. Tskr.* 63:506–23
78. Hankes, L. V., Politzer, W. M., Touster, O., Anderson, L. 1969. Myo-inositol catabolism in human pentosuria: The predominant role of the glucurnate-xylulose-pentose phosphate pathway. *Ann. NY Acad. Sci.* 165: 564–76
79. Hannett, B., Thomas, D. W., Chalmers, A. H., Rofe, A. M., Edwards, J. B., Edwards, R. G. 1977. Formation of oxalate in pyridoxine or thiamin deficient rats during intravenous xylitol infusions. *J. Nutr.* 107:458–65
80. Hardinge, M. G., Swarner, J. B., Crooks, H. 1965. Carbohydrates in foods. *J. Am. Diet. Assoc.* 46:197–204
81. Hartles, R. L. 1965. Dietary and environmental factors influencing caries resistance. In *Caries-Resistant Teeth, Ciba Found. Symp.,* ed. G. E. W. Walstenholme, M. O'Connor, pp. 289–312. Boston: Little, Brown. 338 pp.
82. 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
83. Hauschildt, S., Chalmers, R. A., Lawson, A. M., Schultis, K., Watts, R. W. E. 1976. Metabolic investigations after xylitol infusions in human subjects. *Am. J. Clin. Nutr.* 29:258–73
84. Hauschildt, S., Watts, R. W. E. 1976. Studies on the effect of xylitol on oxalate formation. *Biochem. Pharmacol.* 25: 27–29
85. Haydon, R. K. 1961. The antiketogenic effects of polyhydric alcohols in rat-liver slices. *Biochim. Biophys Acta* 46:598–99
86. Hedley, V. M., Yudkin, J. 1959. The effect of dietary sorbitol and related substances on the vitamin B requirements of the rat. *Proc. Nutr. Soc.* 18:xxiv–xxv
87. Heinz, F., Lamprecht, W., Kirsch, J. 1968. Enzymes of fructose metabolism in human liver. *J. Clin. Invest.* 47:1826–32
88. Herman, R. H. 1974. Hydrolysis and absorption of carbohydrates and adaptive response of the jejunum. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, 11:145–72. New York: Academic. 768 pp.
89. Hers, H. G. 1955. The conversion of fructose-1-C^{14} and sorbitol-1-C^{14} to liver and muscle glycogen in the rat. *J. Biol. Chem.* 214:373–81
90. Hers, H. G. 1956. Le mecanisme de la transformation de glucose en fructose par les desicules seminales. *Biochim. Biophys. Acta* 22:202–3
91. Hers, H. G. 1960. Le mecanisme de la formation du fructose seminal et du fructose foetal. *Biochim. Biophys. Acta* 37:127–28
92. Hiatt, H. H. 1958. Studies of ribose metabolism. VI. Pathways of ribose synthesis in man. *J. Clin. Invest.* 37:1461
93. Hiller, J. 1955. Die Laevulosever wertung des acidotischen Diabetes mellitus. I. Mitteilung zur Analyse der Acetonurine und der Glucosurie. *Z. Klin. Med.* 153:388–96
94. Hollmann, S., Touster, O. 1964. *Non-Glycolytic Pathways of Metabolism of Glucose.* New York: Academic. 276 pp.
95. Hoshi, M. 1963. Clinical application of sorbitol in patients with diabetes mellitus and in patients with liver disease. *Med. J. Osaka Univ.* 14:47–60
96. Hue, L. 1974. The metabolism and toxic effects of fructose. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, 22:358–86. New York. Academic. 768 pp.
97. 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, final report, Vol. I, Huntingdon Research Center, Huntingdon, Cambridgeshire, England. In *Xylitol,* Vol. 11. Basel: Hoffmann La Roche
98. Hunter, B., Graham, C., Heywood, R., Prentice, D. E., Roe, F. J. C., Noakes, D. N. 1978. Tumorigenicity and carcinogenicity study with xylitol in long-term dietary administration to mice, final report, Vol. I, Huntingdon Research Center, Huntingdon, Cambridgeshire, England. In *Xylitol,* Vol. 20. Basel: Hoffman La Roche
99. Huttunen, J. K., Mäkinen, K. K., Schenin, A. 1975. Turku sugar studies. XI

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100. Idelson, L. I., Rustamov, R. S., Lysenko, A. Y. 1973. An attempt at prevention of hemolytic action of primaquine in persons with deficient glucose-6-phosphate dehydrogenase activity of erythyrocytes by simultaneous prescription of xylitol and riboflavin. *Probl. Hematol. Blood Transfus.* 18: 24–28
101. Imfeld, T., Mühlemann, H. R. 1978. Cariogenicity and acidogenicity of food, confectionery and beverages. *Pharmacol. Therapeut. Dent.* 3:56–68
102. Kameda, H., Abei, T., Nasrallah, S. M., Iber, F. L. 1968. Functional and histological injury to intestinal mucosa produced by hypertonicity. *Am. J. Physiol.* 214:1090–95
103. Karle, E., Gehring, F. 1975. Wirkung der Zuckeraustauschstoffe Fruktose, Sorbit and Xylit auf Kariesbefall und plaqueflora der Ratte. *Dtsch. Zahnärztl. Z.* 30:356–63
104. Keller, V., Froesch, E. R. 1971. Metabolism and oxidation of U-^{14}C-glucose, xylitol, fructose and sorbitol in the fasted and in the streptozotocin-diabetic rat. *Diabetologia* 7:349–56
105. Kimura, K. K., Carr, C. J. 1976. *Dietary Sugars in Health and Disease.* Bethesda, Md: Life Sci. Res. Off., Fed. Am. Soc. Exp. Biol.
106. Kinoshita, J. H. 1974. Cataractogenic effects of lactose and galactose. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 375–86. New York: Academic. 768 pp.
107. Koivistoinen, P., Hyvönen, L., eds. 1980. *Carbohydrate Sweeteners in Foods and Nutrition.* New York: Academic. 289 pp.
108. Korttila, K. K., Mattila, M. A. K. 1979. Increased serum concentrations of lactic, pyruvic and uric acid and bilirubin after postoperative xylitol infusion. *Acta Anaesthesiol. Scand.* 23:273–77
109. Kosaka, K. 1969. Stimulation of insulin secretion by xylitol administration. See Ref. 9, pp. 212–25
110. Laker, M. F., Gunn, W. G. 1979. Natural occurrence disqualifies mannitol as an internal standard when urinary monosaccharides are determined by gas-liquid chromatography. *Clin. Chim. Acta* 96:265–67
111. Lang, K. 1969. Utilization of xylitol in animals and man. See Ref. 9, pp. 151–57
112. Lang, K. 1971. Xylit, Stoffwehsel und Klinische Verwendung. *Klin. Wschr.* 49:233–45
113. Lee, H. A., Morgan, A. G., Waldram, R., Bennett, J. 1972. Sorbitol, some aspects of its metabolism and role as an intravenous nutrient. In *Parental Nutrition,* ed. A. W. Wilkinson, pp. 121–37. Baltimore: Williams & Wilkins. 310 pp.
114. Leutenegger, A. F., Goschke, H., Stutz, K., Mannhart, H., Werdenberg, D., Wolff, G., Allgower, M. 1977. Comparison b tween glucose and a combination of glucose, fructose, and xylitol as carbohydrates for total parenteral nutrition of surgical intensive care patients. *Am. J. Surg.* 133:199–205
115. Levins, G. A., Bissell, M. J., Bissell, D. M. 1978. Conversion of glucose to sorbitol and fructose by liver derived cells in culture. *J. Biol. Chem.* 253:5985–89
116. Lin, E. C. 1977. Glycerol utilization and its regulation in mammals. *Ann. Rev. Biochem.* 46:765–95
117. Lutz, D., Gülzow, H.-J. 1979. Respirometric investigations into the influence of the sugar substitute xylitol on sucrose degradation in human saliva. *Caries Res.* 13:132–36
118. MacDonald, I. 1968. Ingest glucose and fructose in serum lipid in healthy men and after myocardial infraction. *Am. J. Clin. Nutr.* 21:1366–73
119. Mackay, D. A. M. 1978. Sucrose and sucrose substitutes, industrial considerations. *Pharmacol. Therapeut. Dent.* 3:69–74
120. Mäenpää, P. H., Raivio, K. O., Kekomäki, M. P. 1968. Liver adenine nucleotides: fructose-induced depletion and its effect on protein synthesis. *Science* 161:1253–54
121. Mäkinen, K. K. 1978. Biochemical principles of the use of xylitol in medicine and nutrition with special consideration of dental aspects. *Experentia 30:1–160 (Suppl)*
122. Mäkinen, K. K. 1979. Xylitol and oral health. *Adv. Food Res.* 25:137–58
123. Mäkinen, K. K., Scheinin, A. 1975. Turku sugar studies. VI. The administration of the trial and the control of the dietary regimen. *Acta Odont. Scand.* 33: Suppl. 70, pp. 105–27
124. Mäkinen, K. K., Virtanen, K. K. 1978. Effect of 4.5-year use of xylitol and sorbitol on plaque. *J. Dental Res.* 57:441–46
125. Meng, H. C. 1974. Sugars in parenteral nutrition. In *Sugars in Nutrition,* ed. H. L. Sipple, K. M. McNutt, 528–66 New York: Academic. 768 pp.

126. Minkowski, O. 1893. Untersuchungen über den Diabetes mellitus nach Exstirpation des Pankreas. *Arch. Exp. Pathol. Pharmakol.* 31:85–189
127. Moorhouse, J. A., Kark, R. M. 1957. Fructose and diabetes. *Am. J. Med.* 23:46–58
128. Morgan, T. B., Yudkin, J. 1957. The vitamin sparing action of sorbitol in rats and mice. *Nature* 104:909–10
129. Morgan, T. B., Yudkin, J. 1962. The vitamin sparing action of sorbitol, sugars and related substances. *Vitamins Hormones* 20:39–66
130. Morris, R. C. Jr., Nigon, K., Read, E. B. 1978. Evidence that the severity of depletion of inorganic phosphate determines the severity of the disturbance of adenine nucleotide metabolism in the liver and renal cortex of the fructose loaded rat. *J. Clin. Invest.* 61:209–20
131. Moskowitz, H. R. 1971. The sweetness and pleasantness of sugars. *Am. J. Psychol.* 84:387–405
132. 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. 768 pp.
133. Mühlemann, H. R., Regolati, B., Marthaler, T. M. 1970. The effect on rat fissure caries of xylitol and sorbitol. *Helv. Odontol. Acta* 14:48–50
134. Müller, F., Strack, E., Kuhfahl, E., Dettmer, D. 1967. Der Stoffwechsel von Xylit bei normalen und alloxan diabetischen Kaninchen. *Z. Ges. Exp. Med.* 142:338–50
135. Nasrallah, S. M., Iber, F. L. 1969. Mannitol absorption and metabolism in man. *Am. J. Med. Sci.* 258:80–88
136. Navia, J. M., Lopez, H., Fischer, J. S. 1974. Rat caries promoting properties of sucrose substitutes in foods: mannitol, xylitol and sorbitol. *J. Dent. Res.* 53:207 (Abstr.)
137. Newbrun, E. 1969. Sucrose, the arch criminal of dental caries. *J. Dent. Child.* 36:239–48
138. Newbrun, E., ed. 1978. Symposium on non-cariogenic sweeteners. *Pharmacol. Therapeut. Dent.* 3:49–100
139. Nikkilä, E. A. 1974. Influence of dietary fructose and sucrose on serum triglycides in hypertriglyceridemia and diabetes. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 439–48. New York: Academic. 768 pp.
140. O'Dorisio, T. M., Spaeth, J. T., Martin, E. W. Jr., Sirinek, K. R., Thomford, N. R., Mazzaferri, E. L., Cataland, S. 1978. Mannitol and glucose. Effects on gastric acid secretion and endogenous gastric inhibitory polypeptide(GIP). *Am. J. Dig. Dis.* 23:1079–83
141. Onishi, H., Suzuki, T. 1969. Microbial production of xylitol from glucose. *Appl. Microbiol.* 18:1031–35
142. Oshinsky, R. J., Wang, Y. M., van Eys, J. 1977. Xylitol infusion and oxalate formation in rabbits. *J. Nutr.* 107:792–804
143. Perheentupa, J., Raivio, K. 1967. Fructose induced hyperuricemia. *Lancet* 2:528–31
144. Phillips, M. J., Heteny, G. Jr., Adachi, F. 1970. Ultrastructural hepatocellular alterations induced by in vivo fructose infusion. *Lab Invest.* 22:370–79
145. Pitkanen, E., Bardy, A., Pasternack, A., Servo, C. 1976. Plasma, red cell and cerebrospinal fluid concentrations of mannitol and sorbitol in patients with severe chronic renal failure. *Ann. Clin. Res.* 8:369–73
146. Plüss, E. M. 1978. Effects on plaque growth of xylitol and sucrose-containing chewing gum. *J. Clin. Periodontol.* 5:35–40
147. Pösö, A. R. 1979. Shuttles for translocation of NADH in isolated liver cells from fed rats during oxidation of xylitol. *Acta Chem. Scand. Suppl. B* 33:93–99
148. Raivio, K. O., Becker, M. A., Meyer, L. J., Greene, M. L., Nuki, G., Seegmiller, J. E. 1975. Stimulation of human purine synthesis de novo by fructose infusion. *Metabolism* 24:861–69
149. Raivio, K. O., Kekomäki, M. P., Mäenpää, P. H. 1969. Depletion of liver adenine nucleotides induced by fructose. *Biochem. Pharmacol.* 18:2615–24
150. Rofe, A. M., Conyers, R. A. J., Bais, R., Edwards, J. B. 1979. Oxalate excretion in rats injected with xylitol or glycolate: stimulation by phenobarbitone pretreatment. *Aust. J. Exp. Biol. Med.* 57:171–76
151. Sato, J., Wang, Y. M., van Eys, J. 1980. Methylglyoxal formation in rat liver cells. *J. Biol. Chem.* 255:2046–50
152. Scheinin, A., Mäkinen, K. K., eds. 1975. Turku sugar studies. I–XXI. *Acta Odont. Scand.* 33: Suppl. 70, pp. 1–348
153. Scheinin, A., Mäkinen, K. K., Tammisalo, E., Rekola, M. 1975. Turku sugar studies. XVIII. Incidence of dental caries in relation to 1 yr. consumption of xylitol chewing gum. *Acta Odont. Scand.* 33:Suppl. 70, pp. 307–16
154. Scheinin, A., Mäkinen, K. K., Ylitalo, K. 1975. Turku sugar studies. I. An intermediate report on the effect of su-

crose, fructose, and xylitol diets on the caries incidence in man. *Acta Odont. Scand.* 33: Suppl. 70, pp. 5–34
155. Scheinin, A., Mäkinen, K. K., Ylitalo, K. 1975. Turku sugar studies. V. Final report on the effect of sucrose, fructose and xylitol diets on the caries incidences in man. *Acta Odont. Scand.* 33:Suppl. 70, pp. 67–104
156. Schultis, K., Beisbarth, H. 1972. Post-traumatic energy metabolism. See Ref. 113, pp. 255–65
157. Schumer, W. 1971. Adverse effects of xylitol in parenteral alimentation. *Metabolism* 20:345–47
158. Schweigert, B. S., Shaw, J. H., Phillips, P. H., Elvehjem, C. A. 1945. Dental caries in the cotton rat. III. Effect of different dietary carbohydrates on the incidence and extent of dental caries. *J. Nutr.* 29:405–11
159. Servo, C., Palo, J., Pitkanen, E. 1977. Gas chromatographic separation and mass spectrometric identification of polyols in human cerebrospinal fluid and plasma. *Acta Neurol. Scand.* 56:104–10
160. Sestoft, L., Fleron, P. 1974. Determination of the kinetic constants of the fructose transport and phosphorylation in the perfused rat liver. *Biochim. Biophys. Acta* 345:27–28
161. Shallenberger, R. S. 1974. Occurrence of various sugars in foods. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 67–80. New York: Academic. 768 pp.
162. Shaw, J. H. 1976. Inability of low levels of sorbitol and mannitol to support caries activity in rats. *J. Dent. Res.* 55:376–82
163. Shaw, J. H., Griffiths, P. 1960. Partial substitution of hexitols for sucrose and dextrin in caries producing diets. *J. Dent. Res.* 39:377–84
164. Shaw, J. H., Roussos, G. G., eds. 1977. *Sweeteners and Dental Caries.* Washington DC: Information Retrieval. 404 pp.
165. Shinozura, H., Reid, I. M., Shull, K. H., Liang, H., Farber, E. 1970. Dynamics of liver cell injury and repair. *Lab. Invest.* 23:253–67
166. Siddiqui, I. R. 1970. The sugars of honey. *Adv. Carbohydr. Chem. Biochem.* 25:285–309
167. Sipple, H. L., McNutt, K. W., eds. 1974. *Sugars in Nutrition.* New York: Academic. 768 pp.
168. Slack, G. L., Millward, E., Martin, W. J. 1964. The effect of tablets stimulating salivary flow on the incidence of dental caries. A two-year clinical trial. *Bri. Dent. J.* 116:105–8
169. Smith, W. W., Finkelstein, N., Smith, H. W. 1940. Renal excretion of hexitols (sorbitol, mannitol and dulcitol) and their derivatives (sorbitan, isomannide and sorbide) and of endogenous creatinine-like chromogen in dog and man. *J. Biol. Chem.* 135:231–50
170. Söldering, E., Rekola, M., Mäkinen, K. K., Scheinin, A. 1975. Turku sugar studies. XXI. Xylitol, sorbitol fructose and sucrose-induced physico-chemical changes in saliva. *Acta Odont. Scand.* 33: Suppl. 70, pp. 337–43
171. Sols, A., Krane, R. K. 1954. Substrate specificity of brain hexokinase. *J. Biol. Chem.* 210:581–95
172. Sowden, J. C. 1957. Occurrence, properties, and synthesis of the monosaccharides. In *Carbohydrates, Chemistry, Biochemistry, Physiology,* ed. W. Pigman, 2:77–137. New York: Academic. 902 pp.
173. Spitz, I. M., Rubenstein, A. H., Bersohn, I., Bässler, K. H. 1970. Metabolism of xylitol in healthy subjects and patients with renal disease. *Metabolism* 19:24–34
174. Staub, H. W. 1978. Caloric availability of dietary polyols. *Fed. Proc.* 37:678 (Abstr.)
175. Stephen, R. W. 1966. Effect of different types of human foods on dental health in experimental animals. *J. Dent. Res.* 45:1551–61
176. Stuart, F. P., Torres, E., Fletcher, R., Crocker, D., Moore, F. D. 1970. Effects of a single, repeated and massive mannitol infusion in the dog: structural and functional changes in kidney and brain. *Ann. Surg.* 172:190–204
177. Swango, P. A. 1977. The current status of research with xylitol: A review of dental caries trials in animals and human subjects. See Ref. 164, pp. 225–37
178. Talbot, J. M. 1978. The need for special foods and sugar substitutes by individuals with diabetes mellitus. Bethesda, Md: Life Sci. Res. Off., Fed. Am. Soc. Exp. Biol.
179. Thomas, D. W., Edwards, J. B., Edwards, R. G. 1970. Examination of xylitol. *N. Engl. J. Med.* 283:247
180. Thomas, D. W., Edwards, J. B., Edwards, R. G. 1974. Toxicity of parenteral nutrition. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 567–90. New York: Academic. 768 pp.
181. Thomas, D. W., Edwards, J. B., Gilligan, J. E., Lawrence, J. R., Edwards, R. G. 1972. Complications following in-

travenous administration of solutions containing xylitol. *Med. J. Aust.* 1:1238–46

182. Thomas, D. W., Gilligan, J. E., Edwards, J. B., Edwards, R. G. 1972. Lactic acidosis and osmotic diuresis produced by xylitol infusion. *Med. J. Aust.* 1:1246–48
183. Topping, D. L., Mayes, P. A. 1970. Direct stimulation by insulin and fructose of very-low-density lipoprotein secretion by the perfused liver. *Biochem. J.* 119:48p
184. Touster, O. 1960. Essential pentosuria and glucuronate-xylulose pathway. *Fed. Proc.* 19:977–83
185. Touster, O. 1974. The metabolism of polyols. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 229–39. New York: Academic. 768 pp.
186. Touster, O., Mayberry, R. H., McCormick, D. B. 1957. The conversion of 1-^{13}C-D-glucuronolactone to 5-^{13}C-L-xylulose in a pentosuric human. *Biochim. Biophys. Acta* 25:196–98
187. Turner, J. L., Bierman, E. L. 1978. Effects of glucose and sorbitol proliferation of cultured human skin fibroblasts and arterial smooth muscle cells. *Diabetes* 27:583–88
188. Ukab, W. A. A. 1978. *Xylitol as a therapeutic agent against glucose-6-phosphate dehydrogenase deficiency hemolytic anemia.* PhD thesis. Univ. Texas, Houston. 61 pp.
189. Van den Berghe, G., Bronfman, M., Vanneste, R., Hers, H.-G. 1977. The mechanism of adenosine triphosphate depletion in the liver after a load of fructose. *Biochem. J.* 162:601–9
190. van Eys, J., Wang, Y. M., Chan, S., Tanphaichitr, V. S., King, S. M. 1974. Xylitol as a therapeutic agent in glucose-6-phosphate dehydrogenase deficiency. In *Sugars in Nutrition,* ed. H. L. Sipple, K. W. McNutt, pp. 613–31. New York: Academic. 768 pp.
191. Wang, Y. M. 1977. Drug-induced hemolysis. *Gen. Pharmacol.* 8:13–19
192. Wang, Y. M., King, S. M., Patterson, J. H., van Eys, J. 1973. Mechanism of xylitol toxicity in the rabbit. *Metabolism* 22:885–94
193. Wang, Y. M., Oshinsky, R. J., Lantin, E., Ukab, W., van Eys, J. 1977. Zur Frage der Toxizitat von Xylitinfusionen bei Kaninchen. *Infusionstherapie* 4: 251–57
194. Wang, Y. M., Oshinsky, R. J., van Eys, J. 1977. Xylitol metabolism and oxalte formation. *Am. J. Clin. Nutr.* 30: 837–38
195. Wang, Y. M., Patterson, J. H., van Eys, J. 1971. The potential use of xylitol in glucose-6-phosphate dehydrogenase deficiency anemia. *J. Clin. Invest.* 50: 1421–28
196. Watson, J. D., Yudkin, J. 1959. Effect 1973. Qualitative and quantitative study of sugar alcohols in several foods. *J. Food Sci.* 38:1262–63
197. Watson, J. D., Yudkin, J. 1959. Effect of sorbitol on the urinary excretion of some B vitamins in man. *Nature* 104:911
198. Weast, R. C. 1980. Carbohydrate. In *CRC Handbook of Chemistry and Physics,* 61:. C720–21, Fla.
199. Wekell, M. M., Hartman, W. J., Dong, F. M. 1980. Incidence of increased numbers of clostridium perfringens in the intestinal tract of rats fed xylitol. *J. Nutr.* 110:2103–8
200. West, K. M. 1973. Diet therapy of diabetes: an analysis of failure. *Ann. Intern. Med.* 79:425–34
201. Wieland, O., Matschinsky, F. 1962. Zur Natur der Antiketogenen Wirkung von Glycerin und Fructose. *Life Sci.* 2:49–54
202. Wick, A. N., Morita, T. N., Joseph, L. 1954. The oxidation of mannitol. *Proc. Soc. Exp. Biol. Med.* 85:188–90
203. Williamson, J. R., Jakob, A., Scholz, R. 1971. Energy cost of gluconeogenesis in rat liver. *Metabolism* 20:13–26
204. Winegrad, A. I., Burden, C. L. 1966. L-Xylulose metabolism in diabetes mellitus. *New Engl. J. Med.* 274:298–305
205. Winegrad, A. I., Clements, R. S. Jr., Beisswenger, P. J., Burden-Russell, C. L. 1969. The activity of the glucuronic acid pathway in human and experimental diabetes. See Ref. 9, pp. 258–74
206. Winters, R. W., Scaglione, P. R., Nahas, G. G., Verosky, M. 1964. The mechanism of acidosis produced by hyperosmotic infusion. *J. Clin. Invest.* 43:647–49
207. Wolf, H. P., Queisser, W., Beck, K. 1969. Der initiale Phosphatabfall im Serum von Gesunden und Leberkranken nach intravenöser Verabreichung von Hexosen und Zuckeralkoholen. *Klin. Wschr.* 47:1084–86
208. Wood, H. F., Eggleston, L. V., Krebs, H. A. 1970. The cause of hepatic accumulation of fructose-1-phosphate on fructose loading. *Biochem. J.* 119: 501–10
209. Wood, H. F., Krebs, H. A. 1973. Xylitol metabolism in the isolated perfused rat liver. *Biochem. J.* 134:437–43

210. Wright, L. W. 1974. Sorbitol and mannitol. *Chemtech* Jan:42–46
211. Yamagata, S., Goto, Y., Ohneda, A., Anzai, M., Kawashima, S., Chiba, M., Maruhama, Y., Yamauchi, Y. 1965. Clinical effects of xylitol on carbohydrate and lipid metabolism in diabetes. *Lancet* 2:918–21
212. Yashuk, W. D. 1971. Control mechanism of adenine nucleotide metabolism of ascites tumor cells. *J. Biol. Chem.* 246:1607–17
213. Ylikahri, R. H., Leino, T. 1979. Metabolic interactions of xylitol and ethanol in healthy males. *Metabolism* 28:25–29
214. Young, T. K., Lee, S. C., Tai, L. M. 1980. Mannitol absorption and excretion in uremic patients regularly treated with gastrointestinal perfusion. *Nephron* 25:112–16
215. Zakim, D., Pardini, R., Herman, R. H., Sauberlich, H. 1967. The relation of hepatic α-glycerophosphate concentration to lipogenesis in rat liver. *Biochim. Biophys. Acta* 137:179–80
216. Zakim, D., Pardini, R. S., Herman, R. H., Sauberlich, H. E. 1967. Mechanism for the differential effects of high carbohydrate diets on lipogenesis in rat liver. *Biochim. Biophys. Acta* 144: 242–51