DIETARY SUGARS IN HEALTH AND DISEASE

I. FRUCTOSE

October 1976

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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by

K.K. Kimura, Ph.D., M.D.
C. Jelleff Carr, Ph.D.

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
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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 C. J. Carr, Ph. D., and K. K. Kimura, Ph. D., M. D., Special Medical Consultant to LSRO, with the assistance of the Staff, named in Section XI, in accordance with the provisions of Contract No. 223-75-2090.

The LSRO acknowledges the contributions of the investigators and consultants who have assisted with this study. The listing of the consultants' names in Section XI does not imply that they endorse the conclusions of the study. The authors accept responsibility for the report and the opinions expressed.

The report has been reviewed and approved by the LSRO Advisory Committee consisting 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 will have been 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 opinions of the individual members of its constituent societies.

C. Jelleff Carr, Ph. D.
Director
Life Sciences Research Office
SUMMARY

Until recently the unavailability of crystalline fructose in this country has precluded much utilization of fructose in food manufacture outside of the use of high-fructose corn syrup in beverages and other foods using liquid sweeteners.

This review will look at several aspects of fructose metabolism in man, consider any toxic effects from injudicious use, and appraise the role of fructose in health and disease.

A two-year oral feeding study in volunteers (Finland) showed dramatically the safety of using fructose as part of carbohydrate intake in addition to reducing caries incidence by 25 percent as compared to sucrose controls. There are no serious biochemical changes elicited by the use of fructose as an additive in food consumed by healthy individuals without specific diseases such as hereditary fructose intolerance.

The unique feature of fructose metabolism utilizing the hepatic route to the trioses had led to the suggestion of using fructose in diabetics. This review concluded that there is no clinical advantage to substituting fructose for glucose either orally or parenterally. This conclusion was substantiated by a recent survey of university diabetologists.
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I. INTRODUCTION

A. BACKGROUND

The Office of the Associate Director for Nutrition and Consumer Sciences, Bureau of Foods, Food and Drug Administration (FDA) has a continuing interest in the nutritional quality of the American diet. The Agency is responsible for evaluating and monitoring the safety of foods, establishing regulations, and providing nutrition information to consumers. In addition, the Agency encourages a healthy regulatory climate to develop foods for special dietary use and to protect the consumer from nutrition fraud and misleading labeling.

In keeping with these functions the Life Sciences Research Office was requested by FDA to review current scientific information and technological developments related to the changing pattern of consumption of refined carbohydrates in the American diet and to evaluate these issues in terms of their nutritional impact and safety.

There are two concerns regarding the consumption of refined carbohydrates. One relates to the unrecognized and unidentified quantity of "sugars" in the American diet; the other is the changing pattern of specific sugars in the diet as a result of technologic changes and economic factors. High fructose corn syrup obtained from starch hydrolyzates, containing several saccharides in addition to fructose, is now used in foods in place of sucrose. There has been a major increase in consumption of this sugar mixture in recent years and it is anticipated that it will replace sucrose and invert sugar to a greater degree in the next five to ten years. In addition, crystalline fructose is now commercially available and this form of fructose may be used in foods in increasing amounts.

The health aspects of dietary changes of this nature must be evaluated especially if there are any physiologic and metabolic differences resulting from the consumption of these carbohydrates. Overconsumption of any single food ingredient may have serious nutritional consequences and "sugars" such as sucrose have been associated with disease states such as obesity and dental caries. Recently some evidence presented purport a direct relationship between refined sugars and diseases as diabetes and heart diseases. Because the relationships between refined carbohydrate ingestion and several disease states is not clear, the study reviews the more significant dietary sugars added to foods and addresses these singly as a series of reports.
B. SCOPE

This report reviews the general chemical nature of the ketose, fructose, its current production as a dietary sugar, and its metabolic fate in the human body. Because fructose has been studied extensively as a substitute sugar for diabetics this literature had been reviewed and appraised in terms of modern diabetic therapy. Both oral and parenteral routes of administration are considered. The untoward effects of fructose ingestion, including enzyme deficiency fructose intolerance, are discussed because a small percentage of people may exhibit an undesirable response from consuming diets containing fructose. However, the report is not intended to review the total literature on fructose or to cover all of the finite details of chemistry, biochemistry, metabolism or clinical use.
II. FRUCTOSE

A. CHEMICAL ASPECTS

Monosaccharides are aldehydes or ketones with two or more hydroxyl groups — their empirical formula is \((\text{CH}_2\text{O})_n\). The simplest sugars are glyceraldehyde and dihydroxyacetone.

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{CH}_2\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{C} \\
\text{CH}_2\text{OH} & \quad \text{OH} \\
\end{align*}
\]

D-Glyceraldehyde Dihydroxyacetone

Both are trioses and the formulas show the aldehyde group \((\text{CHO})\) of glyceraldehyde and the keto group \((\text{C}=\text{O})\) of dihydroxyacetone.

D-Fructose is a 6-carbon ketose consisting of an equilibrium mixture in solution of the open chain and the ring forms (pyranose and furanose) of fructose. Figure I shows the stereochemical relationships of the hexose, fructose and its relationship to sucrose. Conventional nomenclature designates the \(\alpha\) form where the hydroxyl group is attached to C-1 carbon (called the anomeric carbon atom) below the plane of the ring; the \(\beta\) form designates the hydroxyl above the plane of the ring.

Fructose is very soluble in water. At 20\(^\circ\) C fructose is soluble to the extent of 79 percent, glucose 47 percent, and sucrose 67 percent.

D-Fructose is levorotatory to polarized light. The degree of rotation is a function of time after dissolving crystalline fructose in water because the pyranose form of fructose changes to the furanose form. In the crystalline state fructose exists as the pyranose form. In an equilibrium mixture of fructose in aqueous solution, Curtius \textit{et al.} (1968) reported 33 percent furanoside, 67 percent pyranoside, and a small fraction in an open chain form whereas Shallenberger (1974) reported 20 percent, 76 percent and 4 percent, respectively.
FIGURE I

STEREOCHEMICAL FORMS OF FRUCTOSE AND ITS RELATIONSHIP TO SUCROSE

α-D-Fructopyranose  Keto-D-fructose  β-D-Fructopyranose

α-D-Fructopyranose (perspective formula)  β-D-Fructofuranose (perspective formula)

(d-glucose portion)  (d-fructose portion)  (α-D-glucopyranosyl-β-D-fructofuranoside)
Sucrose
B. OCCURRENCE AND MANUFACTURE
FRUCTOSE (Levulose, Fruit Sugar, D-Fructose)

Dubrunfaut isolated fructose from cane sugar in 1847 (Doty and Vanninen, 1975) by precipitating fructose from strong alkaline sucrose solutions as a calcium complex that were subsequently acidified to release fructose. Cane sugar (β-D-fructofuranosyl-α-D-glucopyranoside) hydrolyzes to glucose (grape sugar) and fructose (fruit sugar).

Honey contains approximately 40 percent fructose, while cherries, pears, bananas, apples, and grapes have from 5 to 7.7 percent. Strawberries, grapefruit, oranges, blackberries, and blueberries contain from 2 to 3 percent fructose (Doty and Vanninen, 1975). Although glucose is also found in these fruits, the historical term "fruit sugar" is applied to fructose.

It is claimed that fructose is approximately 15 to 80 percent sweeter than sucrose (Shallenberger, 1963). However, the relative sweetness of solutions of fructose depend on the pH, temperature and the concentration. The highest value of 140-150 (sucrose sweetness = 100) obtains when the fructose solution is diluted, cool and neutral or slightly acidic. Sweetness of fructose decreases as the temperature, concentration, and acidity are increased (Doty and Vanninen, 1975). The pyranose configuration is said to be sweeter than the furanose configuration (Doty, 1976); the sweetness decreases during heating such as in baking, but reappears upon cooling.

In aqueous solutions with control of pH, temperature and other factors fructose is sweeter than sucrose. However, the sweet taste is modified by incorporation into foods, cooking and the taste threshold of the individual consumer. Under conditions of consumption the authors of this report have not found fructose to be sweeter than sucrose when added to hot tea and coffee, cold cereals, or desserts at the table where pH, concentration and temperature of food are quite variable.

Because fructose seems sweeter than sucrose to some people, claims have been made that substantially less fructose would be required to give the equivalent degree of sweetness to a food and hence fewer calories per serving would result. This theoretical advantage may not obtain for hot or cooked foods, for those individuals who do not prefer sweetened foods, or who upon tasting do not find fructose to be sweeter than sucrose. Fewer calories with equivalent sweetness appears to be only a minor advantage of using fructose in lieu of sucrose in foods.

Early industrial methods for the production of pure fructose were based on hydrolysis of the starch-like material inulin. Currently the
source of commercial crystalline fructose or fructose syrups is sucrose. The basic process developed in 1970 for large scale production of fructose involves hydrolyzing sucrose into fructose and glucose and then physically separating the sugars chromatographically in ion exchange columns and purifying the two monosaccharides. Fructose manufacturing methods in which hydroalcoholic solutions are used to crystallize the fructose are costly and more economical methods utilize a process for direct fructose crystallization from aqueous solutions of hydrolyzed sucrose (Melaja, 1972).

C. USE IN FOODS

In some European countries (West Germany, Sweden, Norway and Finland) crystalline fructose has been marketed as a dietary sugar for about ten years, usually in 250 g packages. In Finland, fructose represents approximately 0.5 percent retail sugar sales, probably the highest in Europe. However, pure fructose is not widely used primarily because of its high price. In West Germany the food labeling regulations for crystalline fructose require it to be labeled as a "sugar substitute."

The market for fructose in Europe is approximately as follows:

<table>
<thead>
<tr>
<th>Metric Tons (MT)/year</th>
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<tbody>
<tr>
<td>West Germany and other EEC countries</td>
</tr>
<tr>
<td>Finland</td>
</tr>
<tr>
<td>Sweden</td>
</tr>
<tr>
<td>Other Scandinavian countries</td>
</tr>
<tr>
<td>Other European countries (including USSR)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

In Europe approximately 20 percent is marketed for pharmaceutical uses, 25 percent as a retail product through food stores and 55 percent as a sweetener in industrial manufactured food products. The majority of the industrial uses in Europe are for special dietary food products.

The total present market for fructose in the United States and in Japan is estimated to be approximately 600 metric tons each. The total world consumption of fructose is approximately 13,000 metric tons.
D. HIGH FRUCTOSE CORN SYRUP (HFCS)

The wet milling industry defines corn syrups as starch hydrolyzates having a dextrose equivalent (DE) of 28 or higher. The DE is defined as the percentage of reducing sugars in the syrup, calculated as dextrose (D-glucose), on dry weight or dry substance basis (Junk and Pancoast, 1973). Corn syrups with degrees of conversion with DE greater than 68 have greater degrees of sweetness, flavor enhancement, and hygroscopicity. Commercial HFCS have DE of about 95.

In recent years a high fructose corn syrup obtained by enzymatic isomerization of starch hydrolyzates containing on the the dry basis approximately 42 percent fructose, 52 percent glucose, and 6 percent higher saccharides has been introduced into commercial production in the United States. Its principal sugars, glucose and fructose, make its sweetness comparable to sucrose (Table I).

High fructose corn syrups are reported to be equivalent in sweetness on a solids basis to sucrose, relatively inexpensive, and offer economic advantages for the food processors who can use liquid sweeteners. The estimated production of HFCS in 1974 of 0.92 billion pounds on a dry solid basis, was projected to become one billion pounds for 1975 (Wardrip, 1975) comprising about one-fifth of the corn syrups marketed. Forecasts of up to 30 percent of the sucrose markets by 1980 to 1995 have been made (Cantor, 1975; Wardrip, 1975).

On the other hand, Kolodny (1976) estimated that HFCS would comprise only about 14 percent of the total sweetener market in 1980 as compared to about 6 percent in 1975. He estimated that all corn syrup sweeteners would increase from about 24 percent of the sweetener market in 1975 to about 30 percent in 1980.

A new high fructose corn syrup which contains more than twice the fructose of existing commercial formulations -- 90 percent versus 42 percent (dry basis) -- is scheduled for commercial production in late 1976. The new product is rated 20-60 percent sweeter than sucrose. Its greatest potential appears to be in combination with saccharine for sweetening low calorie foods and beverages. Less saccharine can be used with the 90 percent fructose product, thus reducing the metallic aftertaste often associated with saccharine (Anonymous, 1976).
<table>
<thead>
<tr>
<th>Crystalline Fructose</th>
<th>High Fructose Corn Syrup</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 100% fructose</td>
<td>1. 42% to 90% fructose (variable)</td>
</tr>
<tr>
<td>2. Crystalline solid</td>
<td>2. Liquid</td>
</tr>
<tr>
<td>4. 50% sweeter than sucrose but not in hot drinks</td>
<td>4. Equi-sweet with sucrose</td>
</tr>
<tr>
<td>5. Good humectant</td>
<td>5. Good humectant</td>
</tr>
<tr>
<td>6. Enhances flavors of fruits and berries</td>
<td>6. Different enhancing characteristic due to fructose-glucose combination</td>
</tr>
<tr>
<td>7. Costly</td>
<td>7. Inexpensive</td>
</tr>
<tr>
<td>8. Currently not produced in USA (1976)</td>
<td>8. Produced in USA</td>
</tr>
<tr>
<td>9. Synergistic use with artificial sweeteners</td>
<td>9. No reported use with artificial sweeteners</td>
</tr>
</tbody>
</table>
III. METABOLISM OF FRUCTOSE

A. BIOCHEMICAL ASPECTS

Fructose is a natural compound that the human body can synthesize and metabolize. However, in the adult organism de novo synthesis occurs to a very small extent while the biochemical mechanisms in the liver have a very high capacity for assimilation of exogenous fructose.

The primary pathway of carbohydrate metabolism is the conversion of stored or ingested substances to phosphorylated intermediates and anaerobic oxidation to pyruvates (glycolysis). Dietary fructose can be phosphorylated at the C-1 or C-6 position. Fructose-6-phosphate is formed at a relatively slow rate in all tissues by non-specific hexokinases. However, more than 50 percent of ingested fructose is converted to fructose-1-phosphate in the liver by fructokinase (Figure 2) and the half-life of fructose in man is approximately 18 minutes (Froesch, 1972a).

In man, there is no mutase enzyme which can interconvert the fructose-6-phosphate and fructose-1-phosphate. Similarly, 6-phosphofructokinase does not act on fructose-1-phosphate to produce fructose-1,6-bisphosphate.\(^1\) Thus the fructose-1-phosphate is metabolized by cleavage to dihydroxyacetone phosphate and D-glyceraldehyde by hepatic fructose bisphosphate aldolase. The dihydroxyacetone phosphate may enter the glycolytic pathway through isomerization while D-glyceraldehyde enters through phosphorylation into D-glyceraldehyde-3-phosphate by triokinase as the principal route. The pathways by which fructose enters intermediate carbohydrate metabolism are schematized in Figure 2.

Glycolysis is the sequence of reactions that converts glucose to pyruvate with the associated production of adenosine triphosphate (ATP). Details of fructose and glucose metabolism are reviewed by Shreeve (1974).

\(^1\) Fructose 1, 6-bisphosphate formerly was known as fructose 1, 6-diphosphate. New international rules of nomenclature for phosphate esters reserve the expression "... diphosphate" for components of the type adenosine diphosphate (ADP) that contain two phosphate groups connected together in anhydride linkage. Compounds that contain two phosphate groups at two different positions in the molecule are to be called bisphosphates.
FIGURE 2

ABBREVIATED SCHEMATA FOR PATHWAYS FOR FRUCTOSE METABOLISM

FRUCTOSE \[\text{in tissues}\] \[\text{(1)}\] \rightarrow \text{Fructose-6-phosphate}

\[\text{in liver}\] \[\text{(2)}\] \downarrow

Fructose-1-phosphate \[\text{(3)}\]

\[\text{Fructose-1,6-bisphosphate}\] \[\text{(7)}\] \downarrow

Glucose-6-phosphate \[\text{(12)}\] \downarrow

D-Glyceraldehyde \[\text{(9)}\] \rightarrow \text{D-Glycerol-3-phosphate}

Dihydroxyacetone phosphate \[\text{(5)}\]

Glycolysis to Pyruvate

Glycerol \[\text{(4)}\] \rightarrow \text{D-Glycerol-3-phosphate}

D-Glyceraldehyde \[\text{(11)}\] \rightarrow \text{D-Glycerol-3-phosphate}

\[\text{D-Glyceric acid}\] \[\text{(10)}\] \rightarrow \text{Glycerate-3-phosphate}

(1) Hexokinase (EC 2.7.1.1)
(2) Ketohexokinase (EC 2.7.1.3)
(3) Fructose Bisphosphate Aldolase (EC 4.1.2.13)
(4) Glycerol Kinase (EC 2.7.1.30)
(5) Triosephosphate Isomerase (EC 5.3.1.1)
(6) Glucosephosphate Isomerase (EC 5.3.1.9)
(7) 6-Phosphofructokinase (EC 2.7.1.11)
(8) Triokinase (EC 2.7.1.28)
(9) Aldehyde Dehydrogenase (EC 1.2.1.3)
(10) D-Glycerate Kinase (EC 2.7.1.31)
(11) Glycerol-3-Phosphate Dehydrogenase (EC 1.1.1.94)
(12) Glucose-6-Phosphatase (EC 3.1.3.9)

\[\text{Found only in livers of man, mammals and birds}\]
B. ABSORPTION

The mechanisms controlling fructose absorption are not completely known but it has been suggested that this monosaccharide is absorbed from the gastrointestinal tract much more slowly but utilized much faster in the tissues than glucose (Heinz et al., 1968).

In some animal species transformation of fructose into glucose and lactic acid in the small intestine occurs via the hexokinase and fructokinase portions of the glycolytic pathway. This occurs more in the rat, guinea pig and hamster. In man, there is only minor conversion of glucose to lactate during absorption (Herman, 1974).

Cori (1925) found that sugars administered orally to hamsters disappeared at different rates: galactose > glucose > fructose > mannose > xylose > arabinose. These rates are not necessarily seen in all species. Rats form very little glucose from fructose in the intestine. The specificity for in vitro sugar absorption is noted in Table II.

TABLE II

SUGAR TRANSPORT IN HAMSTER'S SMALL INTESTINE IN VITRO

<table>
<thead>
<tr>
<th>Actively Transported</th>
<th>Not Actively Transported</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>Fructose</td>
</tr>
<tr>
<td>Galactose</td>
<td>Mannose</td>
</tr>
<tr>
<td>3-0-Methylglucose</td>
<td>Xylose</td>
</tr>
<tr>
<td>1-Deoxyglucose</td>
<td>2-Deoxyglucose</td>
</tr>
<tr>
<td>6-Deoxyglucose</td>
<td>Sorbitol</td>
</tr>
</tbody>
</table>

³Revised from Crane, 1960.

Sucrose is hydrolyzed by sucrase into its two component monosaccharides in the brush border cells of the intestinal epithelium and the monosaccharides are absorbed. Relatively little sucrose is absorbed as such (Dahlqvist, 1967). The claims of Ockerman and Lundborg (1965) that as much as 70 percent of fructose may be converted to glucose in the human jejunum have not been confirmed. In man, up to 80-90 percent of oral fructose is absorbed from the jejunum as fructose (Cook, 1969). Fructose is absorbed into and across intestinal epithelial cells of man and rat but not by an active transport mechanism (Crane, 1960).
In the case of man or rats, there is an absence of intestinal glucose-6-phosphatase (Ginsberg and Hers, 1960) and therefore man is unable to convert much fructose to glucose in the intestinal mucosal cell. However, the conversion of some fructose to glucose by the human intestine has been demonstrated (Ockerman and Lundborg, 1965; White and Landau, 1965).

Dietary fructose in man at the level of 40 percent of the calories in a 3,000-kcal diet causes diarrhea. This is in contrast to dietary glucose which can be tolerated at levels of 60 to 80 percent. The rat differs from man in that it can tolerate dietary fructose levels as high as 70 percent of the calories without significant diarrhea (Hill et al., 1954).

Fructose tolerance tests in healthy subjects cause an elevation of the blood glucose and fructose levels; the elevated blood glucose results from the conversion of fructose to glucose by the liver and the intestine. In man the major part of absorbed fructose passes via the portal vein as fructose prior to conversion to glucose in the liver (Cook, 1969).

In the duodenal region of the rat intestine, fructose can be phosphorylated at a rate of 1.2 mg per minute; in the jejunum 7-40 mg per minute; and in the ileum 3-12 mg per minute. If absorption of monosaccharides is stopped in the distal jejunal area, only a small amount of fructose (42 mg per minute) can be phosphorylated by the whole intestine. Disaccharidases hydrolyzing sucrose into glucose and fructose are localized in the distal region of the jejunum and in the ileum (Dahlqvist, 1967). In the ileum aldolase and triokinase activity is low and this may explain in part the differences in the metabolic effects of fructose compared to sucrose (Heinz et al., 1975a).

C. FATE IN THE BODY

Fructose is metabolized mainly in the liver and to some extent in the kidney and the intestinal mucosa (Hue, 1974); however, the metabolism of fructose appears to be different in different tissues depending on the tissue distribution of the various enzymes involved in fructose metabolism.

Muscle utilizes fructose at a relatively slow rate in comparison with liver. The higher the concentration of fructose, the greater is fructose utilization in adipose tissue. The capacity for hepatic utilization when delivered into the human portal vein is at least twice as high for fructose as for glucose. As much as 450 grams of fructose can be given daily by gastric intubation in diabetics without detecting significant amounts of fructose in the arterial blood. Approximately one-third of the fructose is converted in the liver to circulating glucose in human subjects (Shreeve, 1974).
Fructose is able to bypass the phosphofructokinase step required for glucose to enter the glycolytic pathway in the liver. Its uptake by liver is, therefore, much more rapid than that of glucose (Zakim and Herman, 1968). Orally administered fructose in man is removed largely by the liver, in contrast to glucose (Butterfield et al., 1964).

In liver, half of the carbon atoms of fructose, that is, the glycer-aldehyde portion, escape the control of phosphofructokinase and are available directly for glycolysis to produce lactic acid, which is detrimental under some circumstances, and the increased production of lactate and pyruvate serve as a substrate for fat synthesis.

A major portion of ingested fructose is utilized by the liver by way of the specific fructose-1-phosphate pathway shown in Figure 2. Because three different pathways have been proposed for the metabolism of d-glycer-aldehyde, attention is given to this triose which is formed in the liver.

In the liver, fructose is phosphorylated to fructose-1-phosphate (F-1-P) by ketohexokinase. F-1-P is then split by liver aldolase to form D-glyceraldehyde and dihydroxyacetone phosphate. The same enzyme catalyzes the splitting of fructose-1-phosphate and the condensation of dihydroxyacetone phosphate and glyceraldehyde-3-phosphate into fructose-1-6-bisphosphate.

The affinity of liver aldolase for fructose-1-phosphate is 10 to 30 times greater than that of brain or muscle aldolase. The liver aldolase is therefore well adapted to play its dual role in both glycolysis and fructose metabolism. The D-glyceraldehyde formed in the liver from fructose-1-phosphate can be converted into a triose phosphate by three mechanisms:

1. Direct phosphorylation of D-glyceraldehyde into D-glycer-aldehyde-3-phosphate by triokinase. L-glyceraldehyde is not a substrate for this enzyme. Phosphorylation of D-glycer-aldehyde seems to be the metabolic pathway for fructose in both human kidney cortex and human liver (Heinz et al., 1975b).

2. Reduction of D-glyceraldehyde catalyzed by two different enzymes into glycerol which is subsequently phosphorylated:

   a. NADH-dependent or so-called "normal" alcohol dehydrogenase system or;

   b. NADPH-dependent alcohol dehydrogenase (formerly called aldehyde reductase or glycerol dehydrogenase).
3. D-glyceraldehyde conversion by oxidation via aldehyde dehydrogenase to D-glyceric acid and phosphorylation to glycerate-3-phosphate.

Heinz et al. (1968) suggested that the main pathway for fructose metabolism in man is triokinase mediated phosphorylation.

As reviewed by Froesch (1972a), some tissues metabolize fructose by other metabolic routes. Rat epididymal adipose tissue in vitro takes up fructose in a concentration dependent fashion. In addition, adipose tissue metabolizes almost as much fructose as glucose when the total hexose concentration in the medium is 200 mg per dl of equal parts of fructose and glucose. Fructose transport into adipose tissue cells is stimulated by insulin only in the absence of glucose and thus the metabolism of fructose depends on the rate of entry into these cells which in turn depends on the concentration of fructose. While adipose tissue is not very important in the overall metabolism of either glucose or fructose in vivo, fructose does promote reesterification of free fatty acids and thus tends to decrease their blood level. It has been postulated by Froesch (1972b) that insulin is not required for this reesterification effect of fructose as it is for glucose. In man, the adipose tissue is not very active in converting glucose to fat; in the pig, the adipose tissue is primarily responsible for fatty acid synthesis from glucose. The rat falls in between where both liver and adipose tissue can convert significant amounts of glucose to fat.
IV. FRUCTOSE IN DIABETES

A. EARLY HISTORY

For many years, an approach to the control of diabetes was the search for a sugar or sugar fragment that would be metabolized without insulin. While this goal was never realized, a number of foods were studied including plant polysaccharides hydrolyzable into fructose from sources such as Jerusalem artichokes and Burdock root. Subsequently, other substances were tried including fructose, dihydroxyacetone, and sorbitol. Gluconeogenesis occurs in ultimate glucose utilization in the periphery and requires insulin for catabolism of these substances.

Clinical studies over many decades have encouraged the widely held belief that slowly metabolized carbohydrates such as fructose are useful in the dietary management of diabetics. Fructose, at least in the first stage of its metabolism is less dependent on insulin than glucose, and fructose administration causes a less precipitous increase in the blood glucose level than equal amounts of oral glucose. This subject has been reviewed by Arvidsson Lenner (1976a) and Mehnert et al. (1970).

B. MODERN DIETARY CONCEPTS

The hexoses and pentoses are absorbed from the intestinal tract and transported via the portal vein blood to the liver. The liver cells transform the major portion of these sugars into glucose. In the absence of insulin, glucose transport into skeletal muscle, cardiac muscle and peripheral tissue cells in general is markedly inhibited. Indeed, the activation of this transport system by insulin represents the dominant effect of this hormone upon carbohydrate metabolism -- to enable the body to store and utilize circulating glucose. Therefore, evidence for the direct utilization of fructose in the diabetic requires demonstration of alternate, non-insulin dependent steps.

Controls of glucose metabolism can be "evaded" to some extent by fructose in the following manner:

1. In yielding glyceraldehyde phosphate directly from fructose-1-phosphate, fructose bypasses hexokinase reaction, one of the major rate-limiting steps of glycolysis.
2. The utilization of ingested fructose can proceed via the insulin independent pathway in the liver because insulin does not have an effect on ketohexokinase activity.

3. Transport into adipose tissue is independent of insulin; phosphorylation by hexokinase is not inhibited in adipose tissue by glucose (Froesch, 1965).

Keller and Froesch (1971) injected streptozotocin-diabetic rats with 20 mg of unlabeled fructose and 1 μCi of either 14C-labeled fructose, sorbitol or xylitol alone or together with 18 mU of insulin. There was no incorporation of radioactivity into the diaphragm glycogen from any of these three substrates in the absence of insulin. Adipose tissue took up fructose in significantly greater quantities than xylitol or sorbitol; fructose incorporation was not increased in the presence of insulin. The investigators concluded that the fructose was not dependent upon insulin for intracellular penetration.

On the other hand, the response of the diabetic liver to insulin was different from that of the normal liver. In the liver of normal animals the effect of insulin was counteracted by hyperglycemic and insulin antagonistic hormones. In contrast a significant stimulation of glycogen synthesis by insulin occurred in diabetic animals. In the case of fructose this effect of insulin on liver glycogen synthesis was statistically significant (Keller and Froesch, 1971).

The diabetic liver undergoes a change in its metabolic activity which results in a lower transformation of fructose to glycogen compared to that found in normal liver tissue (Keller and Froesch, 1971). Thus, in spite of the fact that fructose is taken up in the normal liver as fast as in the diabetic liver and even though the diabetic liver has the ability to phosphorylate fructose, the degree of insulin deficiency and the associated change in gluconeogenic activity play an important role in the further fate of fructose metabolites. The more rapid utilization of fructose compared to that of glucose in the diabetic liver, the higher rate of glycogen formation, and the formation of lactate and pyruvate (metabolized independently of insulin) have been substantiated in man (Keller and Froesch, 1971). The antiketogenic effect of fructose decreased proportionally to the degree of diabetic acidosis and the tendency towards gluconeogenesis.

The metabolism of fructose and polyols differs from that of glucose with respect to the initial steps by which they enter the glycolytic pathway in the liver. These steps are independent of insulin, a fact which led to the misunderstanding that the entire utilization of fructose and the polyols is also insulin-independent (Lang, 1971). Fructose, xylitol and sorbitol are rapidly converted to glucose by the liver. However, the relatively rapid
conversion of fructose to glucose does not contradict the fact that oral doses of xylitol, sorbitol and fructose do not produce significant hyperglycemia in normal animals and in man.

Nikkilä (1974) believes that diabetics with uncontrolled disease or those treated with insulin can consume approximately 75 g of fructose daily without evidence of adverse effects.

However, in well-regulated adult diabetics, fructose does not appear to possess dietary advantages over equivalent isocaloric amounts of sucrose. Arvidsson-Lenner (1976b) 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 breakfasts with isocaloric amounts of sucrose, sorbitol or fructose. She also noted that it seems unnecessary to have specially sweetened foods designed for diabetics.

Because there are profound differences between the two main types of diabetes, the effects of substituting fructose for other carbohydrates in the diet may be expected to be different. For example, obese diabetics usually have generous amounts of insulin while lean youth-onset diabetics do not. While the present evidence is incomplete, the advantages of dietary substitution of fructose appear to be slight or negligible. On the other hand, there is no evidence of hazard from the ingestion of fructose provided the total calorie intake is controlled at appropriate levels.

It should be re-emphasized that while the glycolytic pathway of dietary fructose in liver may be independent of insulin, the fact remains that much of the ultimate tissue utilization is via glucose and requires insulin.

Another consideration that tends to diminish enthusiasm for substitution of fructose for sucrose or starch is the demonstration that carbohydrate restriction is not as important in diabetic diets as previously thought (West, 1973). The most important determinant of insulin requirement and degree of hyperglycemia appears to be total fuel supply rather than the qualitative features of the diet. This is because liver is so efficient (with the aid of other tissues) in interconversions. Likewise Bierman and Nelson (1975) have emphasized that "the cornerstone of treatment of the diabetic is control of the total caloric intake to attain ideal body weight." This means proportionate restricting of all foods and not necessarily restricting carbohydrates disproportionately. There may be some slight advantage with fructose because glycemia immediately after the meal is less than that with sucrose or certain starches.

Because there were no clear-cut statements in the recent literature regarding the use of fructose in the clinical management of diabetes a survey letter was sent to a group of diabetologists. Twenty-five respondents out of
thirty-eight queried (thirteen did not respond) stated categorically and uniformly that there were no advantages to using fructose in the clinical management of diabetics. The small advantage offered by fructose being somewhat sweeter than sucrose was not considered to be significant in the dietary management of diabetes.\footnote{Memo dated October 13, 1976 from K.K. Kimura to A.L. Forbes, Associate Director of Nutrition and Consumer Sciences, Bureau of Foods, FDA, regarding a Survey of Diabetologists on use of fructose in diabetes.}
V. PARENTERAL USE OF FRUCTOSE

It appears there may be some fundamental metabolic differences in the fate of fructose when it is injected intravenously as contrasted to oral administration. For example, Atwell and Waterhouse (1971), using $^{14}$C-labeled D-fructose, showed that about 30 percent of the infused fructose is converted to glucose which appears in the circulating blood. In addition, there was a paradoxical hepatic production of lactate. Glucose and lactate production has also been demonstrated by Odievre et al. (1970) in children receiving fructose infusions. Presumably, these conversions take place in the liver (Mäenpää et al., 1968).

In normal adult subjects the half-life of intravenously-infused fructose averages 18 minutes, whereas that of glucose averages 43 minutes. At constant infusion rates of 0.5, 1.0 and 1.5 g fructose per kg per hour, only 2, 5 and 5.7 percent, respectively, of the administered doses were excreted in the urine. Concentrations of blood lactate, pyruvate, α-ketoglutarate, and citrate rise more rapidly and higher after intravenous administration of fructose than after glucose (Froesch, 1972b). Accumulation of lactic acid in blood (exacerbating acidosis in patients with ketoacidotic diabetes) has been noted during rapid infusion of large amounts of fructose. The fall of inorganic serum phosphorus is more pronounced and is shorter lived than that seen following glucose injection. These observations indicate a rapid phosphorylation of fructose. In general, fructose utilization is proportional to the fructose concentration in blood.

Bergström and Hultman (1967) reported that large quantities of fructose were taken up by the liver and that lactate was formed after infusions of fructose. In addition, the formation of glycogen in peripheral tissues takes place by a direct uptake of fructose and not by fructose being first converted in the liver to glucose. This is not seen after oral administration.

The quantitative relation of fructose conversion among various organs is not clearly understood (Froesch, 1972a). For example, Hue (1974) pointed out that fructose is not utilized as such by muscle, heart, or brain.

Adipose tissue utilizes fructose in a concentration-dependent fashion. At a blood concentration of 100 mg per dl fructose and glucose uptakes by adipose tissue are equal. However, in vivo adipose tissue plays only a minor

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5Modified by circumstances such as adiposity of subjects, dosages of hexoses, amount of endogenous insulin, and level of blood glucose.
role in removal of glucose from the blood and is not very important in the overall metabolism of glucose or fructose (Froesch, 1972a). Goda (1938) reported that the animal kidney possessed the ability to convert fructose into glucose while Reinecke (1944) later identified the kidney as a focus of fructose metabolism. Since then, Cori et al. (1951) showed that fructose was not phosphorylated in the liver to fructose-6-phosphate by hexokinase in the presence of physiological concentrations of glucose but into fructose-1-phosphate by fructokinase. In reviewing metabolic data in the literature, there is a considerable amount of species specificity and data may not necessarily apply in all cases to man.

Despite the earlier clinical use of intravenous infusions of fructose to replace or supplement the oral consumption of foods, there seems to be little rational advantage of this ketose over glucose for this purpose, and the use of fructose for intravenous therapy in medicine has diminished.

Daughaday and Weichselbaum (1953) observed that patients with severe diabetic acidosis were able to utilize intravenous fructose up to 1.9 g per kg per hour. According to some authors, parenteral fructose is particularly useful in diabetic patients with pancreatitis and sometimes in those with uremia (Mehnert et al., 1970). Fructose has been advocated in the early or intermediate stage of therapy for diabetic acidosis. The main reason for this is the possibility that fructose would inhibit ketone production. This effect is achieved but others argue that the deleterious effects at least balance the favorable effect in ketone production. These deleterious effects include intensification of hyperglycemia and of lactic acid in blood. Thus, the advisability of such therapy is uncertain. It is not used by most experts (West and Mako, 1976).

A clinical need for administering rapidly utilizable calories in the perinatal period led Pribylova et al. (1973) to investigate the effect of fructose infusions. Fifteen healthy newborn infants were given fructose and 10 healthy newborns given glucose intravenously (umbilical vein) in doses of 0.5 g per kg in 2 minutes. Although fructose stimulated insulin production, there appeared to be no advantage of fructose over glucose during the perinatal period in the healthy newborn. In addition, the authors cautioned against the use of fructose solutions in the neonatal period because of the possibility of hereditary fructose intolerance (Pribylova et al., 1973).

The clinical use of parenteral infusions of fructose may produce important side effects. For example, the limit for fructose turnover is over 1.5 g per kg per hour, but nausea and epigastric pain appear after doses between 0.75 and 1.0 g per kg per hour and elevated blood lactate appears after doses of between 0.5 and 0.75 g per kg per hour. However, fructose-induced hyperuricemia requires doses beyond the range generally used in parenteral alimentation. The work of Kekomäki (1971) suggests
that usual clinical doses (i.e., 1.3 g per kg per hour) of fructose cause no more nucleotide metabolism than glucose. However, rapid infusion of fructose produced a fall in liver ATP in rats; a slower rate of administration did not produce this effect (Brinkrolf and Bässler, 1972).

Hessov (1974) infused ten peptic ulcer patients with either glucose or fructose alternately during 3-hour periods and found that glucose or fructose may be given during the postoperative period at a rate of 0.5 g per kg per hour without risk of metabolic acidosis.

Froesch and Jakob (1974) suggested that the use of fructose offers no advantage for parenteral nutrition, but leaves the physician with the mistaken belief that he does not harm the patient because fructose is easily "utilized" without extra insulin. In addition, there is the possibility of lactic acid acidosis if large amounts of fructose are administered parenterally.
VI. FRUCTOSE INTOLERANCE

A. ESSENTIAL FRUCTOSURIA

In essential fructosuria, there is a deficiency of hepatic ketohexokinase so that the liver cannot metabolize dietary fructose. The estimated incidence of this relatively rare disorder in the general population is approximately 1 in 130,000. In these individuals fructose is absorbed but cannot be converted to fructose-1-phosphate. The condition is benign and the subjects are asymptomatic despite the fructosuria. Their urine gives positive test for reducing sugars and the oral fructose tolerance test gives blood fructose values of 25 mg per dl or higher as compared to normal values of 15-25 mg per dl. About 10 to 20 percent of the administered dose of fructose is excreted in the urine as compared with one to two percent by normal individuals. Glucose and galactose metabolism is normal in subjects with essential fructosuria and the condition remains unchanged after insulin treatment. After oral or intravenous fructose administration, blood lactate and pyruvate become elevated in normal subjects but not in individuals with essential fructosuria. Fructose infusion normally induces hyperuricemia but not in individuals with essential fructosuria.

B. HEREDITARY FRUCTOSE INTOLERANCE

Hereditary fructose intolerance, discovered in 1957, is the result of a deficiency of fructose bisphosphate aldolase that normally converts fructose-1-phosphate into D-glyceraldehyde and dihydroxyacetone phosphate (see Figure 2). The genetic basis is an autosomal recessive trait and members of the same family may be afflicted to different degrees. This deficiency can manifest itself in diverse fashion: neonatal jaundice, persistent vomiting with failure to thrive, hepatomegaly, and rejection of food. Symptoms in infants typically start after weaning and in some cases weaning may be difficult to accomplish because of aversion to sucrose in sweetened foods. In the older person, hypoglycemia, tremulousness, sweating, vomiting, confusion, hypotension, coma, cyanosis and convulsions have been observed (Froesch, 1972b).

The treatment consists of intravenous glucose in the acute stage and exclusion of fructose, sucrose, fruits and many vegetables from the diet. The hepatomegaly related to fructose intolerance may be due to an accumulation of lipids and the disturbance of kidney function, the result of the accumulation of fructose-1-phosphate in the renal cortex (Froesch, 1972a). The kidneys
do not have the ability to secrete an acid urine and phosphate reabsorption is impaired. Fructose-induced renal tubular acidosis becomes normal as soon as the exposure to fructose ceases.

Diagnosis is made by one rapid single intravenous injection of fructose. The smallest amount of fructose which produces the typical symptoms with nausea and vomiting is 0.25 g per kg in adults or 3 g per m² surface area in children (Froesch, 1972a).

Individuals in the general population with some form of fructose intolerance may experience untoward effects if significant amounts of fructose are substituted for other sugars in the diet.
VII. FRUCTOSE AND DENTAL CARIES

Current concepts hold that dental caries is an infectious disease of multifactorial etiology. In addition to acidophilic microbial organisms in the mouth, there must be a susceptible target surface on the tooth and an environment conducive to the growth of the microorganisms. Prior tooth plaque formation is apparently essential for caries to develop and the relationship between chemical and microbial constituents of plaque are being developed.

A heterogeneous population of facultative and anaerobic gram-negative and gram-positive bacteria have been identified in plaque but recent attention has been directed to the acid and polysaccharide forming Streptococcus mutans in the oral cavity (Fitzgerald and Jordan, 1968). Long chain polysaccharides (polyglucans or dextrans) assist in adhering and entrapping bacteria in plaque and force close contact between the cariogenic organisms and the tooth surface (Glickman, 1971; Hartles, 1965). However, the low pH of the plaque-tooth interface is apparently the ultimate cause of the enamel breakdown in the tooth surface.

For caries production a sugar substrate is required for bacterial growth. Thus, individuals with hereditary fructose intolerance who learn to avoid all forms of sweets in order to omit dietary fructose, have less dental caries than the general population (Newbrun, 1969). Numerous investigators have reported that sucrose is the most cariogenic sugar in animal experiments. However, fructose has also been reported to be approximately as suitable as a substrate for bacterial growth and caries production in these animal models (Grenby, 1967; Grenby and Hutchison, 1969; Navia et al., 1974; Stephan, 1966).

While the bacterial mass of plaque is believed to be essential for caries production, the formation of plaque as observed visually is not necessarily cariogenic. In studies with sucrose, glucose, fructose, and xylitol, human dental plaque formation was demonstrated by Scheinin and Mäkinen (1971) but not with the same incidence of caries. The significance of these findings remains to be determined.

In a definitive 2-year study of 125 young adults receiving sucrose, fructose or xylitol as the major sweetener in their diets, Mäkinen (1974) found remarkable differences in the subsequent development of caries. The average monthly intakes of these sugars were 2.2 kg sucrose, 2.1 kg fructose, and 1.5 kg of xylitol when incorporated into specially prepared foods. The subjects were encouraged to eat their special foods but other foods were not strictly excluded from their diets.
Employing the index of "decayed," "missing," and "filled" teeth at the beginning and the end of the two-year period, these authors expressed their results as indicating a 25 percent reduction of "caries incidence" in the fructose group (38 subjects), and a 90 percent reduction in the xylitol group (52 subjects), as compared with the control sucrose group (35 subjects). Although the findings in experimental animals indicate fructose to be equi-cariogenic as sucrose it appears that fructose may be somewhat less cariogenic for man.

Based on the reports available it appears unlikely that the projected substitution of fructose for dietary sucrose in the United States would elicit a clinically significant decrease in the incidence of dental caries. Only less than 3 percent of a diet would be substituted with fructose if the projected sale of 600 MT is used.
VIII. UNTOWARD METABOLIC EFFECTS OF FRUCTOSE

A. EFFECT ON SERUM TRIGLYCERIDES AND FATTY ACIDS

Oral feeding of fructose or sucrose can lead to hyperlipidemia in man. The fructose portion of sucrose appears to be responsible for the hyperlipidemic effect (Bergstrom et al., 1972). Macdonald (1968) reported that the specific activity of the serum triglycerides in healthy men was greater after the oral ingestion of $^{14}$C-fructose than after $^{14}$C-glucose, which suggests that fructose is preferred to glucose by the lipid synthesis pathways in the fasted state.

Zakim (1972) noted that in rats and man fructose is a better precursor of fatty acids than glucose, primarily as a result of the greater rate of glycolysis of fructose. It is commonly stated that a fructose diet tends to produce higher levels of serum-glycerides than a glucose diet.

Bar-On and Stein (1968) noted that guinea pigs fed fructose did not develop hypertriglyceridermia as do rats and man. Furthermore, Sugawa-Katayama and Morita (1975), studying the effect of a high fructose diet on lipogenesis in rats, showed that the lipid content in the liver changed with the feeding conditions. Fructose showed a greater effect on induction of hepatic-glucose-6-phosphate dehydrogenase than did glucose. The enzyme activity became maximum between 3 to 7 days after starvation and refeeding with either a high fructose or a high glucose diet. After 41 days, the enzyme activity returned to control level in the liver of glucose-refed rats but the activity was higher in the fructose-refed rats than in the control rats.

In baboons a cause-and-effect relationship between fructose tolerance and triglyceride specific activity was demonstrated with a high $^{14}$C-tagged sucrose diet (Coltart and Crossley, 1970). Fructose was incorporated into serum triglyceride to a greater extent in the male baboons than in the females because of the higher levels of blood fructose attained in the male animals.

Heinz et al. (1968) who studied the metabolism of glucose and fructose in biopsy material from human liver showed that fructose is converted into glycerol phosphate quicker than is glucose. Thus, the enzymes required for the conversion of fructose are present in human liver and avoid the slower reactions in the glycolysis of glucose. In this respect fructose rather than glucose favors the formation of serum fatty acids.

Studies using humans (Bode et al., 1971; 1973) and rats (Woods et al., 1970) have shown that parenteral infusion of fructose results in a
decreased level of ATP in the liver while glucose did not produce comparable decrease in the nucleotide level. Reiser (1975) believes these results suggest that fructose may act as an "ATP sink" in the liver. Thus a decreased level of hepatic ATP may play a role in preventing normal clearing of blood triglycerides (Schoetz et al., 1966).

Michaelis and Szepesi (1973; 1974) and Michaelis et al. (1975) have reported that lipogenic enzymes can be induced in rat liver by feeding sucrose to a greater extent than by glucose and fructose in equal concentrations. They have called this phenomenon the "disaccharide effect." They have also demonstrated that fructose ingestion will induce these liver enzymes. The association of these effects with excess liver lipid production accompanied by elevated blood lipids and the development of vascular disease is conjectural at this time and requires confirmation in man. In a recent study in a population, West (1976) found no relationship between sucrose consumption and triglycerideremia despite inter-individual differences in sugar consumption that were often fourfold or more.

B. OTHER EFFECTS

Infusion of fructose in normal subjects at the rate of 1 g per kg per hour for 4 hours resulted in an increase in the glycogen content of samples of the quadriceps muscle obtained by biopsy. The increase in glycogen content arose from the fructose taken up by the muscle. Fructose given intravenously is rapidly taken up by the liver and partly metabolized to lactic acid and may be the cause of the fatal acidosis reported by Andersson et al. (1969) after massive intravenous administration of fructose to children with preexisting metabolic acidosis.

In 1972, Heuckenkamp and Zöllner studied continuous intravenous administration of glucose, fructose, and galactose in healthy persons. High-fructose loads (1.5 g per kg per hour) were followed by a significant rise in serum uric acid. Elevation of plasma insulin level was higher with glucose than fructose infusions. Previous work reported by Bergström et al. (1968) showed increased lactic acid production with fructose and precludes its use in long standing acidosis of any origin.
IX. CONCLUSIONS

The availability of high-fructose corn syrups and crystalline fructose as relatively low cost sweeteners suggests that fructose may replace sucrose to a greater degree in the United States diet in the years ahead.

Crystalline fructose has been used as a dietary sugar in some European countries for years without reports of adverse effects. A 1975 definitive study of 38 normal adult subjects who consumed an average of 2.1 kg of fructose monthly in their diet for two years, did not reveal any consistent changes in any of the major biochemical parameters followed in these studies. These findings suggest that fructose is well-tolerated in the diet of normal subjects.

Oral feeding of fructose has been claimed to cause hyperlipidemia in man. Prolonged parenteral administration of fructose or other sugars may produce increased serum uric acid, triglycerides, and fatty acids. It is unlikely that the ingestion of foods with the amount of fructose as suggested will lead to significant changes in lipid metabolism.

Fructose is absorbed more slowly from the gastrointestinal tract than glucose and produces a less precipitous increase in the blood glucose level than seen with glucose or sucrose. However, it must be emphasized that even if diabetics can convert fructose to glucose, tissue utilization of glucose derived from fructose does require insulin. The major potential for misuse would be a notion that fructose products could be used by diabetics without exchanging them for other calories in the diet prescription.

Based on the reports available at this time, it appears that the projected substitution of fructose for dietary sucrose in the United States will not significantly change the incidence of dental caries in this country.

It is the prevailing medical opinion that there are no clinical advantages of substituting fructose for glucose either orally or parenterally in any disease state.


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