DIETARY SUGARS IN HEALTH AND DISEASE

II. XYLITOL

July 1978

Prepared for

BUREAU OF FOODS
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C. 20204

under

Contract Number FDA 223-75-2090
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LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
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Bethesda, Maryland 20014
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB) provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This technical report was prepared for the Bureau of Foods, Food and Drug Administration (FDA), by the staff of the LSRO in accordance with the provisions of Contract No. 223-75-2090. Special appreciation is expressed to K.K. Kimura, Ph.D., M.D., and C. Jelleff Carr, Ph.D., who critically reviewed the literature, met with clinicians and representatives of industrial firms and prepared drafts of the report.

The LSRO acknowledges the contributions of the investigators and consultants who have assisted with this study. The listing of the consultants' names in Section VIII does not imply that they endorse the conclusions of the study. The LSRO accepts the responsibility for the report and the opinions expressed. The report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the report was approved and transmitted to FDA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
SUMMARY

This report on xylitol is the second in a series on refined carbohydrates in the diet. Xylitol is a naturally occurring pentitol. Xylitol and sucrose have approximately equal sweetness on a weight basis. Improved technology for commercial production has contributed to the potential for increased xylitol utilization and led to the successful introduction of xylitol-sweetened products in several countries.

Xylitol is largely converted to glucose in the liver and is non-ketogenic. The rise in blood glucose is of lower magnitude and the insulin response is less after xylitol ingestion than after ingestion of sucrose or glucose. In the dietary management of diabetes, a limited number of short-term clinical trials suggest that xylitol as a substitute for rapidly absorbed simple carbohydrate sweeteners, may, in proper dosage, be of value in prevention of postprandial fluctuations of blood glucose levels.

Studies in humans at the University of Turku, Finland provide evidence that xylitol is without adverse effects when consumed at an average level of 53 g per day over a 2-year period. In these studies, the occurrence and severity of dental caries were reduced in subjects consuming xylitol in place of sucrose in the diet.

Adverse effects of dietary xylitol were reported in a recent study but not in earlier animal feeding trials. If the chronic animal toxicity studies indicating that xylitol is associated with tumor induction are confirmed, the safety of xylitol as a food ingredient would need to be reconsidered and levels of the polyol in foods containing xylitol as a natural ingredient would need to be assessed in terms of possible adverse health effects. Additional studies on metabolism and pharmacodynamics of ingested xylitol are suggested.
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I. INTRODUCTION

A. BACKGROUND

The Bureau of Foods, Food and Drug Administration (FDA) has a continuing interest in the nutritional quality of the American diet. The Bureau is responsible for evaluating and monitoring the safety of foods, establishing regulations, and providing nutrition information to consumers.

In keeping with these responsibilities, the FDA requested that the Life Sciences Research Office review current scientific information and technological developments related to the use in foods of the sugar alcohol, xylitol. Until recently, propylene glycol, glycerol, sorbitol, and mannitol have been the only polyols of commercial importance in the food industry. Xylitol is of considerable current interest because of technological developments in its commercial production and because extensive clinical studies suggest that this polyol may be noncariogenic when used in foods and chewing gums as a sugar substitute (Shaw, 1978). However, recent reports have attributed toxic effects to xylitol when administered parenterally to human subjects (Thomas et al., 1970) or when fed at high dosages to experimental animals (Anonymous, 1978). Therefore, it is desirable to reassess the health aspects of the use of xylitol in foods. This study was undertaken to provide a critical appraisal of current knowledge on this subject.

Xylitol is identified in the Code of Federal Regulations [21 CFR 172.395] as one of several special dietary and nutritional additives. These regulations state that it may be safely used in foods for special dietary uses, provided the amount used is not greater than that required to produce its intended effect. As such, xylitol would be a nutritive sweetener substituting for sucrose or corn sweeteners in certain special dietary foods.

The first proposal for special dietary use of xylitol in foods in the United States was published by FDA in 1963 (Office of the Federal Register, 1963a). It permitted the addition of xylitol to nonstandardized marmalade and jams for special dietary uses. The proposal indicated that the label must specify the amount of xylitol per average serving and should include a warning that ingestion of more than 15 g of xylitol per day may cause diarrhea. These two caveats were omitted in an amended order published on July 31, 1963 (Office of the Federal Register, 1963b).

However, reports of adverse effects of intravenous administration of xylitol in 1971 led to a proposed revocation of the regulation [21 CFR 172.395] permitting its use in special dietary foods (Office of the Federal Register, 1971). The revocation proposal indicated that allowing unlimited use of xylitol in foods was not warranted even though there was no evidence that it was being used in foods in the United States at that time. The proposed revocation of 21 CFR 172.395 is currently pending, even though there is considerable developmental work on use of xylitol in several types of foods. Petitions to FDA during this interim period have commented upon the intravenous toxicity studies, have provided additional data on oral use, and have requested revision of the regulations to permit use of xylitol in chewing gum, chewable vitamins, jams, and jellies (Moore, 1977).
The regulatory status of xylitol in countries other than the United States is somewhat varied (Moore, 1977). In West Germany, xylitol is permitted as a sugar substitute without limitation in dietetic foods. If the dietetic foods contain more than 10 percent xylitol, they must be labeled to indicate that xylitol has replaced sugar and the caloric content must be stated. Switzerland, Finland, and the Soviet Union allow its use as a sweetener in dietetic foods. Switzerland, Denmark, Finland, Norway, and Sweden permit use of xylitol in chewing gums and allow labeling claims of reduced cariogenicity. Only pharmaceutical uses are permitted in Japan. France is considering the adoption of, and Canada has adopted, regulations permitting use of xylitol in chewing gums and foods (Department of National Health and Welfare, Canada, 1977). These differences in regulatory management of xylitol reflect the increasing interest in, and development of, new products with substitute sweeteners that could increase the use and consumption of xylitol in these several countries (Russo, 1976; Moore, 1977).

It is necessary to determine whether the information concerning metabolism and possible toxicity of xylitol is adequate to provide a basis for predicting nutritional effects that might result from a significant increase in the quantity of this polyol in the dietary of the United States. The alleged parenteral toxicity of xylitol for man requires careful evaluation if this polyol is to be consumed in greater quantities in various foods. Furthermore, the claimed cariostatic properties of xylitol should be validated.

B. SCOPE

This report reviews briefly the chemical and biochemical aspects of the sugar alcohol, xylitol; its current production; its use in foods; and its metabolic fate in the human body. Studies conducted on animals and man that assess the safety of xylitol are reviewed and critically evaluated. In addition, the influence of xylitol on cariogenesis in animals and man is reviewed.

Sources of information included computerized biomedical literature files of the National Library of Medicine, comprehensive compilations of the scientific literature and reports from industrial laboratories. Additional literature references were kindly supplied by the consultants, who provided in addition their opinions and views on various industrial, technical, and clinical aspects of the use of xylitol.

The report is one of a series of reports on the nutritional significance of refined carbohydrates. A previous study reviewed the role of fructose as a dietary carbohydrate (Kimura and Carr, 1976) and similar reports on sorbitol and mannitol are being prepared. In addition, another study conducted by LSRO has addressed the need for special dietary foods and sugar substitutes by individuals with diabetes mellitus (Talbot, 1978). This latter report includes the possible role of fructose, xylitol and sorbitol in the dietary management of patients with diabetes mellitus.
II. XYLITOL

A. CHEMICAL PROPERTIES

Xylitol is a 5-carbon sugar alcohol that may be derived from the wood sugar, xylose. It has the following structural formula:

```
H
H-C-OH
|    |
H-C-OH
|    |
HO-C-H
|    |
H-C-OH
|    |
H-C-OH
```

Xylitol and sucrose have approximately equal sweetness on a weight basis; for example, 4 to 5 percent solutions are essentially equisweet (Moskowitz, 1971). Although sucrose is a nonreducing disaccharide with little structural similarity to xylitol, Lindley et al. (1976) concluded that the Shallenberger theory of sugar sweetness, which relates intensity of response to degree of intramolecular hydrogen bonding, explains satisfactorily the approximately equal sweetening characteristics of these two sugars. Xylitol gives no Maillard reaction when heated with amino acids and related substances. It is a white, crystalline, stable substance having a molecular weight of 152 and a melting point of 93 to 95°C. It yields 4.06 kcal per g, and a 4.56 percent solution of xylitol is physiologically isotonic.

Xylitol was prepared in 1891 by sodium amalgam reduction of D-xylose; however, the resultant product was an unstable syrup (Manz et al., 1974). A metastable form crystallized from the syrup is hygroscopic and melts at 61.0 to 61.5°C. Carson et al. (1943) synthesized xylitol and obtained orthorhombic crystals that melted at 93.0 to 94.5°C. This more stable form is nonhygroscopic and usually crystallizes from methanol, ethanol, or aqueous solutions.

As with all acyclic polyols, xylitol has two identical terminal -CH2OH groups. The molecule is symmetrical and has no optical activity; thus, the use of D or L in the name is unnecessary.

Certain properties of xylitol are listed in Table 1. Xylitol has a negative heat of solution. The energy required to dissolve crystalline rhombic
**TABLE 1**

**PHYSICAL AND CHEMICAL PROPERTIES OF XYLITOL***

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>$C_5H_{12}O_5$</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>152.15</td>
</tr>
<tr>
<td>Optical character</td>
<td>Inactive</td>
</tr>
<tr>
<td>Melting range</td>
<td>Rhombic 93.0 to 94.5°C</td>
</tr>
<tr>
<td></td>
<td>Monoclinic 61.0 to 61.5°C</td>
</tr>
<tr>
<td>Solubility in water</td>
<td></td>
</tr>
<tr>
<td>(g per 100 g solution)</td>
<td>4°C 55</td>
</tr>
<tr>
<td></td>
<td>20°C 62.8</td>
</tr>
<tr>
<td></td>
<td>40°C 74.2</td>
</tr>
<tr>
<td>Solubility in water</td>
<td></td>
</tr>
<tr>
<td>(g per 100 g water)</td>
<td>4°C 122</td>
</tr>
<tr>
<td></td>
<td>20°C 168.8</td>
</tr>
<tr>
<td></td>
<td>40°C 291.3</td>
</tr>
<tr>
<td>Possible impurities</td>
<td>Mannitol, sorbitol, galactitol, arabitol**</td>
</tr>
</tbody>
</table>

---

* Adapted from Mäkinen (1978).

** The presence of impurities depends on raw material and process techniques. Other polyols may be present in trace amounts in xylitol depending on the source.
xylitol comes from the solvent, and produces a cooling effect. The endothermic reaction creates pleasant organoleptic sensations in persons consuming certain xylitol products (Shaw, 1978). Other sugar alcohols and glucose also display this cooling effect, but to a lesser extent than xylitol.

Mäkinen (1978) has prepared a comprehensive review of the chemistry and biological effects of xylitol. He attributes the unique physiological effects of xylitol to the open-chain structure, absence of reducing carbonyl groups, the short "length" of the molecule, similarities in the configuration at various carbon atoms with sugars, and the ability to form complexes with essential metal cations. However, these observations are equally applicable to mannitol and possibly with other polyols which are less sweet than xylitol.

B. OCCURRENCE AND MANUFACTURE

Virtually all plants contain xylitol and it is present in significant amounts in many berries, fruits, leaves and mushrooms. The pentose xylose is the precursor of xylitol in plants (Washüttr et al., 1973). Most wines also contain xylitol as a fermentation product (Onishi and Suzuki, 1969). Xylitol has been consumed by animals and man since antiquity.

Although xylitol is widely distributed in the plant kingdom, occurrence in low concentrations makes direct extraction from fleshy plant sources commercially impractical. The richest natural dietary sources are plums, strawberries, raspberries, cauliflower and endive, in which the concentration may reach 0.3 to 0.9 g in 100 g dry material (Table 2). Considerable amounts of xylitol (5 to 15 g daily) are formed as an intermediate of carbohydrate metabolism in man (Touster, 1974).

Xylitol is produced commercially from xylan or other xylose-rich sources by chemical, enzymatic or microbiological conversion. The current commercial method in Finland uses xylan derived from birchwood chips, and accounts for most of the 1000 tons produced worldwide annually. Other suitable starting materials are larch, beech and other hardwood chips, bagasse, coconut, almond and pecan shells, cottonseed hulls, stalks, and corn cobs (Emodi, 1978; Moore, 1977). These xylan sources are hydrolyzed to D-xylose, which is then reduced by pressure hydrogenation in the presence of nickel catalyst, purified and crystallized as xylitol. Xylitol also can be produced from xylose by yeast fermentation or by oxalic acid treatment of plant materials (Moore, 1977).

The present world production of xylitol has been estimated at about 1000 tons per year, derived mostly from hardwood and partly from cottonseed hulls and coconut shells. Large-scale production is planned as a joint Swiss-Finnish venture at the sucro-chemical factory in Kotka, Finland, where xylitol has been produced from birchwood since 1974. Commercial production from corn cobs is being considered by several United States manufacturers (Moore, 1977).
<table>
<thead>
<tr>
<th>Item</th>
<th>Xylitol (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plums (Prunus domestica subspec. italica)</td>
<td>935</td>
</tr>
<tr>
<td>Strawberries (Fragaria var.)</td>
<td>362</td>
</tr>
<tr>
<td>Cauliflower (Brassica oleracea L. var. botrytis)</td>
<td>300</td>
</tr>
<tr>
<td>Lamb's lettuce (Valerianella olitoria L.)</td>
<td>273</td>
</tr>
<tr>
<td>Raspberries (Rubus idaeus L.)</td>
<td>268</td>
</tr>
<tr>
<td>Endives (Cichorium endivie L.)</td>
<td>258</td>
</tr>
<tr>
<td>Eggplant (Solanum melongena L.)</td>
<td>180</td>
</tr>
<tr>
<td>Lettuce (Lactuca sativa)</td>
<td>131</td>
</tr>
<tr>
<td>White mushrooms (Boletus edulis Bull.)</td>
<td>128</td>
</tr>
<tr>
<td>Apple wine</td>
<td>120</td>
</tr>
<tr>
<td>Spinach (Spinacia oleracea L.)</td>
<td>107</td>
</tr>
<tr>
<td>Pumpkins (Cucurbita pepo L.)</td>
<td>96.5</td>
</tr>
<tr>
<td>Kohlrabi (Brassica oleracea L. var. gongylodes L.)</td>
<td>94</td>
</tr>
<tr>
<td>Fennel (Foeniculum vulgare Mil.)</td>
<td>92</td>
</tr>
<tr>
<td>Onions (Allium cepa L.)</td>
<td>89</td>
</tr>
<tr>
<td>Carrots, fresh (Daucus carota L.)</td>
<td>86.5</td>
</tr>
<tr>
<td>Red cherry jam</td>
<td>56</td>
</tr>
<tr>
<td>Morello cherry jam</td>
<td>54.5</td>
</tr>
<tr>
<td>Leeks (Allium porrum L.)</td>
<td>53</td>
</tr>
<tr>
<td>Black currant jam</td>
<td>34</td>
</tr>
<tr>
<td>Bananas (Musa sapientum L.)</td>
<td>21</td>
</tr>
<tr>
<td>Pineapple, canned (Ananas sativus)</td>
<td>21</td>
</tr>
<tr>
<td>Chestnuts, edible (Castanea vesca)</td>
<td>14</td>
</tr>
<tr>
<td>Carrot juice</td>
<td>12</td>
</tr>
<tr>
<td>Brewers' yeast</td>
<td>4.5</td>
</tr>
<tr>
<td>Licorice</td>
<td>4.5</td>
</tr>
<tr>
<td>Cornmeal</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Expressed as mg per 100 g of dry matter, or as mg per 100 g liquid. Modified from Washüttl et al. (1973).
C. USE OF XYLITOL IN FOODS

Products for general dietary use containing added xylitol are not available in the United States. However, Emori (1978) stated that there would be few technological problems in substituting xylitol for sucrose or other sugars in a wide diversity of processed foods. Several United States firms are developing special dietary foods containing 50 percent xylitol plus mannitol and sorbitol in place of sucrose or corn sugar as the sweetening agents (Moore, 1977). Until recently, the limited availability and relatively high cost of crystalline xylitol (about $3.00 to $6.00 per kg) discouraged general use as a sugar substitute.

Chocolate, gelatin desserts, cakes and pastries, as well as bakery goods with xylitol substituted for sucrose, are generally available in several Scandinavian countries. Foods containing xylitol as the sweetening agent in Switzerland and Germany include beverages, chocolate, custard, milk drinks, bakery products, hard candy, jams, preserves, marmalades, and sugar-coated products (Russo, 1976).

Based upon results of the cariogenicity studies of Mäkinen and Scheinin (1975), xylitol chewing gums have been marketed in several European countries and have been introduced into this country.∗

∗FinnFoods Company, Inc., New Jersey, (American Sales subsidiary of Hellas®, Turku, Finland) and William Wrigley Jr. Co., Chicago, Illinois, are marketing chewing gum containing varying amounts of xylitol. FinnFoods distributes Hellas Original Xylitol Gum® which reportedly contains 67 percent xylitol, while the Wrigley gum Orbit® contains 10 percent xylitol.
III. ABSORPTION AND METABOLISM

Most xylitol ingested in moderate amounts is absorbed from the gastrointestinal tract in healthy human subjects. The rate of absorption is about 20 percent that of glucose (Mehnert, 1976); and, the dose and the rate of utilization by the body influence the total amount absorbed (Keller and Froesch, 1972). Large doses are less well absorbed because of the osmotic effect in the gastrointestinal tract produces diarrhea.

The recognition of xylitol as a normal metabolite in man stems from studies of patients with the genetic abnormality, essential pentosuria (Touster, 1974). These persons excrete large quantities of L-xylulose in the urine. L-xylulose is normally metabolized to xylitol by a specific NADPH-linked enzyme, L-xylulose reductase (Touster, 1974). This enzyme has been demonstrated to be deficient in the erythrocytes of persons with essential pentosuria (Wang and van Eys, 1970). The xylitol formed is then dehydrogenated to D-xylulose by an NAD-linked enzyme, D-xylulose reductase. Touster's studies led to the recognition of the glucuronic acid-L-xylulose pathway that occurs in all mammals, generally in the liver and kidneys (Figure 1).

While other cell membranes are relatively impermeable, the liver cell membrane is permeable to the two polyols sorbitol and xylitol (Froesch and Jakob, 1974). Xylitol enters the hepatic cell without difficulty although little is known of the mechanism of its uptake. According to Jakob et al. (1971) more than half of the xylitol taken up by perfused rat livers is rapidly converted to glucose while the remaining portion is oxidized to lactate or oxidized completely via the citric acid cycle. In the presence of lactate, xylitol uptake by the liver is reduced by approximately 20 percent, but the relative quantity of xylitol conversion to glucose is altered only slightly.

Xylitol can be metabolized in the liver in the absence of insulin for liver glycogen synthesis; in addition, it can serve as an energy source for hepatic metabolism (Mehnert and Förster, 1976). Unlike the storage of glycogen formed from ingested glucose, storage of liver glycogen from xylitol is independent of the blood glucose level and the availability of insulin. In general, the fate of the intermediary products of xylitol metabolism in the liver depends on the prevailing metabolic situation; for example, in the presence of hypoglycemia, xylitol is rapidly transformed into glucose (Mehnert and Förster, 1976).

Woods (1975) studied the hepatic metabolism of xylitol in isolated perfused livers of female Wistar rats. There was an increase in xylitol uptake and increased production of glucose, lactate and pyruvate by the perfused livers as the initial xylitol concentration in the perfusing medium was increased from 0 to 20 mmol per liter. The ATP, ADP, AMP and inorganic phosphate of livers were decreased when livers were perfused for 40 minutes with a solution containing an initial xylitol concentration of 20 mmol per liter. Total liver adenine nucleotide concentration dropped to half that of control livers not exposed to xylitol. The cytoplasmic redox state (NAD/NADH) fell to about
FIGURE 1

Schematic diagram of hepatic metabolism of xylitol and related carbohydrates
(Adapted from Touster, 1974).
1. D-Xylulose reductase (1.1.1.9)  
2. Xylulokinase (2.7.1.17)  
3. L-Xylulose reductase (1.1.1.10)  
4. Keto-L-gulonate decarboxylase (4.1.1.34)  
5. L-Gulonate dehydrogenase (1.1.1.45)  
6. Glucuronate reductase (1.1.1.19)  
7. UDPglucose dehydrogenase (1.1.1.22)  
8. Glucosephosphate isomerase (5.3.1.9)  
9. Phosphoglucomutase (2.7.5.1)  
10. Glucose 1-phosphate uridylytransferase (2.7.7.9)  
11. Glucokinase (2.7.1.2)  

12. Glucose-6-phosphatase (3.1.3.9)  
13. 6-Phosphofructokinase (2.7.1.11)  
14. Fructose bisphosphate aldolase (4.1.2.13)  
15. Triosephosphate isomerase (5.3.1.1)  
16. L-Iditol dehydrogenase (1.1.1.14)  
17. Ketohexokinase (2.7.1.3)  
18. Fructose bisphosphate aldolase (4.1.2.13; liver isozyme)  
19. Triokinase (2.7.1.28)  
20. Hexosediphosphatase (3.1.7.11)  

----indicates multistep pathway

NAD = nicotinamide adenine dinucleotide  
NADH = reduced NAD  
NADP = NAD phosphate  
NADPH = reduced NADP  
UDP = uridine diphosphate  
ATP = adenosine triphosphate  
ADP = adenosine diphosphate  
AMP = adenosine monophosphate
20 percent of control values following 80 minutes' perfusion with a medium containing an initial xylitol concentration of 20 mmol per liter. Woods (1975) attributed the drop in liver adenine nucleotide levels to two factors: (1) the demand for ATP for phosphorylation of substrates; (2) the sequestration of phosphate as phosphorylated intermediates, and a resultant lowering of inorganic phosphate levels, leading to the activation of enzymes degrading AMP.

Lang (1971) noted that the metabolism of xylitol, fructose and sorbitol differs from that of glucose with respect to the initial steps by which they enter the glycolytic pathway of the liver. These steps are independent of insulin, and according to Froesch and Jakob (1974), may have been responsible for the widely held misinterpretation that the entire catabolic utilization of these carbohydrates is also insulin-independent.

Prompt hyperglycemia is absent following ingestion of xylitol, sorbitol or fructose, and the transient rise in blood sugar levels is less with xylitol than with either sorbitol or fructose (Förster, 1974; Mehnert and Förster, 1976). The reduced hyperglycemic response is related to the relatively slow rate of xylitol absorption and the subsequent rapid conversion, phosphorylation, and metabolism via the hexose monophosphate-pentose pathway. Serum insulin levels which would be expected to rise following glucose administration, are barely altered by intravenous administration of xylitol, sorbitol or fructose to rats at rates up to 0.7 g per kg body weight per hour (Förster, 1974). Presumably, oral administration of xylitol would result in a similar lack of insulin response. However, subsequent peripheral metabolism of glycolytic products from liver metabolism of xylitol would be insulin-dependent.

Förster (1974) infused human volunteers intravenously with 1.5 g per kg of glucose, fructose, sorbitol, or xylitol as 20 percent solutions over a 20-minute period. The glucose concentration of venous blood was significantly increased only during the glucose infusion. Förster (1974) concluded that xylitol, sorbitol and fructose were transformed to glucose relatively slowly. Blood lactate levels increased most with fructose infusion, although sorbitol and glucose also caused significant rises. The low serum concentrations of xylitol noted during continuous infusions suggest its effective elimination by metabolic utilization. According to Förster (1974), the free fatty acids in serum are reduced by the so-called "xylitol effect." This is a combination of stimulated hepatic esterification and diminished peripheral release of fatty acids. This combined mechanism produces a prolonged depression of the concentration of serum free fatty acids. However, Wang et al. (1977b) have shown that fluctuation of intermediate metabolites and nucleotides resulting from parenteral xylitol infusions appears to be dose-dependent.

Xylitol has been studied clinically as a carbohydrate that may be utilized by the diabetic because it causes minimal postprandial hyperglycemia and presumably requires less insulin for its total metabolism. Thus, Lang (1969) reported that xylitol produced little change in plasma insulin levels in human subjects. The use of parenteral xylitol in Germany and Japan was based on a presumed value of xylitol in nutrition, especially for diabetic and
other patients with debilitating diseases (Touster, 1974). However, following oral administration, the xylitol entering the pentose phosphate pathway (and hence metabolized to hexose phosphate) can be utilized for energy via the citric acid cycle, or converted to glucose or glycogen. Obviously, any glucose or glycogen formed will ultimately depend on insulin for peripheral utilization. It is likely that the slow gastrointestinal absorption results in a less pronounced rise in the blood sugar level compared with that resulting from an equal amount of glucose. This type of prolonged, diminished hyperglycemia is similar to the response to complex carbohydrates, a well-known clinical phenomenon in the management of the patient with diabetes mellitus.

Förster (1974) has reviewed the numerous studies on comparative metabolism of xylitol, other polyols, and sugars in normal volunteers and diabetic patients. Touster (1974) and others have surveyed the metabolic pathways in animals and man, and Froesch and Jakob (1974) have reviewed the studies in experimental animals on the metabolic fate and biochemical changes that follow intravenous or oral administration. The conclusions from these studies emphasize the metabolic differences in various animal species and man. The most significant findings with xylitol in normal subjects and diabetic patients appear to be: hyperglycemia that appears more slowly, is milder, and is more prolonged than that with glucose; decreased serum lactate levels; low serum insulin levels; and lack of ketogenicity (Förster, 1974). Based on these observations, Förster suggested that this sugar alcohol was useful in general nutrition and presumably for the diabetic patient. However, in spite of the extensive studies with xylitol in Europe and Japan in the management of patients with diabetes mellitus, there appears to be little interest in its use by clinicians in the United States (Talbot, 1978).

This situation may be related to the adverse effects alleged by Thomas and associates (1972a) in Australia, Donahoe and Powers (1974) and others; to the lack of convincing evidence of long-term benefits from ingestion of dietary xylitol; or to the lack of familiarity by many clinicians in this country with the European studies on the advantages of xylitol in management of diabetes mellitus.
IV. SAFETY EVALUATION STUDIES

Xylitol is present in many natural foods and has been consumed by man for centuries without obvious untoward effects. In addition, it has been estimated that in man from 5 to 15 g are produced daily as an intermediate in carbohydrate metabolism. Few chronic studies of human xylitol ingestion have been conducted. Recently, evidence for lack of toxicity of xylitol as a food ingredient ingested over a prolonged period has been derived from the Turku University studies on 49 subjects who consumed an average of 1.5 kg monthly for a two-year period (Scheinin and Mäkinen, 1975). Comprehensive evaluations of the health of these subjects revealed no toxic effects. According to Mäkinen (1978) xylitol-containing foods have been consumed for several years in the Soviet Union, West Germany and other European countries without reports of adverse effects. These uses have been reviewed by Brin and Miller (1974), Förster (1974), Frosch and Jakob (1974), Manz et al. (1974), Touster (1974), and Mäkinen and Scheinin (1975).

A. ANIMAL STUDIES

Kieckebusch et al. (1961) showed that xylitol was relatively nontoxic, with an estimated oral LD$_{50}$ in mice of 25.7 g per kg body weight. In a 12-week feeding study on groups of 30 to 60 rats (strain not specified), 10 or 30 percent xylitol in the diet (about 10 or 30 g per kg per day) was well tolerated. No adverse effects on growth, protein utilization efficiency, reproduction, or morphology of major organs were evident. Lens opacities did not occur and the caloric requirements of the animals were adequately met by xylitol.

Hosoya and Iitoyo (1969) increased gradually the xylitol content of the diet of rats by 5 percent weekly to a maximum of 20 percent. The rats were maintained on this diet with 20 percent xylitol for eight to ten weeks without significant differences in body weight gains compared with control animals fed laboratory chow without xylitol. A second group of rats was adapted to 20 percent xylitol in the diet in 3.5 days by 2.5 percent incremental increases. Osmotic diarrhea occurred in the second group, but adaptation occurred within four days. No adverse effects were reported for either group except for a 10 percent weight loss in the second group of rats following osmotic diarrhea. After the fourth week, no significant differences in body weights among the control animals and the two experimental groups were evident. Hosoya and Iitoyo (1969) concluded that in the rat, the initial step in xylitol metabolism is rate-limiting because it involved the induction of a hepatic NAD-linked xylitol dehydrogenase brought about by the prolonged feeding. This explanation is not in complete agreement with other investigators who have concluded from liver perfusion and animal studies that, once absorbed and transported to the liver, xylitol is rapidly phosphorylated (Förster, 1974; Mehnert and Förster, 1976).
Wang et al. (1972) estimated the LD₅₀ for the rabbit at about 4 to 6 g per kg when a 50 percent xylitol solution was intravenously infused at a rate of 87 mg per kg per minute. A 5 percent solution was essentially isotonic and nontoxic to rabbits in doses up to 1 g per kg per 12 hours even after repeated infusions. In other experiments, Wang et al. (1973) showed that rabbits can tolerate intravenous injections of 0.5 g per kg xylitol every 6 hours for 6 days. These studies suggest that the "toxicity" of highly concentrated xylitol infusions may be due to a hyperosmolar effect.

Oshinsky et al. (1977) have confirmed that rabbits can safely tolerate infused xylitol at doses of up to 2.0 g per kg body weight in a 50-minute period. Their study of infused radiolabeled xylitol and glucose indicated that plasma oxalate levels of rabbits receiving xylitol were not elevated significantly above normal but plasma oxalate levels in animals receiving glucose were higher than levels attained in xylitol infused rabbits. Based on these and related experiments, Hauschildt et al. (1976) and Oshinsky et al. (1977) concluded that xylitol administration results in no more oxalate production than does glucose administration. In addition, they concluded that there was no direct pathway for conversion of exogenous xylitol to oxalate. Thus, the suggestion of oxalate as a mediator of xylitol toxicity in humans is not supported by these observations in rabbits.

B. HUMAN STUDIES

1. Parenteral Studies

Xylitol and other nonglucose carbohydrates have been used in parenteral nutrition in Europe and Japan for a number of years without apparent adverse effects. For example, Lang et al. (1966) reported that 5 and 10 percent solutions of xylitol administered intravenously to 1135 surgical patients caused no side-effects. Similar favorable experiences in the nutritional support of 1189 patients by intravenous administration of xylitol solutions were reported by Halmágyi and Israng (1968). Coats (1969) described the clinical course of a patient with short bowel syndrome who was maintained by total parenteral nutrition for 7.5 months. Of the several substances employed (fructose, sorbitol, xylitol, and ethanol), xylitol was utilized most efficiently. Even at concentrations of 50 percent and infusion rates up to 62.5 g per hour, urinary loss of xylitol did not exceed 4 percent of the input. No untoward effects were reported. Schultis and Geser (1970) concluded that intravenously administered xylitol (5% solutions) alleviated the severity of impaired glucose tolerance and increased ketonuria typically found in postoperative recovery of surgical patients. They observed that xylitol administrations were beneficial in this regard while intravenous administration of 5% glucose solutions had little effect on postsurgical glucose tolerance or ketonuria. Amador and Eisenstein (1971), as cited by Brin and Miller (1974), observed reversible elevation of plasma urate and lactate as well as diarrhea and flatulence in patients receiving high doses of xylitol intravenously, but these manifestations were transient or absent in patients receiving less than 90 g xylitol per day.
Berg and his associates (1973) found no changes in blood lactate, pyruvate or bicarbonate when xylitol solutions were infused into healthy male volunteers at dose rates up to 0.25 g xylitol per kg per hour. Eight fasting, healthy subjects who received rapid intravenous injections (in 30 minutes) of 50 g xylitol daily for 3 consecutive days demonstrated postinfusion decreases of blood glucose, but no hypoglycemia (Brodan et al., 1973). They also reported blood-lactate and lactate-pyruvate ratios rose following xylitol infusions. Matzkeles et al. (1975) measured blood levels of insulin, xylitol and glucose following 6-hour intravenous infusions of 10 percent xylitol to 16 healthy men. At 0.5 and 0.375 g per kg body weight per hour of xylitol, insignificant increases in serum insulin levels occurred. At lower dose rates, no increase of serum insulin was observed. Blood glucose levels decreased in all test groups, but not to hypoglycemic levels.

Mehnert and Förster (1976) reported a relatively small influence of intravenously administered fructose, sorbitol or xylitol on blood glucose levels compared with that of intravenous glucose. They concluded that with proper dosages and rates of infusion (0.25 g per kg body weight per hour suggested with an upper limit of 0.4 to 0.5 g per kg per hour also noted) xylitol does not cause clinically significant side-effects such as excessive blood levels of urea, lactate, triglycerides and bilirubin. Förster (1976) reported no specific and dramatic side-effects from the use of glucose substances (fructose, sorbitol, xylitol) apart from increased uric acid synthesis. Lactic acidemia was controlled provided proper dosage and infusion rates were observed. At the Second Symposium on Sugar Substitutes at Würzburg, Förster (1977) reaffirmed that in extensive, well-controlled investigations with human subjects, he and his colleagues were unable to demonstrate any significant side-effects resulting from oral administration of xylitol in doses up to 100 g per day or from the parenteral use of xylitol in doses up to 400 g per day. He indicated that reports of isolated observations of adverse effects following administration of fructose or xylitol are, in principle, invalid in the absence of appropriate comparisons with glucose. Of the presumed untoward effects of parenterally administered glucose substitutes that have been reported, Förster (1977) stated that increased uric acid synthesis is the only metabolic effect in which there is a distinct difference between glucose and the glucose substitutes. After a review of the available information on this effect, Förster (1977) concluded that:

"The rise in uric acid concentration produced by glucose substitutes is a metabolic phenomenon which, whilst as yet not fully clarified, is devoid of any pathophysiological relevance."

A number of investigators, including Förster have reported that the intravenous administration of fructose, sorbitol, or xylitol at high doses and high rates may result in significant increases in uric acid production, serum bilirubin, lactate, and oxalate levels as well as transient decreases in hepatic organic and inorganic phosphorus (Foerster, 1972; Förster, 1974; Froesch and Jakob, 1974; Kaiser et al., 1974; Schumer, 1971; Thomas et al., 1972 a,b; Touster, 1974; Wang et al., 1972). For instance, Donahoe and Powers (1974) reported hyperuricemia in adult male volunteers 2 to 3 days after receiving 2 two-hour infusions of 25 g xylitol in one day and 1 to 2 days after 2 two-hour infusions of 100 g xylitol. Förster et al. (1972) noted increases of normal
serum uric acid levels from 4 to 5 mg per 100 ml up to 6 to 7 mg per 100 ml within 90 minutes following intravenous infusion of 1.5 g xylitol per kg body weight. Förster et al. (1972) also reported that oral administration of fructose, sorbitol, xylitol, or sucrose caused similar effects. Later, he suggested that serum uric acid increases might occur in persons consuming a typical North American diet (Förster, 1974). According to Förster (1974), Edwards and Edwards (1971) and Schumer (1971) confirmed the increase in uricemia after intravenous administration of xylitol. Although a number of scientists regarded the elevated blood uric acid as a toxic effect of xylitol, Förster (1977) and Mehnert and Förster (1976) concluded that its pathophysiological significance is doubtful. It should be noted that a similar effect is produced by fructose or sorbitol. A small increase of serum bilirubin may be produced by fructose, glucose, xylitol or sorbitol, but this is not considered to be physiologically significant (Förster et al., 1970; Förster, 1977). Stress situations alone may give rise to an increase in serum bilirubin, lactate, and uric acid, and increased serum uric acid occurs after ingestion of meat-containing meals (Förster, 1977).

However, the clinical reports of Thomas and his coworkers on the adverse effects of parenteral administration of xylitol solutions have been widely cited (see Literature Cited, Section VII). Thomas et al. (1972a) reviewed clinical laboratory data and postmortem pathology findings of patients from several different hospitals who had received parenteral xylitol during treatment. Their reports suggested that concentrated solutions, up to 50 percent xylitol in distilled water, were administered either for high calorie supplementation or for their antiketotic effect. Of 22 patients ranging in age from 17 to 74 years, 17 were in intensive care, and 10 had serious preexisting diseases (Thomas et al., 1972a). Ten patients developed various symptoms and adverse reactions which, according to the authors, included diuresis, oliguria, azotemia, liver disturbances, increased serum uric acid and calcium oxalate deposition. Only one patient, a 54-year-old man with a renal transplant, exhibited all these reactions. The authors stated the adverse reactions were not related to preexisting diseases although the following conditions and reasons for admission to the hospital were listed for nine patients:

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Preexisting Conditions</th>
<th>Reason for Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>68/M</td>
<td>None</td>
<td>Ruptured aortic aneurysm</td>
</tr>
<tr>
<td>13</td>
<td>41/M</td>
<td>None</td>
<td>Traumatic carotid artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>thrombosis</td>
</tr>
<tr>
<td>15</td>
<td>72/F</td>
<td>Pelvic mass</td>
<td>Diverticulitis</td>
</tr>
<tr>
<td>17</td>
<td>55/F</td>
<td>Mild hypertension</td>
<td>Multiple fractures,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fat embolism</td>
</tr>
<tr>
<td>18</td>
<td>26/M</td>
<td>None</td>
<td>Multiple fractures,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fat embolism</td>
</tr>
<tr>
<td>19</td>
<td>54/M</td>
<td>Renal transplant</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>20</td>
<td>40/M</td>
<td>None</td>
<td>Tetanus</td>
</tr>
<tr>
<td>21</td>
<td>31/F</td>
<td>None</td>
<td>Viral hepatitis</td>
</tr>
<tr>
<td>22</td>
<td>69/M</td>
<td>Pyloric stenosis</td>
<td>Lung abscess</td>
</tr>
</tbody>
</table>
Several aspects of this report require more information and further analysis. Better identification of the xylitol solutions is necessary, as are the precise dosage given the patients, the concentrations of the xylitol solutions, the volumes administered, the rates of injection, and the purity of the parenteral solutions (Brin and Miller, 1974; Förster, 1974). Thomas et al. (1972a) have identified the product used as a "xylitol-containing solution as a form of parenteral nutrition" but further information concerning the xylitol solutions is lacking.

Over the past three decades, xylitol solutions have been used parenterally in hundreds of patients in Europe and Japan without similar effects being reported. Although approximately 5 percent xylitol in distilled water is isotonic with blood, the patients reported by Thomas et al. (1970) received solutions containing 10, 20, 40, or 50 percent xylitol. Thomas et al. (1974) later noted that there is difficulty in attributing the adverse reactions cited to xylitol itself. The cases are clinically complicated and multiple factors from the diseases involved contributed to the biochemical aberrations reported. They stated:

"The problem of whether this is due to xylitol being present in large amounts, to a normal metabolite of xylitol in large quantities, to an abnormal metabolite acting as a toxic substance, or to there being other toxic factors acting cannot be resolved with the data from these cases alone."

The induction of oxalosis and deposition of calcium oxalate crystals are among the most serious of the adverse reactions reported to result from parenteral administration of xylitol. This concern is related particularly to the postsurgical or traumatized patient receiving parenteral infusions who may be stressed nutritionally. For example, hyperoxaluria following pyridoxine deficiency is known to occur in rats (Andrus et al., 1959) and man (Faber et al., 1963; and Ludwig, 1963). However, Zollinger (1966) in a study of oxalate deposits in the kidneys of postoperatively deceased patients who had received infusions of highly concentrated glucose or fructose solutions, stated that some preexisting injury of the kidneys such as shock and/or hypoxia is a prerequisite for this type of oxalate deposition.

In a recent review of the use of nonglucose carbohydrates in parenteral nutrition, Ahnefeld et al. (1975) concluded that observation of proper dosage guidelines avoids the possible side-effects including deposition of oxalate crystals, which is in accord with the recommendation of the German Drug Commission to limit the dosage of all intravenously infused glucose substitutes (fructose, sorbitol and xylitol) to 0.25 g per kg body weight per hour.

Hauschildt and Watts (1976) and Hauschildt et al. (1976) conducted investigations to determine whether or not xylitol infusions are associated with biochemical reactions that promote calcium oxalate crystallization, or with changes in organic acid excretion patterns. Because of the reported hyperoxaluria associated with severe vitamin B₆ deficiency, they assessed the thiamin and pyridoxine nutritional status of their 14 subjects and found all were within normal limits. In their clinical study none of the patients showed hyperoxalemia or hyperoxaluria following xylitol infusions; however, glycolate excretion increased by 2 or 3 orders of magnitude and there was an increased
excretion of tetronic acids. Hauschildt et al. (1976) suggested that while xylitol breakdown may generate oxalate precursors, oxalosis occurring in
association with xylitol infusions is caused by some factor other than the
metabolism of xylitol, and that the most likely (predisposing) variable invol-
ved in the reported Australian cases was abnormal renal function. In addition,
they concluded that, inasmuch as most patients are unlikely to have significant
vitamin B₆ deficiency, the oxalosis reported in vitamin B₆-deficient experi-
mental animals is not relevant to clinical conditions in which xylitol is used.
Wang et al. (1977a) stated that it is highly unlikely that oxalate formation
was the cause of the toxicity in the cases reported from Australia. In addition,
Wang et al. (1977b) have shown that in rabbits receiving 2 g xylitol per kg
body weight intravenously at 40 mg per kg per minute, oxalate formation with
xylitol is essentially the same as that produced from glucose infusions in the
same amount and at the same rate. Finally, according to Mehnert and Förster
(1976) no metabolic pathway has been discovered that links xylitol to oxalic
acid.

2. Oral Studies

Reports on the use of xylitol as a substitute for sucrose in foods are essentially uniform in indicating an absence of adverse effects in healthy
persons as well as diabetic patients (Amador and Eisenstein, 1971; Asano et al.,
1973; Dubach et al., 1969; Förster, 1977; Mäkinnen, 1978; Mehnert and Förster,
1976; Mertz et al., 1972; Scheinin and Mäkinnen, 1975). Except for its laxative
effect when ingested in excessive doses, xylitol apparently causes no undesir-
able side-effects. Its advantages as a sucrose substitute in the diet of diab-
etic patients include production of relatively little hyperglycemia, reduced
hyperglycemic peaking, no ketosis, and minimal insulin response (Talbot, 1978).
These effects tend to stabilize catabolism of readily assimilable carbohydrates.
Another advantage is the negative effect on caries induction (See Section V,
page 25). Although orally administered xylitol can induce increased uric
acid synthesis, this is transient, of low degree, and considered to be with-
out pathophysiological significance (Mehnert and Förster, 1976; Förster, 1977).

The effects of oral administration of xylitol on uric acid production are dissimilar to those observed when the polyol is administered parenterally.
Mehnert and Förster (1976) concluded that a slight, dosage-related rise in
serum uric acid levels does occur when xylitol is ingested, but the increase
and its significance are much less than those associated with intravenous ad-
ministration. Similarly, Huttunen et al. (1975) found no consistent increases
in serum uric acid levels in subjects consuming foods containing fructose,
xylitol, or sucrose for a 2-year period. Rates of urinary excretion of urate
were similar in individuals consuming fructose, xylitol, or sucrose even in
subjects consuming over 100 g per day of one of these carbohydrates in more
than 100 days of the study period.

Mäkinnen (1978) reported that the human subjects participating in the
2-year chronic intake studies who were consuming high xylitol diets did not de-
velop any eye abnormalities. Because animal experiments have shown that cata-
rects may be induced by feeding high-xylose diets (van Heyningen, 1969) a logi-
cal question has been whether feeding xylitol may produce similar effects.
The crystalline lens absorbs aldoses (for example, xylose, galactose, glucose) from the aqueous humor (Chylack and Kinoshita, 1969). It is generally accepted that a mechanism leading to the formation of lens opacities involves the formation of the corresponding polyol by aldose reductase: sorbitol from glucose, galactitol from galactose, and xylitol from xylose. Because the sugar alcohols do not readily penetrate most biological membranes including those of the lens cells, such polyols accumulate in the lens and cause osmotic changes, swelling and disturbances of cation kinetics, leading to disruption of the lens cells, vacuolization, and lens opacities.

There is no evidence that exogenous xylitol has any effect on the lens. Absorbed exogenous xylitol is removed from the blood as it is metabolized by the liver. More significantly, even if it were possible to induce high levels of circulating xylitol, there appears to be no possibility of a direct influence on the lens because of the poor diffusibility into cells of the lens (Chylack and Kinoshita, 1969; Froesch and Jakob, 1974). Hence, the only way that exogenous xylitol could influence cataractogenesis is the hypothetical situation in which high doses might lead to sustained hyperglycemia in an individual, such as an uncontrolled diabetic patient with disturbed carbohydrate metabolism. However, clinical experience with xylitol as a sucrose substitute in the dietary management of diabetic patients has shown that, with proper control of dosage, a significant hyperglycemia following ingestion of xylitol does not occur (Förster, 1977).

In reviewing the subject of cataract formation, Mäkinen (1978) pointed out that the senile cataractous lenses of diabetic individuals contain glucose and sorbitol. He also noted that these substances are present in similar amounts in the lenses of older nondiabetic persons. Therefore, the lens opacities are not necessarily related to the diabetic condition except that cataracts are known to develop more rapidly in diabetic than in healthy persons. In any event, it is unlikely that the consumption of xylitol-containing foods will constitute a hazard of cataract formation by normal individuals or by diabetic persons who maintain their blood sugar levels within normal limits.

C. SPECIAL STUDIES

During the preparation of this report, preliminary results of several long-term feeding studies were announced by the Huntingdon Research Centre, Huntingdon, England (Schiffrin, 1977). These chronic toxicity trials included a 2-year feeding experiment with mice, 1-year feeding and multigeneration feeding studies with rats, a 2-year feeding trial with dogs, and teratogenicity testing in rabbits. In addition, a series of microbial and other tests have provided some data on potential mutagenicity of xylitol.

In one 2-year feeding trial, CFLP male and female mice were fed 0, 2, 10, or 20 percent xylitol or 20 percent sucrose in the diet for 102 to 106 weeks (Hunter et al., 1978a). Mean intakes for 20 percent sucrose, 2, 10, and 20 percent xylitol during the experimental period totaled 11.3, 1.3, 8.5 and 17.4 g per kg per day for males and 16.5, 1.9, 9.8, and 19.6 g per kg per
day for females. Animals receiving the diet with 20 percent xylitol exhibited diarrhea during the habituation period (weeks 4 to 11). Males exhibited increased mortality during the first 52 weeks and some evidence for reduced body weight gain was found in both males and females.

At the termination of the study, male mice on the 10 percent and 20 percent xylitol diets had more crystalline calculi in the bladder than male mice on the control, 2 percent xylitol, or 20 percent sucrose diets. When compared to control mice examined similarly, histological study of mice fed 10 or 20 percent xylitol revealed a reduction in the number of male mice with hepatocellular tumors, but an increase of hyperplasia, metaplasia and neoplasia of the transitional epithelium of the bladder associated with urinary calculi. On the other hand, female mice fed 20 percent sucrose exhibited an increased number of hepatocellular tumors but no significant bladder pathology.

Sprague-Dawley (CD strain) male and female rats (Hunter et al., 1978b) fed 2, 5, 10, or 20 percent xylitol, 20 percent sorbitol, or 20 percent sucrose in the diet for 26 to 52 weeks and beagle dogs (Heywood et al., 1978) fed analogous diets for two years showed no evidence of increased urinary calculi or hepatocellular abnormalities at autopsy. However, rats fed 5, 10, or 20 percent xylitol or 20 percent sorbitol exhibited an increased incidence of adrenal medullary hyperplasia, and at 20 percent xylitol, increased incidence of adrenal medullary pheochromocytomas. No such pathology was evident in the male and female dogs; however, dogs fed the 20 percent xylitol diet did exhibit increased liver weights at the end of the two-year feeding study. Histologically, the slight hepatomegaly was associated with hepatocyte enlargement and altered appearance of the periportal hepatocytes in five of 12 dogs fed the 20 percent xylitol diet and three of 12 dogs fed the 10 percent xylitol diet.

Hummler (1978) has reported a study on potential teratogenicity of xylitol. Female rabbits (strain not specified) were fed 2, 5, 10, or 20 percent xylitol, or 20 percent sucrose or sorbitol in the diet from the 7th to the 19th day of gestation. At the 20 percent level of dietary incorporation, xylitol, sorbitol or sucrose was fed at approximately 6.8 to 7.8 g per kg body weight per day. All doses of xylitol, sorbitol and sucrose were well tolerated and no effects on reproductive behavior were observed. Litter size, fetal weights and resorption rates were within normal ranges for all carbohydrates and doses tested. Subsequent fetal examinations provided no evidence of skeletal or other abnormalities. Hummler (1978) concluded that xylitol produced no embryotoxic or teratogenic effects in rabbits under the conditions of study.

Palmer and Bottomley (1978) and Palmer et al. (1978) conducted studies on the possible occurrence of teratogenic effects of feeding xylitol. In multigeneration studies on rats fed up to 20 percent xylitol in the diet, some variations in litter size were noted as was some reduction in weaning weight; however, no evidence of teratogenic effects was reported.

In regard to potential mutagenicity of xylitol, Batzinger et al. (1977) have reported that neither xylitol at 200 μg or 500 μg per petri plate (approximately 17 mg and 42 mg per litre) nor urine from mice fed xylitol (2.5 g per kg body weight) was mutagenic in microbial assay systems. These investigators tested xylitol either directly on histidine-dependent strains (TA-98
and TA-100) of *Salmonella typhimurium* or indirectly with the mouse host-mediated assay system. Gallandre (1978), as a portion of data submitted to the FDA by Hoffmann-LaRoche Inc., has reported that xylitol at doses from 0 to 125 mg per plate failed to induce mutation in the Ames Test (*S. typhimurium* strains TA 1535, TA 1537, and TA 1538); in the host-mediated assay (strains TA 1530, TA 1532, and TA 1534) at doses of 0 to 5333 mg per kg body weight; or in the micronucleus test with Füllensdorf Albino mice at doses of 0 to 5333 mg per kg body weight. Chromosome analysis with cultured human lymphocytes with similar dosages showed no genetic aberrations. These studies remain to be confirmed but suggest strongly that xylitol is not mutagenic in generally accepted microbial assay systems.

In summary, studies on possible carcinogenic, teratogenic, and mutagenic effects are limited. Evidence from these investigations suggests that xylitol is neither teratogenic nor mutagenic when evaluated with accepted microbial and animal test protocols. The occurrence of urinary calculi in male mice fed diets with 10 and 20 percent polyols is of concern; however, the increased incidence of bladder neoplasia associated with urinary calculi and of adrenal medullary hyperplasia and pheochromocytomas in rats is disturbing. It should be noted that at the 20 percent level in the diet, mice were receiving 17.4 g (males) and 19.8 g (females) per kg body weight per day. This level of consumption is close to the oral LD₅₀ value of 25.7 g per kg body weight reported by Kieckebusch et al. (1961). Similarly rats on the 20 percent xylitol diet were receiving 7.4 g (males) and 9.8 g (females) per kg body weight daily. These ingestion levels are close to or exceed the maximum metabolic turnover rate for xylitol in man as calculated by Bickel and Halmágyi (1974) [0.375 g per kg body weight per hour up to six hours and 0.25 g per kg body weight per hour for parenteral administration over a 48 hour period].

The occurrence of urinary calculi and bladder neoplasia in mice, the adrenal medullary hyperplasia and pheochromocytomas in rats, as well as the hepatocellular tumors in female mice fed diets with 20 percent sucrose, and the possible increase in adrenal medullary hyperplasia and pheochromocytomas in rats fed 20 percent sorbitol, suggest strongly that the intake of these simple carbohydrates at extremely high doses during lifetime feeding trials may contribute to some type of metabolic sequelae that invalidate the extrapolation to man of the findings with respect to tumorigenicity. In addition, the hyperosmotic effects of the diet and the almost universally reported diarrhea during adaptation to the diet suggest metabolic responses in electrolyte balance and kidney function. The relationship between these effects and urinary calculi and bladder neoplasia remains to be clarified.

There is a need to repeat these chronic and multigeneration animal feeding trials using the same and additional protocols, with the same and other strains of rodents, as well as subhuman primates. Consideration should be given to restricting dosages in lifetime and multigeneration feeding studies to levels at or below the maximum metabolizable dose for the species under test. Until a number of corroborative and other investigations are completed, it is not possible to determine with certainty the tumorigenic potential of dietary xylitol.
V. XYLITOL AND DENTAL CARIES

A. DISCOVERY OF LACK OF CARIOGENICITY

It has been recognized for some years that dietary sugars may play a significant part in caries development and that some sugar alcohols appear to be less cariogenic than their corresponding aldoses or ketoses. A previous report in this series briefly outlined the current concepts of plaque formation and its role in the origin of dental caries (Kimura and Carr, 1976). The striking findings of Scheinin, Mäkinen and their colleagues in 1975 that xylitol was not only noncariogenic in human subjects but that it also may have a "therapeutic and remineralizing effect" require explanation. To understand the scientific basis for the utilization of sugar substrates for bacterial growth, plaque formation, and their association with the tooth surface in caries, it is necessary to review certain aspects of contemporary research on dental caries.

B. FACTORS INFLUENCING CARIES PRODUCTION

Caries production follows plaque formation, and the latter is influenced by surface components of the variable bacterial species indigenous to the mouth as well as the composition of the extracellular polysaccharides of these bacteria and other polysaccharides in the plaque. In addition, the contributions of the extracellular polysaccharides in the adherence of plaque and the nature of the acids formed in dental plaque must be considered. Such issues as the frequency of sugar intake, the "age" of the plaque on the tooth surface, the general dietary habits, and oral hygiene of the individual appear to be important.

It has been suggested that caries could be eliminated if polysaccharides were substituted for sucrose and other sugars in the diet. For example, individuals with hereditary fructose intolerance who learn to avoid all forms of sugar in their desire to avoid fructose have been reported to have less dental caries than the general population (Newbrun, 1969). While this extreme measure may indeed reduce caries incidence, it is not likely to be followed by many people.

There is evidence from several laboratories that polyols such as sorbitol, mannitol, and xylitol are less likely than sucrose to cause plaque formation and caries in animals and man (See Section V, page 27). Sorbitol especially seems to be suitable as a sweet-tasting substance that is substantially less cariogenic in animals than the commonly used sugars (Dallmeier et al., 1970). A possible explanation of the lower cariogenicity of sorbitol may be the manner of its metabolism by microorganisms. Dallmeier et al. (1970) noted that the end products of bacterial metabolism of sorbitol were mainly formic
acid and ethanol rather than lactic acid. However, subsequent studies on oral Streptococcus mutans mutants have established that this species possesses inducible sorbitol and mannitol dehydrogenases which produce fructose-6-phosphate during fermentation (Brown, 1974).

One hypothesis attributes the cariogenicity of sucrose to its better utilization than other sugars in synthesis of the bacterial polysaccharides of plaque (Hehre, 1955). The extracellular polysaccharide produced from sucrose by a cariogenic streptococcus creates a "heavy" plaque (Wood and Critchley, 1966). Extracellular dextrans and/or levans, contributory to dental plaque, are produced by the action of the bacterial enzymes 6-glucosyl-transferase and 6-fructosyl-transferase on sucrose. Carlsson and Egelberg (1965) reported that in man, a sucrose diet produced "considerably larger amounts" of dental plaque than a glucose diet as estimated by a photographic recording method. It has been proposed that a "heavy" plaque might promote caries to a greater degree by holding acidogenic bacteria and fermentable carbohydrates in close contact to the tooth surface. However, it is generally held that the bacterial composition of plaque and substrate availability are more important aspects of the type of plaque which is highly cariogenic.

Gehring et al. (1975) studied the occurrence of polysaccharide-forming streptococci and the ability of mixed plaque microbiota to ferment various carbohydrates. In these studies, they collected dental plaque samples from subjects during the last 20 months of the two-year feeding experiments in the Turku studies (Scheinin and Mäkinen, 1975). Qualitative analyses were made of the occurrence of S. mutans, S. sanguis, and S. salivarius and variations of the recognized taxonomic strains of these organisms. There was a lower incidence of S. mutans in the xylitol-fed group compared with that in the sucrose- or fructose-fed groups. In addition, the authors concluded that no adaptation or mutation of the plaque flora occurred over a two-year period that enabled these microorganisms to degrade xylitol to acids. Narkates and Navia (1974) reported that xylitol or sorbitol induced a flora on the teeth of rats that was cariogenic. The streptococci present were differentiated by colony morphology and fermentation patterns, but the species found were similar to those present in the oral cavity of rats fed a sucrose-sweetened diet (Narkates and Navia, 1974). In a subsequent study with this rat model, Narkates et al. (1976) observed that the dietary concentration of xylitol as well as the ratio of cornstarch to xylitol in the diet affected caries induction. It is logical to assume that the presence of cornstarch in the diet may have altered the oral flora, and thus influenced caries production.

It is generally accepted that plaque formation on the tooth surface is the prelude to a carious lesion. However, a crucial factor in supragingival plaque formation is the attachment of microorganisms onto the tooth surface. A number of theories have been proposed to explain the phenomenon of bacterial attachment including an acquired enamel pellicle derived from salivary glycoproteins adsorbed onto the enamel (Meckel, 1965). Surface components of one bacterial species may enable other organisms subsequently to attach themselves (Gibbons and van Houte, 1975). Lowered pH may favor bacterial clumping (Kleinberg, 1970); and the synthesis of sticky extracellular polysaccharides by some organisms (Gibbons and van Houte, 1975) may contribute to plaque formation.
As has been discussed, the chemical and microbial constituents of plaque are extremely complex and are just beginning to be understood (Gibbons and van Houte, 1975). Plaques contain a heterogeneous population of facultative and anaerobic gram-negative and gram-positive bacteria (primarily streptococci and gram-positive bacilli) and their products. Viable and dead organisms are embedded and held together by extracellular glycoproteins, polysaccharides, dextrans and other glucans, and other polymers originating from the secretions of the mouth. Many bacterial species colonize teeth and their distribution varies from person to person, tooth to tooth and with tooth surface. The term, dental plaque, is only a general descriptor of a complex mixture of bacteria, their products, substances from the host, and products of the host/bacterial interactions.

However, many authors have observed that the mere presence of an organism in plaque does not necessarily mean that it plays any role in plaque formation or the disease process. Considerable attention has been given to the concept of extracellular polysaccharide formation by S. mutans when sucrose is a component of the diet of man (Fitzgerald and Jordan, 1968). It should be noted that plaque formation can occur without concomitant caries and, while fermentation of dietary sugars as substrates by oral bacteria may encourage plaque formation, plaque alone does not necessarily lead to caries.

C. RELATIVE CARIOPHOBICITY OF VARIOUS CARBOHYDRATES

Animal experiments have permitted the study of various sugars, sugar alcohols, and other dietary components as substrates for bacterial growth and in relation to caries production. Of the numerous sugars and carbohydrates studied, sucrose usually has been found to be the most cariogenic substance when tested as a component of animal diets (Stephan, 1966; Grenby, 1967; Grenby and Hutchinson, 1969; Navia et al. 1974; and Russell, 1974). The findings of Frostell et al. (1967) in hamsters and rats fed diets of various sugars and inoculated orally with cultures of caries-conducive streptococci are typical of these studies. These workers reported that animals receiving 56 percent sucrose diets developed "highly active carious lesions." When fructose, dextrose, maltose, hydrogenated starch, sorbitol, or mixtures of starches were substituted for sucrose in the animals' diets, differences were evident. In hamsters, each of the substitutes in the diet caused a reduction in plaque accumulation, "less active progression of lesions and little or no new lesion incipience." In rats almost all the substitutes in the diets caused "less active cavitation in crevices, and on buccal, lingual, and proximal surfaces." Hydrogenated starch diets alone were associated with a low grade of caries activity in crevicular areas. The authors noted that presumably the lower degree of caries with starch diets is related to the slow degradation of starch (Frostell et al., 1967).

There is a growing body of evidence from animal and human studies that the anatomical locus of carious lesions is related to the microenvironmental conditions created by the anatomical peculiarities of the different sites, the flora colonizing these sites, and the substrate availability (Keele, 1977). Most findings suggest that crevice decay is more prominent.
than smooth-surface cavitation. These variations in localization of caries make assays of the degree of cariogenicity of different sugars difficult to assess in even the controlled conditions of animal experimentation.

In 1970, Mühlmann et al. reported that xylitol was less cariogenic than sorbitol when fed in the diet of rats. Karle and Büttner (1971) reported that the sugar alcohols, sorbitol and xylitol, were less cariogenic than sucrose. Additional confirmation of the low incidence of caries in rats fed xylitol was reported by Grunberg et al. (1973). These workers noted that approximately the same degree of dental caries was found after feeding diets of either 10 percent glucose or 10 percent sucrose. Slightly less caries induction was associated with comparable diets of mannitol or sorbitol. However, in rats fed a diet of 10 percent xylitol, no carious lesions developed in the first and third molars, and only minimal involvement of the second molars was observed. The suggestion was offered that the caries-producing strains of streptococci were unable to utilize xylitol as a substrate and hence the caries-producing complex was not present (Grunberg et al., 1973). Subsequently, other reports have supported these animal findings (Karle and Gehring, 1975; Gehring and Karle, 1975). Navia et al. (1974) found that substituting xylitol, mannitol, sorbitol or a mixture of fructose and lactose for sucrose at 5 percent of the diet in the feed of rats did not cause a reduction in buccal or sulcal cavities. They concluded on the basis of their animal studies and confirmatory studies by other investigators that substituting small amounts of sugar alcohols for sucrose in snack foods offered no special therapeutic effects (at 5 percent of the diet) on caries induction or severity.

D. XYLITOL CARIES STUDIES IN MAN

1. Two-Year Dietary Studies

The experimental animal findings in part stimulated the elaborate collaborative studies by the workers in the Institute of Dentistry, University of Turku, Finland, to explore the effects of sucrose, fructose and xylitol on the dental, oral and general health of human subjects (Scheinin and Mäkinen, 1975). These investigations were conducted with young adults (mean age 27.6 years), largely professional personnel who were motivated to follow the dietary regimen over the two-year period. The Turku Sugar Studies included 117 subjects of both sexes whose monthly intakes averaged 2.4 kg sucrose, 2.3 kg fructose, or 1.6 kg xylitol from a wide array of dietary items that were prepared especially for this study.* The participants were encouraged

* Of the 125 voluntary subjects, 117 concluded the study; 33 belonged to the sucrose group, 35 to the fructose group, and 49 to the xylitol group. Two edentulous subjects were included in the xylitol group for survey of the general metabolic effects only and, for obvious reasons, were not included in the dental and periodontal findings. The final results were based on 115 individuals with respect to the dental caries findings, 39 males and 76 females. One female was less than 15 years old; the majority, male and female, were between 20 and 30 years of age.
to use their specially prepared foods but other foods were not strictly excluded from their diets. Of particular interest to this report were the findings from the 49 male and female subjects who consumed an average amount of 53 g per day of xylitol in their food. In addition to the clinical and radiographic identification of dental caries, biochemical and microbiological studies were carried out on plaque and saliva, and comprehensive blood and urine tests were made to monitor the general health of the subjects and to aid in detecting any toxic effects.

The details of the clinical examinations and the baseline values of caries prevalence in the subjects are given in the reports of Scheinin and Mäkinen (1975). The methods of clinical examinations were those recommended by the Commission on Classification and Statistics for Oral Conditions (Horowitz et al., 1973). The original three groups of 125 subjects were composed of 35 individuals allotted to the sucrose diet, 38 to the fructose diet, and 52 to the xylitol diet. The last group was deliberately oversize because it was originally feared that xylitol in the diet might cause gastrointestinal disturbances and some subjects would need to be removed from the study. However, gastrointestinal disturbances did not prove to be a problem.

The methods of clinical examination are given in detail by the authors of these reports. Unusual care was exercised in the examination of the tooth surfaces; for example, an advanced lesion designated as C2 "included all visible loss of substance, including interproximal cavity detection through the sticking of a PRO-FT-12 explorer used for no more than two times before,... in doubtful cases a completely new explorer was used."

The technique for estimating carious lesions employed radiographic examination of the condition of the distal surface of the canine teeth, as well as the mesial and the distal surfaces of the premolar and molar teeth of all subjects. The data were recorded as "additional radiographic primary or secondary caries, with or without defects." The method used was that of Backer Dirks et al. (1951). "A radiographic lesion was recorded as incipient caries (CR-1 or CSR-1) when there was a radiolucent area involving part of the enamel. An advanced lesion (CR-2 or CSR-2) was recorded when a radiolucent area involved whole enamel up to amelodental junction or involved also dentin."

In order to comprehend the conclusions of the study it is necessary to consider the evaluation techniques used in the clinical and radiographic findings. These are described by Scheinin and Mäkinen (1975) as follows:

"The parameters at the clinical (C1, C2, CS1, CS2, F) and radiographic (CR1, CR2, CSR1, CSR2) registrations were utilized as a basis for calculating the reversals in diagnosis between the examinations, and the resulting net change. The positive reversals involved a change in diagnosis from an intact surface (0) to C1 or C2, or when considering separately the increment in lesion size, from C1 to C2. A negative reversal indicated a corresponding change in the opposite direction. Consequently, the net increment was expressed as new
carious surfaces (positive reversals) minus negative reversals. The various possibilities for the occurrence of positive and negative clinical and radiographic reversals are schematically indicated in a diagram which should be considered also with regard to changes in the condition of prestudy lesions. These parameters for the clinical and additional radiographic findings, were calculated separately for all (28) teeth excluding the wisdom teeth, and the (4) wisdom teeth, and formed the essential basis for establishing the caries increment during the study."

It should be noted that a "positive reversal" was an increased degree of clinically or radiographically detected caries according to the schedule adopted for the study. A "negative reversal" indicated a lesser degree of caries.

The authors studied the method error as evaluated in a series of duplicate determinations for the clinical and radiographic examinations (Scheinin and Mäkinen, 1975). During the study the dental condition of the subjects was assessed on eight occasions. The overall comparison of differences was carried out using the Kruskal-Wallis test and the differences between the groups tested for significance with the Mann-Whitney U-test (Bradley, 1968; Chilton, 1967). The reproducibility of the duplicate radiographic findings, the most definitive test, was within the range generally accepted for work in this field, according to the authors.

2. Results of the Two-Year Dietary Studies

Employing these evaluative methods, the authors concluded that after two years on the experimental diets the mean increment of decayed, missed and filled tooth surfaces was +7.2 in the sucrose group, +3.8 in the fructose group, and 0.0 in the xylitol group (Table 3). The DMFS-index is not fully illustrative of the development of new secondary caries, or the increase in size of the lesions. Therefore, the caries activity was also expressed in terms of indices showing the total quantitative and qualitative development. "The results showed a massive reduction of the caries increment in relation to xylitol consumption" (Scheinin and Mäkinen, 1975).

An alternative explanation of the effects found in the subjects on the xylitol diet might be the reduction in intake of dietary sucrose. Any diet that excludes or reduces the sucrose intake apparently will reduce the incidence of caries in most people.

The conclusions reached by the authors of these reports that the process of caries development is affected in various, even antagonistic, ways by dietary carbohydrates are remarkable because no prior experience demonstrated an "anticariogenic" property for a dietary component unless one includes fluorides as dietary components.


<table>
<thead>
<tr>
<th>DMFS-Index</th>
<th>Sucrose</th>
<th>Fructose</th>
<th>Xylitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>42.1</td>
<td>48.0</td>
<td>50.7</td>
</tr>
<tr>
<td>Termination</td>
<td>49.2</td>
<td>51.8</td>
<td>50.7</td>
</tr>
<tr>
<td>2 year Increment</td>
<td>+7.1</td>
<td>+3.8</td>
<td>0</td>
</tr>
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DMFS: Decayed, missed, and filled tooth surfaces.
DMFS-Index: See pages 29, 30 for synopsis of examination procedures; see also Scheinin and Mäkinen, 1975.

*Adapted from Scheinin and Mäkinen, 1975.
The Finnish investigators initially suggested that a xylitol diet produced an alteration of the ecological balance of the oral microbial flora which accounted for the significant reduction in dental caries in these subjects. To evaluate this concept, the opinions of active investigators in cariology were sought and a review of relevant literature was conducted.

The remarkably low caries activity in those subjects on a xylitol diet correlated with the decreased amount of plaque, the accompanying biochemical changes in plaque and saliva including salivary lactoperoxidase, and the corresponding microbiological changes. The demonstration that almost all oral acidogenic microorganisms were unable to metabolize xylitol suggests that the effects observed were in part related to this fact. However, the "lactoperoxidase effect" (page 33) and the physicochemical changes in the saliva are solely attributed to the consumption of xylitol and its subsequent utilization in the body (Mäkinen and Scheinin, 1975).

Finally, while polyols such as xylitol or sorbitol may not be cariogenic, the ingestion of these sugar alcohols may so modify the bacterial flora that S. mutans or some other bacterial species may be able to utilize sucrose to a greater degree (Gehring et al., 1975). There may be the hazard that discontinuing the sugar alcohol would create an environment for higher levels of S. mutans to attack sucrose and the end result could be a higher degree of caries. This concept has not been tested.

3. Xylitol Chewing Gum Studies

In order to explore the effects of consumption of relatively small amounts of xylitol on caries incidence, a one-year study was conducted on subjects consuming a xylitol chewing gum (Scheinin et al., 1975). Young adults, predominantly dental or medical students, were randomly divided into two groups. One group chewed a gum containing 50 percent sucrose (1.5 g), and the other a gum containing 50 percent xylitol (1.5 g). Both gums contained 26 percent gum base (0.78 g), 6 percent sorbitol (0.18 g) and 14.5 percent other long-chain polyols (0.44 g). The subjects were instructed to follow their regular dietary habits and oral hygiene procedures. They chewed an average of 4 sticks of gum per day which would be an average daily consumption of 6.0 g of either xylitol or sucrose.

The dental conditions of the subjects were determined initially and at intervals during the study. Essentially, the registration of the clinical and radiographic findings was the same as described in the dietary studies (Scheinin and Mäkinen, 1975). The caries incidence expressed as the mean increment of decayed, missed and filled tooth surfaces was 2.92 in the sucrose chewing gum group and 1.04 (less than the initial reading) in the xylitol chewing gum group. As in the previously reported two-year feeding study, the authors suggest that the non- and anticariogenic properties of xylitol principally depend on its lack of suitability for microbial metabolism, and on the physicochemical effects in plaque and saliva through low and repeated dosage of xylitol (Scheinin et al., 1975).
Seeking an explanation for the noncariogenic effect of xylitol, the authors studied the peroxidase and invertase-like enzyme activity (lactoperoxidase effect) of saliva of subjects in this one-year study (Mäkinen and Scheinin, 1975). There were no differences in the activity of these enzymes as compared with the control groups. After study of the activity of a number of enzymes, the protein content, calcium level and other ions in the centrifuged whole saliva of the subjects, the authors (Scheinin and Mäkinen, 1975) concluded that xylitol may form complexes with calcium and certain other cations that may interfere with the adhesion of bacterial cells in plaque. Subsequent investigations of the biochemical and physical properties of the saliva of an additional 50 subjects each using chewing gum sweetened with xylitol or sucrose suggested possible explanations (Mäkinen, 1978). Various acidic groups of salivary mucins may be modified to change the physical properties of mucin, and the fate of xylitol in the gastrointestinal tract may modify the activity of oral mucous secretory cells to cause some unknown effects. However, it should be noted that Ainamo et al. (1978) have reported no reduction in plaque formation or amount in subjects after 2.5 hours of chewing a xylitol-containing gum (quantity not stated), daily for three weeks.

It is remarkable that none of the oral microorganisms developed the capacity to utilize xylitol over a one- to two-year period of exposure. It appears to be a biological principle that microorganisms do develop such an ability over time. However, Amos et al. (1978) noted in their studies on the metabolism of xylose and xylitol as energy sources for bacteria that the oral flora includes such a variety of organisms that it may be impossible to assign acidogenesis to the cariogenic process. Amos et al. (1978) suggest that xylitol may exert an "abnormally powerful influence on a nutritionally complex environment by modulating the fermentation of 'acidogenic' sugars by caries-inducing bacteria of the mouth flora." This hypothesis remains to be tested experimentally.

4. Discussion of the Results of the Xylitol Chewing Gum Studies

The index of a "primary incipient carious surface" (C1) as compared to "advanced carious surface" (C2) as used by the investigators in Finland (Table 3) is considerably different from the criteria employed by investigators in the United States and in other parts of the world where clinical trials are carried out. The C1 level of decay does not represent any loss of tooth tissue and would not be considered decay by American workers. Thus, investigators in this country would use C2 as a base for their estimation of the first degree of caries. Therefore, they would not have found as large a treatment effect as reported by the Finnish studies. According to the report of the Finnish investigators, "secondary incipient carious surfaces" (CS1) and "advanced carious surfaces" (CS2) were also evaluated. However, the DMFS index gives an overall evaluation that illustrates the condition of the subjects' dental status. In this regard, the results reported after feeding a high-xylitol diet for two years or using a xylitol chewing gum for one year would still be impressive even if modified criteria had been employed.

The question of suitable control groups for the chewing gum studies has been debated. Perhaps a control group that does not chew gum could be used. However, it is agreed by most investigators that such a group
would be difficult to find and might be inappropriate because the objective is to find a noncariogenic sweetener for those people who use chewing gum.

The chewing of sucrose containing gums promotes dental caries (Finn and Jamison, 1967). The use of a sugarless gum would be a suitable control. The negative reversals observed in the Turku Sugar Studies were all in the C1 category. If these are eliminated, and the caries promoting effect of sucrose excluded, the net result would be zero. This suggests that xylitol is to be considered noncariogenic and not cariostatic.

The effects of xylitol in dental caries were considered by Scheinin and Mäkinen (1975) to be of a dual type; partly local and partly systemic. The local effect appeared to be related to the change in bacterial ecology and physiology. The systemic effects were ascribed to a mechanism that operated through the stomach, circulation, and salivary glands. However, until more specific knowledge is obtained about these obscure mechanisms, it will not be possible to explain the results reported in these studies.

It is essential that the University of Turku studies be replicated by other workers. The planned investigation of the possible anti-caries effects of xylitol chewing gum in young, caries-prone children could give a partial resolution to this issue (NIH, 1976). However, these studies have been delayed in view of the adverse effects reported from animal studies at the Huntingdon Research Centre (see page 21).
VI. CONCLUSIONS

If the chronic animal toxicity studies indicating that xylitol is associated with tumor induction are confirmed, the safety of xylitol as a food ingredient would need to be reconsidered and the levels of the polyol in foods containing xylitol as a natural ingredient would need to be assessed in terms of possible adverse health effects. In the absence of confirmatory evidence, the following conclusions appear appropriate at this time:

- Equal weights of xylitol and hexoses yield approximately the same number of calories; equal concentrations by weight of xylitol and sucrose are equisweet.

- Although the metabolism of exogenous xylitol in the liver proceeds in the absence of insulin, a large part of it is converted to glucose or liver glycogen. Thus, its subsequent metabolism in the body as glucose is insulin-dependent.

- As a substitute for sucrose or glucose in the diet of diabetic patients, xylitol has the following attributes: (1) it is a palatable sweetener; (2) when compared to sucrose it evokes a slower, low-magnitude rise in blood glucose levels; (3) it causes a minimal insulin response; (4) it is nonketogenic; and (5) in proper dosage, it may aid in achieving a stabilization of the blood glucose level by minimizing postprandial hyper- and hypoglycemic fluctuations.

- Except for the recently reported studies on mice and rats from the Huntingdon Research Centre, limited animal feeding trials indicate that xylitol is not toxic at levels likely to be ingested in foods.

- Male and female adult volunteers receiving average amounts of 53 g per day of xylitol in foods over a 2-year period did not exhibit untoward effects. In addition, normal children were born during this period to subjects in this study. These studies suggest that xylitol orally ingested with meals in these daily amounts is safe.

- When xylitol replaced a major portion of dietary sucrose in studies at the University of Turku, Finland, there was a highly significant reduction of caries incidence.
Reduction in caries incidence also occurred in volunteers using a xylitol chewing gum. Although xylitol appeared to be noncariogenic in these studies, there is need to confirm these observations. In addition, the reported "therapeutic and remineralizing effect" of xylitol on dental caries should be confirmed in a caries-prone population.

While parenteral administration of xylitol at rates in excess of 0.25 g per kg body weight per hour may result in demonstrable changes in blood lactate, pyruvate, bicarbonate, and uric acid levels, at infusion rates of 0.25 g per kg body weight per hour or less, these metabolic alterations are less evident. There is no evidence that these metabolic sequelae of xylitol infusion at proper dosages have pathophysiologic significance. Evidence that parenteral use of xylitol has caused deaths remains to be confirmed.

Additional metabolic and pharmacodynamic studies over a wide dosage range of orally administered xylitol would be useful with respect to more critical determination of an adequate margin of safety for dietary xylitol. Such studies should include xylitol as a food ingredient substituted for other sweeteners. The metabolic effects identified in studies with parenteral administration suggest that studies with oral administration over a wide dosage range should be conducted. Attention should be directed to a better understanding of the physiological limitations that may influence the ability of animals and man to assimilate and catabolize xylitol when it constitutes a major portion of the sweeteners and simple carbohydrates in the dietary.
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