THE NEED FOR SPECIAL FOODS AND SUGAR SUBSTITUTES
BY INDIVIDUALS WITH DIABETES MELLITUS

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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 John M. Talbot, M.D., Senior Medical Consultant, LSRO, FASEB, in accordance with the provisions of Contract No. 223-75-2090.

The LSRO acknowledges the contributions of the numerous investigators and consultants who assisted with this study. The report reflects the opinions expressed by participants in an ad hoc study group that met at Beaumont House, FASEB, on July 18, 1977. A judicious attempt has been made to incorporate the various viewpoints and opinions. The report was reviewed by these consultants; however, the listing of the consultants' names in Section VIII does not imply that they endorse the study. The author accepts responsibility for the contents of the report.

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
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SUMMARY

This report reviews the need for special dietary products marketed for use by individuals with diabetes mellitus and the safety and efficacy of certain nutritive sweetener substitutes for sucrose that are claimed to offer nutritional advantages in the dietary management of diabetes. Contemporary concepts of dietary management of both juvenile-onset and maturity-onset diabetes emphasize control and maintenance of body weight, allowance of 45 to 60 percent of total calories as complex carbohydrate (starch), a corresponding reduction in calories from saturated fat, provision of adequate calories and nutrients to meet the extra nutritional requirements of juveniles and pregnant women, and avoidance of refined sugar as an aid in preventing postprandial hyper- and hypoglycemia.

Special foods for individuals with diabetes mellitus are not necessary to achieve these objectives of dietary management. The dietary principles recommended by leading United States and European authorities can be followed conveniently and at minimum expense through enlightened choices of commonly available food items.

At present, specific and unique characteristics of food products with special therapeutic properties for diets of diabetic individuals cannot be delineated or defined on rational nutritional grounds. Such terms as "diet," "dietetic" and "diabetic" on food labels have no uniform meaning for consumers, and diabetologists have observed that patients tend to consume such foods without regard to their energy content, thus defeating the recommended principles of controlling caloric intake. Some consumers regard the reduced-calorie and low-calorie prepared food products as convenient in diets for weight reduction and diabetes although their use in dietary management of diabetes has no therapeutic basis other than weight reduction and maintenance. Low-calorie soft drinks and water-packed fruits may be useful in the diet of persons with diabetes.

When fed as pure substances to fasted subjects, the nonglucose carbohydrate nutritive sweeteners, fructose, xylitol and sorbitol, are absorbed relatively slowly and produce less postprandial hyperglycemia and insulin response than sucrose or glucose. Adequate studies of their long-term effectiveness when ingested as part of mixed meals have not been conducted. Although these sucrose substitutes are generally considered safe for oral consumption in amounts isocaloric with average sucrose consumption, the significance of recent information on possible carcinogenicity of oral xylitol in long-term feeding studies has not been fully evaluated. In some European countries, these sucrose substitutes are used as nutritive sweeteners in diets for diabetic persons.

In view of the lack of certain essential information on the long-term effectiveness of various diets in preventing or mitigating the chronic debilitating complications of diabetes, suggestions for research are included for future consideration.
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I. INTRODUCTION

A. SPECIAL FOODS FOR DIABETIC PATIENTS

As a part of its effort to improve the health of American citizens, the Department of Health, Education and Welfare, through the Bureau of Foods, Food and Drug Administration (FDA), evaluates, monitors, and regulates the safety of foods. In order to ensure the efficacy and safety of certain foods for special dietary purposes in terms of medical claims made by manufacturers, the agency published a proposed regulation in July, 1977 concerning revised label statements.

These revised regulations cover labeling of special dietary foods that are products designed as aids for weight reduction and maintenance. Because the control of body weight is an important aspect of the dietary management of diabetes, some of these products have also been marketed as "diabetic" foods. So-called "dietetic" and "diabetic" foods are widely available in retail stores. In addition, manufacturers are keenly interested in marketing foods for diabetic patients in which fructose, sorbitol, and xylitol are used as substitutes for sucrose.

The FDA recognizes that new scientific knowledge of the nutritional aspects of diabetes mellitus is evolving; that there are many important gaps in such knowledge; and that expert opinion is not unanimous on the merits of various schemes for the dietary management of diabetes including questions about the claimed benefits of substituting fructose, sorbitol or xylitol for sucrose in foods. However, the FDA requires a factual basis to reach rational judgments on possible distinct medical advantages to diabetic patients of particular food products such as are currently identified with "dietetic" and "diabetic" foods or foods for special dietary purposes, as well as foods that may be planned as special foods in which nutritive sweeteners other than sucrose are used.

The Life Sciences Research Office (LSRO) was requested by the FDA to review scientific information, to obtain the opinions of diabetologists, laboratory investigators, and epidemiologists, and to prepare a comprehensive report on these issues. To assist in this review an ad hoc study group of special consultants was convened at Beaumont House, FASEB, on July 18, 1977 (see Section VIII, pg. 49).

B. SCOPE

This report presents a synopsis of current information on diabetes mellitus and a brief review of FDA regulatory proposals on certain foods for special dietary purposes. It explores the dietary management of diabetes, emphasizing currently recommended principles and the use of nutritive nonglucose
carbohydrate sweeteners in diabetic diets. The nonnutritive synthetic sweeteners such as saccharin and cyclamate are not considered in this review. The question of the need for special foods, including foods marketed as "dietetic" and "diabetic," is addressed. The report focuses on available scientific data and expert opinion that provide information on the following specific questions:

1. When substituted for conventional nutritive sweeteners such as sucrose, or when indigenous to a food, does sorbitol or any other polyol have special nutritional or other significance in the dietary management of diabetes?

2. When used as a substitute for conventional nutritive sweeteners such as sucrose, does fructose or any other carbohydrate have beneficial properties for the dietary management of diabetes?

3. Is there substantive scientific evidence that would permit judgments on the nutritional or clinical value of other foods or food ingredients that may have beneficial properties for the dietary management of diabetes?

4. Are "dietetic" foods useful in the dietary management of diabetes other than their value in weight reduction or maintenance?

5. Can foods for special dietary use intended specifically for diabetics be distinctly delineated or defined?

6. If such foods are distinct, what characteristics can be used to identify them?

The deliberations of the ad hoc group convened at Beaumont House provided the basis for the topics treated in this report and the discussions of the participants provided most of the background material.

Other sources of information included the computerized biomedical literature files of the National Library of Medicine, the comprehensive compilations of the scientific literature from 1920 to 1970 prepared in conjunction with an evaluation of the health aspects of corn sugar, mannitol, sorbose, sorbitol, and sucrose used as food ingredients and Generally Recognized as Safe (GRAS) substances (Informatics, 1972a,b; 1973a,b,c), and the literature collections of the Life Sciences Research Office in the broad field of dietary sugars in health and disease. The consultants who assisted in this study also supplied numerous references.
II. BACKGROUND INFORMATION

A. SYNOPSIS OF CURRENT KNOWLEDGE OF DIABETES MELLITUS

1. Definition and Prevalence

Diabetes mellitus is a syndrome of abnormal metabolic and vascular manifestations associated with insulin deficiency. This deficiency may be total or partial, absolute or relative. Diabetes is characterized by diminished or lost ability to oxidize carbohydrates, alterations in lipid and protein metabolism, and chronic vascular degenerative complications. Four principal abnormalities are associated in the syndrome: hyperglycemia and disturbed metabolism, microvascular disease, accelerated atherosclerosis, and neuropathy and loss of nerve transmission (Porte, 1976). Signs and symptoms resulting from the metabolic disturbances include hyperglycemia, glycosuria, osmotic diuresis with polyuria, dehydration, thirst, hunger, weakness, weight loss, ketoacidosis, and coma. According to Martin (1976), the hyperglycemia and increased levels of circulating free fatty acids and amino acids resulting from the insulin deficiency reflect a concomitant intracellular starvation. The various types of neuropathy, arteriosclerotic heart disease, retinopathy and blindness, nephropathy, and gangrene of the extremities are some of the most debilitating manifestations of diabetes. Cataracts mature relatively rapidly in adult diabetics (Marquardt and Kirschbaum, 1971; Müller and Weber, 1971; Kinoshita, 1976).

It is estimated that in the United States there are about 4.2 million persons with diagnosed diabetes and roughly 5.5 million more with undiagnosed diabetes. The true prevalence of diagnosed diabetes in this country is uncertain, but a crude estimate is 2 percent of the population (Knowles et al., 1976). The prevalence appears to be increasing at a rate of about 6 percent per year (Anonymous, 1977a), and it is predicted that this trend will continue unless a cure or prevention can be found (Steinke and Soeldner, 1977). According to West (1977), 70 to 90 percent of diabetic individuals in most affluent Western societies are of the fat, adult-onset type, while about 5 to 10 percent are lean, youth-onset cases with little or no endogenous insulin and severe diabetes. There are several other less common types. Many patients have normal life spans, but, on the average, life expectancy is reduced about one-third in adult-onset diabetes and by somewhat more in juvenile-onset cases. Morbidity rates from vascular disease are decidedly excessive in diabetes.

2. Etiology and Clinical Picture

The etiology of primary diabetes mellitus, the most common type (also called idiopathic, genetic, hereditary, essential), is unknown; however, certain predisposing factors such as heredity, obesity and possibly stress have been identified (Williams and Porte, 1974; Arky, 1976). Although a variety of hypotheses on modes of inheritance have been proposed, none adequately explains all available data (Williams and Porte, 1974). While some familial clustering can often be identified, it has not been possible to demonstrate a clear mendelian pattern of inheritance. In a study of 106 identical twin pairs in which at least one twin had diabetes, Pyke and Nelson (1976) found concordance (both
twins had diabetes) in only one-half of those whose diabetes was diagnosed before the age of 40. In those with onset of diabetes on or after age 50, concordance was 100 percent. Since 1976, investigators have collected additional cases (Anonymous, 1977d). Pyke and Nelson (1976) concluded that genetic factors cannot be entirely responsible for juvenile-onset diabetes but may be the main cause of adult-onset diabetes; however, they noted that concordance rates do not necessarily indicate the extent of heritability of a condition.

Rubenstein et al., (1977) investigated the genetic predisposition to juvenile diabetes in relation to the inheritance of the human leukocyte antigen (HLA) system. They concluded that the disease is inherited as a recessive trait with a penetrance of about 50 percent. According to Neel (1977), three groups of investigators have been unable to confirm the findings of Rubenstein and his colleagues. Thus the etiologic significance of the disease-associated genetic markers that have been studied in relation to diabetes remains unclear.

In addition, nutritional factors such as starvation and overfeeding, stress states (including infection, trauma, surgery, pregnancy and psychologic disturbances), immune mechanisms, neuroendocrine factors and certain pharmacologic agents are among the items that may have pathogenetic significance in diabetes mellitus (Arky, 1976; Munger, 1976; Porte, 1976). Modern concepts of the heterogeneity of idiopathic diabetes mellitus are based on genetic evidence and insulin response to glucose; the development of vascular disease suggests multiple etiologies and pathogeneses (Fajans and Freinkel, 1976). With regard to infection, certain evidence suggests a viral etiology for some cases of diabetes (Anonymous, 1971; Craighead and Steinke, 1971; Maugh, 1975).

However, other types of diabetes occur in which the etiology may be apparent. For example, carbohydrate intolerance may follow destruction of islets in chronic pancreatitis, pancreatic tumor, associated endocrine disorders and the effects of trauma or certain drugs (Steinke and Soeldner, 1977).

Juvenile-onset (ketosis-prone) diabetes features the sudden onset during childhood or adolescence of the classic disturbed metabolic manifestations of insulin deficiency: polyuria, polydipsia, and polyphagia; hyperglycemia and glucosuria; ketosis or ketoacidosis; and instability of blood sugar levels after exogenous insulin. Remissions are not uncommon, but almost total insulin deficiency eventually supervenes.

The clinical manifestations of maturity-onset (ketosis-resistant) diabetes are usually less dramatic than in the juvenile type, often presenting as signs or symptoms resulting from the vascular components of the disease such as angina, weakness, dyspnea, local paresthesias, anesthesias, and motor disturbances.

3. Classification

None of the various classifications of diabetes is completely satisfactory. In reality, the syndrome varies from a mild form, completely amenable to dietary management, to the severe, insulin dependent, ketosis-prone form. The mild type, usually termed maturity-onset diabetes, is relatively stable, ketosis-resistant, and most frequently diagnosed after age 40. Eighty
to 90 percent of individuals with this form of diabetes are above ideal body weight, and the vast majority can be controlled by a hypocaloric diet and weight reduction alone. The severe form, commonly referred to as youth-onset or growth-onset diabetes, is insulin-dependent, ketosis-prone, and most often diagnosed in childhood and adolescence (Haunz, 1967).

The gross division of primary diabetes into juvenile- and adult-onset types, while very useful, does not distinguish the relatively infrequent, mild, stable juvenile case from the more typical severe case, or the somewhat uncommon, severe, unstable, ketosis-prone maturity-onset patient from the usual mild to moderately severe, relatively stable adult-onset patient. However, the stages of carbohydrate decompensation have formed the basis of a generally accepted system (Steinke and Soeldner, 1977) of classification as follows:

Clinical (overt or decompensated) symptomatic diabetes, typically the ketosis-prone juvenile type or ketosis-resistant adult type

Chemical (asymptomatic) fasting blood sugar usually normal; abnormal glucose tolerance test

Latent (stress) normal glucose tolerance test, but history of diabetes associated with a period of stress (pregnancy, infectious disease, endocrinopathy)

Potential A conceptual term; normal glucose tolerance, but subject is at higher than average risk of developing diabetes (e.g., both parents diabetic or identical twin of a diabetic person)

Etiologic classifications of diabetes mellitus are also useful as an aid in differentiating primary diabetes from the types in which the etiology is identifiable (for example, pancreatitis, tumor of the pancreas, hemochromatosis, pheochromocytoma, adrenocortical hypersecretion). Classification according to therapeutic requirements into mild, moderate, severe, and labile types has proved helpful in selecting the best treatment regimen for avoidance of the immediate consequences of uncontrolled diabetes and possible harm from inappropriate treatment.

According to Sussman (1971a), Molnar's description of brittle diabetes approached an acceptable definition: "...brittle patients have diabetic hyperlability of such a degree that various parameters indicating metabolic derangement fluctuate widely despite attempts at the best possible treatment." Sussman (1971a) added that a cardinal feature is the unpredictable occurrence of hypoglycemic reactions.
In this report, the terms juvenile-onset and maturity-onset (or adult-onset) diabetes are used. Except when otherwise noted, juvenile-onset diabetes refers to symptomatic, insulin-dependent, ketosis-prone, unstable, overt diabetes, and adult-onset pertains to the mild to moderately severe, ketosis-resistant, overt diabetes as well as to the chemical or asymptomatic type.

Extensive information on diabetes mellitus is available in such texts as Ellenberg and Rifkin (1970), Marble *et al.*, (1971) and Sussman (1971b) as well as textbooks of endocrinology such as Williams (1974). A Fogarty International Center monograph on the subject provides a recent review (Fajans, 1976).

4. Treatment of Diabetes Mellitus

The important components of treatment of diabetes are dietary and medicinal. Achievement and maintenance of ideal body weight are accomplished primarily by dietary measures. Ketosis in the insulin-dependent diabetic is prevented by injection of insulin one or more times daily. In patients with some insulin reserves, dietary measures combined with oral hypoglycemic drugs are claimed to be beneficial. The therapeutic aims are to restore normal carbohydrate, fat and protein metabolism and prevent or ameliorate the debilitating and incapacitating complications that result from degeneration of both large and small blood vessels.

Many clinicians believe that oral hypoglycemic agents may be helpful in treating maturity-onset diabetes provided it is nonketotic and uncontrollable by diet therapy alone. The main advantage of the oral hypoglycemic agents is patient convenience, that is, avoiding the use of injected insulin. Two classes of agent are currently used: the sulfonylureas and the biguanides. The sulfonylureas, of which tolbutamide is an example, probably act primarily by enhancing endogenous insulin secretion; the biguanides appear to act by inhibiting hepatic gluconeogenesis, and may decrease intestinal absorption of glucose (Williams and Porte, 1974). Expert opinion is divided on the long-term efficacy of the oral hypoglycemic agents, and questions about their safety have arisen following reports of serious side-effects, toxic reactions and a decrease in life expectancy among users (Davidson, 1975a,b). Because of an associated risk of lactic acidosis, the FDA has recently ordered phenformin, a widely used biguanide, removed from the market (Anonymous, 1977b; Food and Drug Administration, 1977a). Nevertheless, the search continues for better oral antidiabetic medications (Tutwiler and Bridi, 1977).

West (1977) summed up the treatment of diabetic patients in this country:

"In the United States about one-quarter of the known diabetics are being treated with insulin, about half are receiving oral agents, and about one-quarter are not receiving any antidiabetic medication."

He indicated that the high rate of medicinal therapy reflects primarily the low frequency of successful use of available, effective long-term diet therapy.
B. FOOD PRODUCTS MARKETED FOR USE IN DIABETES AND WEIGHT CONTROL

1. Sugar (Sucrose) Substitutes

Food products that are presently available in American markets in which substitutes for sucrose such as fructose, sorbitol, xylitol and mannitol are used include chewing gums, candies, cookies and cake mixes. Similar products sweetened with these sugar substitutes are readily available in certain West European countries such as Germany, Switzerland, and Finland. In addition, jams, jellies and compotes containing these nutritive sweeteners are available in Europe. In the United States, the Code of Federal Regulations (Office of Federal Register, 1977) defines the authorized uses as food ingredients of sorbitol [21 CFR 184.1835], mannitol [21 CFR 180.25 and 182.5470], and xylitol [21 CFR 172.395].

Sorbitol may be used in foods at levels not to exceed good manufacturing practice. Permissible levels of sorbitol as a nutritive sweetener vary from 99 percent in hard candy and cough drops to 12 percent in unspecified foods. In addition, sorbitol is permitted as a food processing ingredient for 19 specified technical purposes including use as an agent for anticking and free-flow, curing and pickling, drying, firming, flavoring, lubricant and release, surface finishing, and as an emulsifier and emulsifier salt, adjuvant, formulation aid, humectant, sequestrant, stabilizer and thickener, and texturizer [21 CFR 184.1835]. Any food whose consumption may result in a daily intake of 50 g of sorbitol must bear the label statement, "Excess consumption may have a laxative effect."

Mannitol is generally recognized as safe (GRAS) when used in accordance with good manufacturing practice, and is listed among the GRAS substances as a nutrient and/or dietary supplement [21 CFR 182.5470]. Its levels of use as a nutritive sweetener are specified for certain foods; in unspecified foods, it may be added at levels less than 2.5 percent. In addition to its use as a nutritive sweetener, it is authorized as a food processing ingredient to achieve 13 specified technical purposes similar to those described for sorbitol [21 CFR 180.25]. Foods whose daily ingestion may result in an intake of 20 g of mannitol must bear a laxative warning similar to that prescribed for sorbitol.

With regard to xylitol, the Code states, "Xylitol 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" [21 CFR 172.395]. However, because of reports of alleged adverse effects (see pgs. 20-23), the FDA is currently reviewing the health and safety aspects of xylitol as a food ingredient (Life Sciences Research Office, 1978).

The nutritional and safety aspects of fructose as a nutritive sweetener have been reviewed recently (Kimura and Carr, 1976).
2. Other Dietary Products Represented as Useful in Weight Control and/or Diabetes

Currently in the United States there are several hundred food products whose label statements include terminology indicating they contain no calories or fewer calories or decreased levels of sugars, carbohydrates or fats. In addition, the labels claim that they are "diet," "dietetic," "diabetic," "for diabetes," or "for diabetics" and/or are artificially sweetened. The FDA recently published a proposed tentative order on the labeling of special dietary foods (Food and Drug Administration, 1977b). As supporting data, the document included information on the currently available food products whose label statements suggest usefulness in weight control and/or diabetes:

<table>
<thead>
<tr>
<th>KEY WORDS IN THE LABEL STATEMENTS</th>
<th>NUMBER OF PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugarless; sugar free; no added sugar; or prepared without sugar</td>
<td>94</td>
</tr>
<tr>
<td>Dietetic</td>
<td>66</td>
</tr>
<tr>
<td>Artificially sweetened</td>
<td>64</td>
</tr>
<tr>
<td>Low calorie</td>
<td>55</td>
</tr>
<tr>
<td>Diet</td>
<td>29</td>
</tr>
<tr>
<td>Diabetic; diabetes; for diabetics</td>
<td>23</td>
</tr>
<tr>
<td>Low in carbohydrate; no available carbohydrate; or starch free</td>
<td>14</td>
</tr>
<tr>
<td>Low fat; lower in fat</td>
<td>9</td>
</tr>
<tr>
<td>Lower in calories</td>
<td>7</td>
</tr>
</tbody>
</table>

These products represent the following food categories that are applicable to ordinary foods as well as special dietary foods:

- Baked goods and baking mixes
- Beverages, nonalcoholic
- Cheese
- Chewing gum
- Condiments
- Confections
- Fats and oils
- Fish products
- Fruit ices, water ices
- Gelatins, puddings, fillings
- Grain products such as pastas, rice dishes
- Hard candy
- Jams, jellies, sweet spreads
- Meat products
- Milk, milk products
- Nuts, nut products
- Processed fruits, juices, drinks
- Snack foods
C. FDA REGULATION OF FOODS OFFERED FOR USE IN DIABETES

In the tentative final order announced on July 19, 1977, FDA (1977b) proposed revised label statements for special dietary foods for use in reducing or maintaining body weight or caloric intake, or in the diet of individuals with diabetes mellitus. The order, which has a tentative effective date of July 1, 1979, would prevent misleading label statements on foods that are not useful for these purposes, and improve labeling in terms of meaningful content and legibility. Section 105.67 of the order states:

"Label statements relating to food for use in the diet of diabetics

(a) A food that purports to be represented or (sic) special dietary use because of usefulness in the diet of diabetics shall bear nutrition labeling in compliance with §101.9 of this chapter, unless exempt under that section, and the statement 'Diabetics: This product may be useful in your diet on the advice of a physician. This food is not a reduced calorie food.' If the food is useful in maintaining or reducing calorie intake or body weight and labeled in conformity with §105.66, the last sentence may be eliminated.

(b) A food shall not be represented to be useful in the diets of diabetics if such representation is false or misleading.

(c) The term "diabetic," "for diabetics," "diabetes," or the like, shall not be included as part of the name of any food, or otherwise be included on the labeling more prominently than the statement required by paragraph (a) of this section.

(d) The term "dietetic," "diet," or the like, shall not be included in the labeling of a food solely because of its possible usefulness in the diet of diabetics.

(e) A food shall not purport to be or be represented for special dietary use because of usefulness in the diet of diabetics solely by virtue of its being a food useful in reducing or maintaining caloric intake or body weight."
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III. DIETARY MANAGEMENT OF DIABETES MELLITUS

A. HISTORICAL PERSPECTIVE

Modern principles of dietary treatment of diabetes mellitus have evolved over a period of more than 3500 years (Wood and Bierman, 1972). Some noteworthy examples listed by these and other authors are:

<table>
<thead>
<tr>
<th>DATE</th>
<th>SOURCE</th>
<th>TYPE OF DIETARY MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>About 1500 B.C.</td>
<td>Ebers parchment, Egypt</td>
<td>High carbohydrate (CHO) (grains, honey, fruit, sweet beer)</td>
</tr>
<tr>
<td>About Year 1</td>
<td>Aretaeus, Asia Minor</td>
<td>High CHO (milk, cereals, starch, fruits, sweet wine)</td>
</tr>
<tr>
<td>1675</td>
<td>Willis, England</td>
<td>High CHO (milk, barley water boiled with bread)</td>
</tr>
<tr>
<td>1797</td>
<td>Rollo, England</td>
<td>Restricted CHO, high protein, high fat</td>
</tr>
<tr>
<td>1922</td>
<td>Banting, Best, McLeod</td>
<td>Discovery of insulin started prolonged decline of clinical interest in dietary management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>except for a few investigators</td>
</tr>
<tr>
<td>1923</td>
<td>Geyelin</td>
<td>High CHO (plus insulin injections)</td>
</tr>
<tr>
<td>1929</td>
<td>Sansum, Gray, Bowden</td>
<td>Normal proportions of CHO and fats; no free sugar</td>
</tr>
<tr>
<td>1931</td>
<td>Rabinowitch</td>
<td>Moderate CHO, low fat, low calories</td>
</tr>
<tr>
<td>1935</td>
<td>Himsworth</td>
<td>High CHO for mild diabetes</td>
</tr>
<tr>
<td>1940-1950</td>
<td>Somogyi</td>
<td>Ample CHO, protein, restrict fat, control weight</td>
</tr>
<tr>
<td>Approx. 1950-1970</td>
<td>Most U.S. Physicians</td>
<td>Restricted CHO, high fat (approximately 40% CHO, 42% fat), low total calories, maintain ideal body weight</td>
</tr>
<tr>
<td>1971</td>
<td>American Diabetes Association</td>
<td>Revised dietary principles (see pages 12, 13)</td>
</tr>
</tbody>
</table>
From about 1950 to 1970, most American physicians adhered to the high fat, restricted carbohydrate concept that, coupled with weight reduction and maintenance of ideal body weight, formed the basic tenets of dietary management. After evaluating all available scientific evidence, the American Diabetes Association issued in 1971 a landmark revision of dietary principles in a report of its Committee on Food and Nutrition (American Diabetes Association, 1971).

Bierman and Nelson (1975) reviewed the scientific rationale for these newly enunciated principles, which were based on recognition that: (a) the only method of producing a remission with reasonable consistency is via weight reduction and adherence to ideal body weight; (b) the reduced glucose tolerance of diabetes is frequently normalized by weight reduction alone; (c) high-carbohydrate diets do not result in hyperglycemia and glucosuria in most diabetics provided that caloric intake is appropriate; and (d) there are significant advantages in allowing diabetic patients a normal proportion of carbohydrates. In practical terms, these principles were the basis of a recommendation for restriction of total calories to achieve ideal body weight and a low-fat diet in which calories from fat are reduced and replaced by carbohydrate (starch, not sugar). Most patients can consume 45 to 60 percent of total calories as carbohydrate. The long-standing advice to restrict intake of simple sugars was retained. Among the reasons for this was the mitigation of postprandial hyperglycemia.

These dietary recommendations have been advocated on the basis of available scientific evidence and clinical judgment without benefit of long-term prospective studies in human patients; however, as reviewed by West (1977), they are supported by a number of clinical, laboratory and epidemiological investigations. Whether or not dietary treatment, coupled as may be needed with antidiabetic medication, will aid in preventing and/or ameliorating atherosclerosis and the serious degenerative concomitants of diabetes remains to be established. Not all diabetologists agree with the consensus expressed above. Some still attach priority to restriction of total carbohydrate even in patients whose levels of caloric intake are optimal.

Meanwhile, particularly in Europe and starting about 1950, scientific reports on the use of fructose and the sugar alcohols, sorbitol and xylitol, as substitutes for the customary simple sugars in diabetic diets, have suggested certain theoretical and practical advantages (see pgs. 15-20).

B. CURRENT CONCEPTS AND PRINCIPLES


The special report of the American Diabetes Association Committee on Food and Nutrition (1971) is widely acknowledged as a consensus that represents the current thinking of most of America's leading diabetologists. The American Diabetes Association and The American Dietetic Association list the following goals of diet therapy in diabetes (Anonymous, 1977a):
• Attain and maintain ideal body weight;

• provide a normal growth rate in children and pregnant women;

• minimize glycosuria and keep the plasma glucose as near normal physiological range as possible;

• prevent and/or delay the development and/or progression of cardiovascular, renal, retinal, neurological and other complications associated with diabetes;

• modify the diet as necessary for complications of diabetes and for associated diseases;

• improve the overall health of the patient by attaining and maintaining an optimal nutritional status; and

• provide for each patient an individualized educational and follow-up program.

2. Recommendations for Dietary Management.

To reach these goals, the American Diabetes Association and The American Dietetic Association recommend: (a) restriction of total caloric intake to achieve and maintain ideal body weight while simultaneously providing adequate nutrition; (b) allowance of 45 to 60 percent of total calories as carbohydrate, with a corresponding reduction in calories from saturated fats; and (c) prevention of hyperglycemic peaking and hypoglycemic dipping by proper scheduling and regularity of eating; avoidance of feasting and simple, rapidly absorbed sugars; and by regular exercise. Avoidance of fasting is particularly important in juvenile-onset type of diabetes because of a risk of hypoglycemic brain damage.


3. Other Dietary Concepts and Principles.

Certain advantages of using fructose, sorbitol, or xylitol as substitutes for sucrose in diabetic diets have been reported by European investigators (see pgs.15-20). For example, it is common practice in West Germany to use fructose or xylitol in diabetic diets to obtain good patient compliance. This is based on recognition of the importance of the need for sweetness and the concept that sweeteners that cause the least disturbance of carbohydrate metabolism should be used.
Weight reduction and maintenance of ideal body weight in the obese, maturity-onset diabetic patient are considered essential because these measures alone have the potential of controlling and even reversing the disease. West (1977), while acknowledging the general lack of success in treating obesity, emphasizes that the benefits of weight reduction in overweight patients justify substantial therapeutic efforts in dietary management.

The ad hoc working group reiterated these principles and objectives and used them as a basis for discussion. Some consultants considered that control of saturated fat intake may be as important as calorie control in preventing or ameliorating the vascular complications of diabetes (West, 1977). However, it was pointed out that not all physicians who treat diabetic patients would agree with the recommended liberalization of carbohydrate calories and the corresponding reduction of fat. Based on the empirical finding that hyperglycemia and glucosuria appear to be more readily controlled with a diet in which carbohydrate is limited to about 50 to 70 percent of the usual carbohydrate intake, some physicians prefer the long-standing dietary principle in which calories from carbohydrate are restricted and replaced by calories from fat (Van Itallie and Campbell, 1967).

The widely held notion that sucrose has no place in the diet of diabetics is not supported by scientific data. However, because simple sugars, particularly glucose and sucrose, are rapidly absorbed and can produce hyperglycemic peaks, their use by diabetic patients should probably by avoided because of the possibility that repeated exposure to hyperglycemia may damage blood vessels and nerves (Marble et al., 1971; Bloodworth, 1973; Lundbaek, 1974). However, sucrose may be appropriate to prevent hypoglycemia in diabetic individuals before or during heavy exercise. Some experts believe that in the large group of maturity-onset diabetic patients, who, under clinical treatment, do not show much glucosuria over the 24-hour period but may have some hyperglycemia, the consumption of sucrose in modest amounts may be harmless when it is a part of their restricted calorie diet. Consumption of high sucrose foods between meals as snacks, such as soft drinks or a glazed doughnut, is considered inadvisable by many diabetologists; but it is noteworthy that fresh fruits and fruit juices are commonly prescribed in diabetic diets. These usually contain substantial amounts of readily available glucose, invert sugar or sucrose.

A major problem in promulgating dietary guidelines to professionals and patients is that the dietary objectives differ greatly in the two main types of diabetes (West, 1977). In cases of juvenile-onset type diabetes or in pregnant women with diabetes, the diet must provide sufficient total calories to meet the growth and development requirements. Unlike most individuals with maturity-onset diabetes, who tend toward obesity, those with juvenile-onset diabetes are typically underweight, and dietary restrictions must be carefully balanced with provision of sufficient calories and essential nutrients. For patients with juvenile-onset diabetes who are receiving insulin, three main meals and a daily bedtime snack are recommended, with the added suggestion that a midmorning and/or a midafternoon snack may be useful (Anonymous, 1977a). Between-meal intervals should not exceed 5 hours except at night.
C. NONGLUCOSE CARBOHYDRATES AS SUCROSE SUBSTITUTES

It is commonly held that man has a preference for sweet-tasting substances, and scientific data suggest a preference for sweet-tasting substances by most human beings and many animal species (Kare, 1969; Lynch, 1971; Desor et al., 1973; Cagan, 1974; Moskowitz, 1974; Pangborn, 1974; Beidler, 1975). Satisfying the human craving for sweetness is often an important aspect of the process of acquiring good patient compliance with the diabetic diet prescription. For example, of 500 diabetic patients questioned by Mehnert (1971), only 84 expressed willingness to do without sweet-tasting foods. Fifty-seven regularly used sorbitol, eight used fructose, and 351 used either cyclamates or saccharin. (At the time of this study, xylitol was not generally available.)

To improve the acceptability and attractiveness of foods for individuals who prefer sweet items with their meals or snacks, investigators have long searched for sugar substitutes that would be compatible with diets for diabetic patients. Some desirable characteristics of a sugar substitute include appearance, consistency, taste, general ease of use, and cost comparable to sucrose. In terms of the metabolic problems of diabetic patients, the substitute should not lead to hyperglycemia, should not adversely affect the stabilization of metabolism of unstable diabetic patients, and should have no other undesirable effects.

1. Absorption and Metabolism.

Some nutritive carbohydrates that have been thought to approach the ideal sugar substitutes for use by diabetic patients are fructose, sorbitol, and xylitol. These have been called nonglucose carbohydrates. They are extensively used in diabetic diets in some Western European countries, particularly West Germany and Switzerland. Compared with sucrose, glucose and maltose, their use leads to less postprandial hyperglycemic peaking, a result in part of slower absorption; the hyperglycemia that does occur with these nutrients is slower in onset and of less magnitude, reducing the need for endogenous insulin in the postprandial period. They are absorbed from the alimentary canal more slowly and to a lesser degree than the ordinary dietary sugars (Dehmel et al., 1969).

In studies with human volunteers who received various test solutions intraduodenally, the amount of glucose absorbed after 30 minutes exceeded the amount of fructose, sorbitol or xylitol by approximately twofold, and, after 60 minutes, by more than threefold except with fructose, for which the difference was less. In rats that were sacrificed at intervals after intragastric administration of test solutions, the amounts of glucose or sucrose absorbed after 15 minutes' exposure were about twice those of sorbitol or xylitol, about 7 times greater than sorbitol or xylitol at 30 minutes, and at 60 minutes, glucose absorption was nearly 8 times and sucrose absorption 6 times greater than that of sorbitol or xylitol. In the rat tests, absorption of glucose and sucrose was greater than that of fructose except that, by 60 minutes, fructose absorption slightly exceeded that of sucrose (Dehmel et al., 1969). Mehnert and Förster (1975a) noted that, under the most favorable conditions for intestinal absorption, the degree of fructose absorption was estimated to be 40 to 50 percent, and sorbitol absorption not more than 10 percent of that of glucose. Xylitol absorption was estimated to be slightly greater than that of sorbitol (Mehnert, 1976; Mehnert and Förster, 1976).
Five healthy young men ingested xylitol in single doses of 4 to 30 g. Intestinal absorption, as measured by direct analyses of the ileal contents, varied between 49 and 95 percent (Asano et al., 1973). Absorption of xylitol did not vary significantly when the subjects ingested 30 g per day for periods of 2 to 3 weeks.

Aside from a dose-related osmotic diarrhea from excessive amounts of sorbitol and, to a lesser extent, xylitol, these substances are generally regarded as harmless when used as foods or food ingredients.

Unlike glucose, most of their initial metabolism occurs in the liver independently of insulin; however, because they are partly converted to glucose, their metabolism is not entirely insulin-independent (Froesch and Jakob, 1974). Nevertheless, in relation to the derangements of glucose metabolism in diabetes, less insulin is needed in a given period of time to keep the blood glucose level constant when some sucrose or glucose is replaced by fructose, sorbitol, or xylitol. Their partial conversion to glucose proceeds at a relatively slow rate governed primarily by their rate of absorption and the metabolic mode of the liver, gluconeogenic with low insulin and high glucagon, or glycolytic with high insulin and low glucagon; however, the degree of long-term reduction of insulin requirement has not been well demonstrated.

According to Cook (1969), 80 to 90 percent of ingested fructose is absorbed in the human jejunum as fructose, and is then rapidly taken up by the liver. In the liver (Figure 1), it undergoes transformation to fructose-1-phosphate and then to dihydroxyacetone phosphate and free glyceraldehyde (Mehnert and Förster, 1975a). Glyceraldehyde is subsequently phosphorylated to glyceraldehyde phosphate. The dihydroxyacetone phosphate and glyceraldehyde phosphate may then undergo glycolysis or transformation to fructose-6-phosphate and ultimately to glucose (Förster, 1974). Even when large doses of fructose are administered intravenously to human subjects, the available evidence indicates a conversion of about one-third to circulating glucose, suggesting that fructose metabolism is largely by the liver. In diabetic patients receiving as much as 450 g of fructose daily by continuous gastric intubation, no significant amount of fructose is detectable in the arterial blood (Shreeve, 1974).

Sorbitol and xylitol are also metabolized preferentially in the liver, sorbitol via transformation to fructose, and xylitol via D-xylulose-5-phosphate to glyceraldehyde phosphate and fructose-6-phosphate (Figure 1). Fructose-6-phosphate is convertible to glucose and glycogen, and glyceraldehyde phosphate to glucose, glycogen, and via the glycolytic pathway, to lactic acid (Froesch and Jakob, 1974).

Animal experiments have shown that substantial amounts of fructose, sorbitol, and xylitol are rapidly converted to glucose by the liver via the insulin-independent metabolic pathways outlined above and that the utilization of this glucose in such tissues as liver, muscle, and fat is clearly insulin-dependent. Nevertheless, these sugar substitutes do not produce significant hyperglycemia in normal (nondiabetic) animals and man in the postabsorptive state (Froesch and Jakob, 1974).

The theoretical and practical advantages of using fructose, sorbitol and xylitol in the diets of diabetics have been reviewed by Dehnel et al. (1969); Cook (1971); Lang (1971); Brin and Miller (1974); Mehnert and Förster (1975a,b; 1976); Scheinin and Mäkinen (1975); Touster (1975); Dwivedi (1977); and Turner et al., (1977). These investigators have reported the following general conclusions:

a. Fructose, sorbitol and xylitol are generally considered safe when taken orally.

b. Their ingestion does not result in significant post-prandial hyperglycemia or in the hyperglycemic peaking that follows ingestion of the rapidly absorbed simple sugars such as glucose and sucrose.

c. Less insulin is needed to keep the blood glucose constant in the postprandial period.

d. They are absorbed from the bowel more slowly than sucrose, glucose, and maltose, and are rapidly taken up by the liver in the absence of insulin.

e. They are metabolized principally in the liver, partially independently of insulin; they enter the metabolic pathway of glucose by different routes and at different steps.

f. Their metabolic conversion to glucose in the liver proceeds at a steady rate mainly determined by their relatively slow absorption and the nature of the sequence of hepatic metabolic reactions.

g. Fructose, sorbitol and xylitol tend to decrease ketogenesis.

h. Contrary to data from previous studies, recent investigations indicate that, compared with glucose, fructose, even in large amounts, does not increase blood triglycerides in humans.

i. Animal data indicate that some fructose is taken up by fatty tissues in the absence of insulin.

j. Patients who use these sugar substitutes tend to follow their diabetic diet prescriptions more faithfully than those whose physicians deny them access to such substances.

k. In fasting experimental animals, these substances exert a direct nitrogen-sparing effect that is not dependent on gluconeogenesis and insulin secretion.
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 (4.1.1.54)
5. L-Gulonate dehydrogenase (1.1.1.45)
6. Glucuronate reductase (1.1.1.19)
7. UDPglucose dehydrogenase (1.1.1.22)
8. Glucoseposphate 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 (5.1.3.11)

--- 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
1. They are superior to the nonnutritive artificial sweeteners for sweetening certain foods because they behave like sucrose during food preparation, requiring no additives for viscosity and bulking, and they do not leave an unpleasant aftertaste.

m. Except for sorbitol, they compare favorably with sucrose in sweetness, and under most conditions fructose confers more sweetness per calorie.

n. Xylitol appears to have noncariogenic properties that may be of great value and sorbitol has been shown to be substantially less cariogenic than sucrose.

In contrast to the experimental and clinical data that suggest the nonglucose carbohydrate sweeteners offer advantages in the dietary treatment of diabetes, Arvidsson Lenner (1976) reported no significant differences in postprandial blood glucose levels and glucosuria when isocaloric test meals containing sucrose, fructose, or sorbitol were fed to nine human adult diabetic and three healthy adult subjects.

3. Possible Disadvantages.

Side-effects of fructose, sorbitol and xylitol may be divided into those that have been clearly demonstrated and those that are suspected but unproven. The principal side-effect of glucose and sucrose administration is hyperglycemia. The nonglucose carbohydrates also cause hyperglycemia, but the degree is considerably lower compared with glucose (Förster, 1976). The relatively slow absorption of fructose, sorbitol, and xylitol from the intestine may result in osmotic diarrhea and flatulence when subjects ingest excessive amounts in single doses (Bässler et al., 1966; Dubach et al., 1969); for instance, single, diarrheagenic oral doses in humans have been reported as 70 to 100 g fructose, 20 to 30 g sorbitol, and 30 to 40 g xylitol. However, large individual differences exist in tolerance to these substances. Sustained use of xylitol leads to adaptation so that higher doses become tolerable (Dubach and Forgò, 1969). The practical amounts of these substances needed for use as sugar substitutes are generally below the laxation levels.

Well-known side-effects of high doses of most carbohydrates include increased serum uric acid, bilirubin and lactate, with a tendency toward acidosis (Baessler and Schultis, 1975). Fructose and the sugar alcohols produce several of these effects such as increased serum lactate levels and lactate-pyruvate ratios, and decreased concentrations of free fatty acids and phosphate (Förster, 1975; Förster et al., 1977). In addition, oral administration of fructose, sorbitol and xylitol, as well as sucrose, increases serum uric acid concentration (Förster, 1974). In a more recent report, Förster (1976) concluded that, except for the increase in uric acid synthesis, these sugar substitutes cause no specific and dramatic side-effects. However, in long-term studies with normal human subjects who ingested fructose or xylitol as part of the diet, serum levels of triglycerides, glucose, insulin, urate, lactate and pyruvate did not differ significantly from those of subjects who consumed sucrose as part of the diet (Huttunen et al., 1975).
Rapid intravenous administration of fructose, xylitol or sorbitol at high doses may result in increased uric acid production, a transient decrease of hepatic inorganic phosphate, and, mainly with fructose, increased lactate production (Donahoe and Powers, 1970; Schumer, 1971; Thomas et al., 1972 a,b, 1974; Wang et al., 1972; Froesch and Jakob, 1974; Förster, 1974; Touster, 1975). However, when these substances are infused intravenously at rates of 0.25 g per kg per h or less, as in the treatment of various stress situations such as postsurgically or in severe burns, the incidence of the so-called side-effects such as increase of serum bilirubin, lactate and uric acid and the decrease of ATP and total adenosine nucleotides in the liver is considered clinically insignificant (Förster et al., 1973/1974). No significant side-effects occur after oral administration of fructose, xylitol or sorbitol at levels that are isocaloric with average amounts of sucrose added to foods (Scheinin and Mäkinen, 1975; Förster, 1976).

Other investigators have a less sanguine attitude about the parenteral use of these substances. Thomas et al. (1974) reported adverse reactions to intravenous administration of solutions containing xylitol in 10 of 22 patients. The report suggests that solutions of up to 50 percent xylitol in distilled water were given. Individual patients exhibited one or more of the following: diuresis, lactic acidosis, hyperuricemia, crystal deposits of calcium oxalate in the renal tubules with tubular epithelial damage, oliguria, azotemia, and cerebral and hepatic disturbances. As a result, parenteral and oral use of xylitol was banned in Australia. It is noteworthy that the patients in these studies were all suffering from severe illnesses that may have compromised crucial physiologic functions such as renal excretion. Other investigators have reported similar reactions to intravenously administered xylitol (Donahoe and Powers, 1970; Schumer, 1971; Wang et al., 1972). Froesch and Jakob (1974) have emphasized the danger of lactic acidosis if large amounts of fructose, sorbitol or xylitol are administered parenterally.

Of the adverse reactions reported by the Australian investigators, the question of parenteral xylitol as a causal factor in the induction of oxalosis and deposition of calcium oxalate crystals appears one of the most pressing. A recent review of non-glucose carbohydrates in parenteral nutrition included the question of oxalate crystal deposits (Ahnfeld et al., 1975). These authors cited a report by Pesch et al., (1974) of 200 autopsies of patients who died in intensive care units, in which no statistical difference was found in oxalate deposits between those who had and those who had not received xylitol or other carbohydrates. Ahnfeld and associates (1975) concluded that observation of proper dosage guidelines avoids the possible side-effects that have been described including deposition of oxalate crystals.

It is known that certain experimental animals with severe pyridoxine deficiency develop hyperoxaluria and that this may possibly occur in man (Andrus et al., 1959; Faber et al., 1963; Ludwig, 1963).

Hauschildt and her associates (1976) conducted clinical investigations to determine whether 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, the thiamin and pyridoxine nutritional status of their 14 subjects was assessed and found to be within normal limits. Although
none of the patients showed hyperoxalemia or hyperoxaluria following xylitol infusions, glycolate excretion increased by two or three orders of magnitude together with an increased excretion of tetronic acids. The authors 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 involved in the reported Australian cases was abnormal renal function (Hauschildt et al., 1976). In addition, they concluded that, inasmuch as most patients are unlikely to have significant vitamin B6 deficiency, the oxalosis reported in deficient animals is not relevant to the clinical conditions in which xylitol is used. Wang et al., (1977) considered it highly unlikely that oxalate formation was the cause of the toxicity in the cases reported from Australia by Thomas et al., (1972a,b).

The possible influence of sorbitol and xylitol on cataract formation was discussed at the ad hoc group meeting, and the consensus was that exogenous sorbitol and xylitol have no specific or direct influence on cataractogenesis. This view is supported by the fact that the intact lens is nearly impermeable to sorbitol and xylitol (Chylack and Kinoshita, 1969; Froesch and Jakob, 1974). Glucose resulting from their metabolism in the liver could contribute to hyperglycemia in a poorly controlled diabetic patient. In the diabetic patient hyperglycemia accompanied by elevated glucose levels in the aqueous humor and lens may result in conversion of the glucose via aldose reductase and reduced nicotinamide adenine dinucleotide phosphate (NADPH) to sorbitol in the lens. These events are considered to be a major factor in cataract development in diabetic patients (Gabbay, 1973; van Heyningen, 1976; Kinoshita, 1976). However, oral sorbitol or xylitol does not enter the metabolic pool in the lens.

Hereditary fructose intolerance is a rare disorder in which a deficiency of hepatic fructose-1-phosphate aldolase leads to intracellular accumulation of fructose-1-phosphate following ingestion of fructose or sucrose (Froesch, 1972). Clinical signs and symptoms include severe hypoglycemia and vomiting and, in small children, a syndrome that may be fatal.

Consideration of the advantages and disadvantages of fructose, sorbitol and xylitol used as substitutes for glucose, sucrose and maltose, suggests that no obvious toxic effects result from their oral and parenteral use provided that intravenous use does not exceed 0.25 g per kg per h and oral intake is approximately isocaloric with average amounts of sucrose added to foods. For diabetic patients, their contribution to total caloric intake must be duly recognized. Fructose and xylitol may offer some advantage, albeit slight, over sucrose or glucose in diabetic diets. Because of its somewhat pronounced diarrheagenic characteristic and its relatively low sweetness, sorbitol was thought to provide little advantage to the patient in the dietary management of diabetes mellitus.

However, feeding trials being conducted at the Huntingdon Research Centre, England, suggest that xylitol in the diet produces tumors in experimental animals (Anonymous, 1978). Preliminary data from these studies indicate that mice fed xylitol at levels of 2, 10, and 20 percent of the diet for 2 years have increased urinary bladder calculi and an associated dose-related bladder epithelial hyperplasia and neoplasia in males receiving xylitol at the 10 and 20 percent levels (Schiffrin, 1977). Similar chronic xylitol feeding studies in rats and dogs at the same laboratory did not show the changes reported in the mice. However, male rats given 20 percent xylitol in the diet
showed an increased incidence of adrenal medullary neoplasms. Final conclusions from these investigations await completion of data analysis, and expanded studies have only recently been initiated. In this connection, it should be noted that Batzinger et al., (1977) have shown that xylitol exhibited no mutagenic activity in microbial assay and host-mediated assay test systems. Using a modified Ames test system with Salmonella typhimurium strains TA 100 and TA 98, these investigators found no mutagenic activity when xylitol was tested directly, in urine of mice fed xylitol both with and without liver microsomal fractions (S9), or in results of the host-mediated assay.

Concern for mutagenicity and carcinogenicity of xylitol requires that additional studies be undertaken to clarify the results reported in these two investigations.

D. EVOLVING CONCEPTS AND TRENDS

Further emphasis by physicians and dietitians on modern concepts of dietary management of diabetes may be expected to lead to a more general acceptance of the high-carbohydrate, low-fat diet and a greater interest in the need for safe and effective sugar substitutes. Additional support for the American Diabetes Association and The American Dietetic Association recommendations should accumulate as more clinical experience is reported on improved glucose tolerance and metabolic status of diabetic patients who receive careful dietary management. There are only limited critical data available that concern the long-term efficacy of dietary management on the complications of diabetes including diabetic angiopathies (Bierman, 1977). In addition, the role of certain environmental factors is unclear; for example, the effect of low molecular weight compounds in the diet, such as inositol, on diabetic neuropathy (Winegrad and Greene, 1976; Clements, 1977).

The results of two large clinical investigations, the Multiple Risk Factor Intervention Trial (Anonymous, 1976c) and the Lipid Research Clinics Coronary Primary Prevention Trial (Department of Health, Education and Welfare, 1977), that are supervised by the National Heart, Lung and Blood Institute may prove applicable to the dietary management of diabetes as well as to advances in the understanding of atherogenesis. Additional experience with combined dietary and pharmacologic treatment should also yield data that will aid in the improvement of dietary management.

Some experts believe that restriction of saturated fat intake may be as important as control of total caloric intake in terms of atherogenesis; however, control of total caloric intake is one of the primary goals in dietary management of obese, maturity-onset patients. Because of uncertainties about the possible long-term effects of consuming substantial proportions of polyunsaturated fats in the diet and because most patients require caloric restriction, the American Diabetes Association has not proposed a general recommendation for substitution of saturated with unsaturated fats in diets for diabetics; however, such substitution is suggested, particularly for diabetic patients with elevated serum triglyceride and/or cholesterol levels.

The question of liberalizing the use of sucrose or sucrose-containing foods continues to be of concern. Isocaloric substitution of small amounts of
natural or refined sucrose for other nutrients usually has little effect on levels of glycosuria or hyperglycemia. Nevertheless, in diabetic patients who are not well controlled, refined sucrose is not advisable, mainly because, when used as part of major meals, sugars tend to produce sharp elevations of blood glucose. Recently published data suggest the possibility of improving the selection of complex carbohydrates in the diet to minimize postprandial hyperglycemia and insulin response (Crapo et al., 1976, 1977).

Discussion of a possible role for high-fiber diets in diabetes indicated that, while the literature on this subject is sparse, some evidence exists that certain types of dietary fiber, such as pectin, added to meals reduce postprandial glycemia and glycosuria in diabetic patients (Jenkins et al., 1976, 1977; Kiehm et al., 1976). The type of fiber appears to influence the effect. For instance, in a study using the oral glucose tolerance test in normal subjects, bran added to the glucose drink improved tolerance, but bagasse (90 percent undigestible carbohydrate) and wood cellulose resulted in elevated blood glucose values compared with those of control subjects (Jeffries, 1974). Another study showed that increasing the total daily fiber intake (cellulose and pectins) of young women from 6.2 g to 31.9 g resulted in an increased gross energy intake from 2340 kcal per day to 2800 kcal per day, largely from increased sugar consumption (Southgate and Durnin, 1970). Effects of various kinds of dietary fiber deserve further study, but available data do not yet appear to warrant general recommendations with respect to increasing fiber in diets of diabetic individuals.

Economic, biologic and educational factors will influence the future use of the nutritive nonglucose carbohydrates. The industrial use of high-fructose corn syrup (approximately 42 percent fructose, 52 percent glucose) as a substitute for sucrose amounted to about 6 percent of the total sweetener market in 1975 (Kimura and Carr, 1976; Kolodny, 1976). However, a trend toward increased use of fructose is anticipated. Estimates of probable increasing use of high fructose corn syrup during the next 10 to 15 years vary from 14 to 30 percent (Cantor, 1975; Wardrip, 1975; Kolodny, 1976).

The biologic effects of long-term consumption of substantial amounts of fructose such as 100 to 150 g per day are not well known. Questions include the long-term effects on blood lipids, effects of a 50 percent substitution of sucrose by fructose, whether cariogenic bacteria may become fructose-dependent, whether toxic metabolites may result from an associated increase in Schiff-base formation, and the long-term effects on glycoproteins.

Certain manufacturers of xylitol and of foods in which sucrose is replaced by one or more of the nonglucose carbohydrates are marketing their products in this country at the present time or are preparing to do so. Two important findings that may stimulate the use of these substances are the non-cariogenic properties of xylitol and the technical advantages outlined above of the nonglucose carbohydrates compared to other nutritive sweeteners when used in the diabetic diet. A biologic factor of fundamental importance concerns the unsettled question of whether precise maintenance of normoglycemia in the diabetic exerts any favorable effect on the course of the disease. If future experience can document that it does, then the sugar substitutes may assume a firmer position as part of the diet provided that the issue of possible carcinogenicity of xylitol is resolved.
The fact that there is currently no generally acceptable artificial sweetener in the United States adds to the potential interest in these non-glucose carbohydrates. Because the nonglucose carbohydrates may offer some limited advantages when used as sugar substitutes in the dietary treatment of diabetes, interest in their use may be expected to increase.

Improved labeling of foods in terms of calories and percentages of carbohydrates, fats, proteins and other essential nutrients should facilitate selection of foods and menu planning for diabetic patients and physicians, dietitians and others involved.
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IV. SPECIAL FOODS IN THE DIETARY MANAGEMENT OF DIABETES

A. "DIETETIC" AND "DIABETIC" FOODS

In addition to the role of nutritive nonglucose carbohydrate sweeteners, the possible efficacy of and need for specially formulated foods in the dietary management of diabetes were central issues in this review. Consequently, considerable discussion was devoted to the so-called "dietetic" and "diabetic" foods and to a judgment as to whether foods for special dietary use intended specifically for diabetic patients can be identified and defined.

Confusion prevails about the meanings of such terms as "dietetic" and "diabetic" when they are applied to foods and food labels (Anonymous, 1976a,d; 1977c; Crumley and Bourdet, 1976). A recent FDA survey revealed that 22 percent of respondents understood the word "dietetic" on a food label to mean for use in a weight reducing diet and 28 percent understood the term to mean for use by persons with diabetes (Food and Drug Administration, 1977b). The balance of the responses was divided among 10 other answers. Similarly, 36 percent thought "diet" foods were for weight reduction and 9 percent thought they were for diabetic patients with the balance of the answers divided among 10 unrelated answers (Food and Drug Administration, 1977b). The recently published tentative order on label statements restricts the use of the terms "diet" and "dietetic" in or in relation to label statements on products identified for use by diabetic patients (Food and Drug Administration, 1977b).

On the basis of current information, it is unlikely that foods for special dietary use intended specifically for persons with diabetes mellitus can be delineated or defined on rational nutritional grounds. Few authorities support the notion that such special foods are necessary. In fact, with the possible exceptions of water-packed fruits and the artificially sweetened soft drinks, labels indicating usefulness in dietary management of diabetes are often undesirable and frequently misleading because patients may be led to believe that they may consume such foods freely without adding calories to their daily caloric allowance. Furthermore, the use of "dietetic foods" complicates the problem of estimating total caloric intakes and of dividing the diet into proper proportions of carbohydrates, proteins and fats, particularly for patients who use exchange lists.

The only rational support for the use of "dietetic foods" by diabetic persons is as convenient aids to weight reduction and control; however, such specially formulated foods are not necessary to restrict caloric intake or in the dietary management of diabetes per se. These opinions of the consultants are consistent with those expressed in the publications of diabetologists, nutritionists and others (Anonymous, 1976b, 1977a; Crumley and Bourdet, 1976; Gorman, 1977; Krall and Joslin, 1971; West, 1977).
Specially formulated convenience or snack foods considered useful in the diet of diabetic individuals, in addition to the water-packed fruits, are the artificially sweetened soft drinks such as the "diet colas." In some Western European countries, the jams, jellies, compotes and bakery products sweetened with fructose, sorbitol or xylitol are considered useful but are less widely recommended in the United States. Some diabetologists believe there is probably a need for an alternative to high-sweetness drinks, that is, a low-calorie, low-sweetness drink containing regular sweeteners. However, it is not known if this alternative would be technologically feasible, or would prove generally acceptable among diabetic patients.

A majority of consultants in this study concluded that there is little value in the use of the terms "dietetic" and "diabetic" on labels of foods intended for use by persons with diabetes mellitus; however, they favor retention of the term "foods for special dietary use." Food labels should be factual; for example, "water-packed, no sugar added."

B. SUGAR SUBSTITUTES

The ad hoc study group reached the consensus that fructose, sorbitol and xylitol are acceptable in diets of persons with diabetes mellitus and that, under certain conditions, they may offer slight advantages compared with the simple, rapidly-absorbed sugars such as glucose, sucrose, and maltose. Sorbitol offers even less advantages than fructose or xylitol because it is less sweet and has a greater potential for causing osmotic diarrhea. However, information is needed on the diurnal, intermediate and long-term influences of each of these nonglucose sweeteners on the course of diabetes. There is a particular need to develop data on their long-term effectiveness when ingested as part of mixed meals rather than as pure substances given to fasted subjects.

The most significant of these advantages in relation to diabetes mellitus is that, when administered orally or intravenously, they do not cause a precipitous peaking of blood glucose levels; the hyperglycemia that does occur is less, as is the insulin response; they are nonketogenic; serum free fatty acids tend to decrease; and fructose, even in large amounts, does not elevate blood triglycerides when substituted isocalorically for other carbohydrates in man. Thus, some experts conclude that these nonglucose carbohydrates exert less stress on blood glucose regulation. In addition, they are technically superior to the artifical sweeteners for use in some foods such as bakery products, jellies, jams, compotes, and canned fruits because in food processing they behave similarly to sucrose. Fructose under some conditions is somewhat sweeter than sucrose; thus it offers equal sweetness for less calories.

The investigations on which the foregoing opinions were based involved animal and human studies in which the sugar substitutes were given parenterally or ingested in the fasting state without meals, and, in a very few cases, given with mixed meals. The results were essentially similar with regard to blood glucose and insulin responses as well as other parameters measured. However, the number of reports of studies in which the sugar substitutes have been administered with meals is very limited; furthermore, little is known about
the influence of sugars and the nonglucose carbohydrates on blood glucose levels during the longer fasting intervals such as between the evening meal and breakfast or on a diurnal basis. As reported by Bierman (1977), only one study of a long-term nature on the effects of diet on diabetes has been reported (Stone and Connor, 1963).

Thus, the available scientific information is insufficient to justify firm conclusions about the influence of diets and dietary components, including the sugars and sugar alcohols, on the diurnal average values and excursions of blood glucose and insulin and on the long-term course of the diabetic syndromes.

In summary, leading authorities on the dietary management of diabetes mellitus affirm that the main emphasis in obese patients should be on control of caloric intake to achieve and maintain ideal body weight. Most authorities now recommend that dietary fat and sugar be reduced and that the proportion of calories as starch be increased in both of the main types of diabetes (obese, insulin-independent and lean, insulin-dependent). In addition, they believe there is a need for only a very few special foods for diabetic patients, specifically the water-packed fruits and the artificially sweetened, low-calorie soft drinks. Some diabetologists believe there may be a need for a selection of foods sweetened with the nonglucose carbohydrates; for instance if nonnutritive sweeteners such as saccharin are not available, then soft drinks containing a nonglucose carbohydrate sweetener might be as useful as the artificially sweetened soft drinks in terms of palatability and acceptability provided that their long-term influence on blood sugar levels were innocuous.
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V. FINDINGS AND CONCLUSIONS

A. PRINCIPAL CONCLUSIONS

• There are insufficient data to determine if sorbitol, xylitol or other polyols substituted for conventional sweeteners such as sucrose, or when indigenous to food, have special nutritional or other significance in the long-term dietary management of diabetes. When fed as pure substances to fasted subjects, these non-glucose carbohydrate nutritive sweeteners are absorbed relatively slowly and produce less postprandial hyperglycemia and insulin response than sucrose or glucose. However, adequate studies of their long-term effectiveness when ingested as a part of mixed meals have not been conducted.

• There are insufficient data to determine if fructose or any other carbohydrate has beneficial properties for the long-term dietary management of diabetes. When fed as a pure substance to fasted subjects, fructose is absorbed fairly slowly and postprandial hyperglycemia and insulin response are less than those with sucrose or glucose. However, adequate studies of the long-term effectiveness of fructose ingested as a part of mixed meals have not been conducted.

• Despite these deficiencies in knowledge, the ad hoc review group acknowledged that the use of sorbitol, xylitol or fructose is accepted by reputable European diabetologists and that these substitutes may provide some minor advantages in dietary management of diabetes mellitus.

• The evidence that other foods or food ingredients may have beneficial properties in the dietary management of diabetes mellitus is limited. Special foods for diabetic individuals are not necessary to achieve objectives of dietary management and dietary principles recommended by leading United States and European authorities. These recommendations and dietary principles can be followed conveniently at minimum expense through enlightened choices of commonly available food items.

• There is no evidence suggesting value of dietetic foods in the dietary management of diabetes other than their usefulness in weight reduction or weight control.

• Specific and unique characteristics of food products with special therapeutic properties for diets of diabetic individuals cannot be delineated or defined on rational nutritional grounds.
B. DETAILED FINDINGS AND CONCLUSIONS

1. DIABETES AND ITS DIETARY MANAGEMENT

- Dietary management, insulin or oral hypoglycemic drug treatments, or a combination of these, are used in the clinical management of diabetes mellitus. The disease, a syndrome with multiple causes, is incompletely understood.

- In 1971, the American Diabetes Association published a major revision of its recommendations for dietary management of diabetes mellitus which emphasized: restriction of total caloric intake to achieve and maintain ideal body weight; increase in the proportion of dietary carbohydrate to 45 to 60 percent with corresponding reduction in saturated fat calories; prevention of abnormal blood glucose excursions by regularity of eating and exercise, proper spacing of between-meal intervals, and limiting refined sucrose in the diet. These general guidelines are useful in the dietary management of both juvenile- and maturity-onset diabetes.

- The quality and quantity of education of physicians, dietitians, nurses and patients in the principles and practice of dietary treatment of diabetes must be improved if progress in dietary management is to be realized.

- In juvenile-onset diabetic patients, the diet must provide sufficient calories for growth and development and yet be designed and scheduled in relation to total calories, insulin requirements, exercise, sleep and other between-meal intervals to prevent hyperglycemic and hypoglycemic swings. A current goal of the American Diabetes Association is to develop recommendations for more precise dietary control by patients with juvenile-onset diabetes.

- Although diabetologists advocate that refined sucrose be omitted from diets of persons with diabetes mellitus, scientific data to support total omission are lacking. The consultants agreed that small amounts of sucrose may be permitted in the diets of diabetic patients under certain conditions; nevertheless, most experts favor curtailment or elimination of refined sucrose from diets of diabetic patients.

- While exceptions are recognized, most human beings have a strong inherent or acquired preference for sweet items as part of their diet. Most diabetologists believe that withholding of sweet foods in diet prescriptions is a frequent cause of rejection of their diets by patients.
Based on the concept that diabetic outpatients will follow dietary directions if allowed sweet items in their diets, European experts have long searched for sugar substitutes with high consumer acceptability and compatibility with the disturbed carbohydrate metabolism of diabetic patients. Fructose, sorbitol, and xylitol, referred to as nonglucose carbohydrates, have properties that theoretically make them attractive as sucrose substitutes. They are available for this purpose in some Western European countries such as Germany, Switzerland, and Finland. The only significant restrictions to their oral use are that they are approximately isocaloric with sucrose, and that in excessive loading doses, sorbitol and xylitol may cause osmotic diarrhea.

Fructose, xylitol and sorbitol are extensively used in Germany and Japan for parenteral nutrition, especially in postsurgical stress states. Despite several clinical reports to the contrary, they cause no significant side-effects when used parenterally at dose rates not exceeding 0.25 g per kg per h. Investigators in Germany and Japan have stated that this clinical experience adds credibility to the conclusion that they are safe for oral use as sugar substitutes; however, recent questions related to possible carcinogenicity of xylitol must be resolved.

The main physiologic advantages of fructose, sorbitol and xylitol in the usual oral doses are the reduced hyperglycemia, hyperglycemic peaking and insulin response resulting from their relatively slow intestinal absorption and rapid hepatic uptake. However, these observations are based almost entirely on studies with pure test substances in fasting animals and human subjects. Essentially no data are available on their use with mixed meals. Thus, on the basis of available evidence, the question of whether they have special beneficial properties for use as part of the diets for diabetic individuals cannot be answered fully. Nevertheless, the ad hoc review group acknowledged that their use in diabetes is accepted by reputable European diabetologists and that these substances may provide some minor advantages in dietary management of diabetes mellitus.

Rational expansion of the use of fructose or xylitol in the dietary management of diabetes mellitus must await additional clinical data on their acute and chronic effects when ingested as a part of mixed meals. However, the ad hoc group suggested that if soft drinks with nonnutritive sweeteners are unavailable, then soft drinks sweetened with nonglucose carbohydrates might prove as useful as the artificially sweetened drinks in terms of palatability and acceptability provided that their long-term influence on blood sugar levels were innocuous.
The apparent advantages of xylitol in the dietary management of diabetes as well as its possible potential as a noncariogenic sweetener appear to be stimulating increased attempts at confirmatory investigations and commercial development.

Available evidence and scientific opinion suggest that sorbitol offers few advantages as a sugar substitute for use by diabetic patients because of its relatively greater potential to induce diarrhea and its low level of sweetness compared with fructose or xylitol. It offers no advantage in controlling caloric intake.

In general, there are no unique requirements for vitamins and minerals by diabetic patients; however, certain specific situations in diabetes may require supplements; for example, added thiamin may be required in the uncontrolled, insulin-dependent patient.

There is evidence that certain types of dietary fiber, such as pectin, reduce postprandial hyperglycemia in normal subjects; however, other types of dietary fiber appear to have the opposite effect. Future studies may show that certain types of dietary fiber may prove beneficial as part of the dietary management of diabetes mellitus.

Control of saturated fat intake may be as important as reduced total caloric intake in retarding the accelerated atherogenesis of diabetes; however, there are uncertainties about the long-term effects of large amounts of unsaturated fats in the diet.

Despite a general consensus of leading diabetologists on the principles of dietary management of diabetes mellitus, uncertainty exists about the long-term efficacy of dietary treatment. Nevertheless, there is nearly unanimous agreement that maintaining blood sugar levels within normal limits by all available means, including dietary management, is essential. This includes the prevention of hyperglycemia as well as hypoglycemic episodes which may lead to brain damage. Notwithstanding the prevailing opinion about the importance of the diet, the key question of whether or not diet retards the development of the debilitating concomitants and complications of diabetes mellitus has not been answered. Lack of clearly documented proof of the efficacy of long-term dietary management of diabetes mellitus has deterred the unanimous adoption of current dietary recommendations by clinicians and dietitians in the United States.
2. FOODS FOR SPECIAL DIETARY USES

- A selection of confections, dessert products, and preserves sweetened with the non-glucose carbohydrates is generally available for diabetic patients in Europe. The acceptance of these products in the dietary management of diabetes is less well established in the United States.

- In the United States there are several hundred food products whose label statements include terminology indicating they contain decreased or no calories, sugars, carbohydrates, or fats and/or that they are "diet," "diabetic," "for diabetics," or are artificially sweetened. The wide variety of these products ranges from non-alcoholic beverages through food categories including baked goods, grain products, milk products, cheese, confections, preserves, fruits, salad dressings, meat products, soups, and snack foods. While most contain nutritive sugar substitutes such as saccharin, some contain nutritive sugar substitutes such as fructose, sorbitol, xylitol, or mannitol.

- Terms such as "diet," "diabetic," and "diabetic" on food labels have no uniform meaning for consumers. There is evidence that significant numbers of people understand "dietetic" and "diet" on food labels to mean for use by persons with diabetes. The so-called "dietetic," "diet," "low-" and "reduced calorie" foods may be useful in weight reduction and weight maintenance; however, beyond the fact that they include popular types of foods with reduced calories and/or restricted amounts of sucrose, they offer no specific therapeutic advantage to diabetic patients. "Diabetic" and "dietetic" on food labels are misleading to diabetic patients, many of whom think such foods may be eaten without restriction. Thus, there is sufficient justification to curtail the use of these terms on labels for foods intended for use by diabetic patients.

- In July 1977, the Food and Drug Administration published a proposed tentative order with an effective date of July 1, 1979, that would require revision of label statements for those special dietary foods for use in reducing or maintaining body weight or caloric intake or for use in the diet of persons with diabetes mellitus. These regulations would prevent mis-leading label statements on foods that are not useful for these purposes. Among its provisions, the order would restrict the manner in which such terms as "diabetic," "dietetic," and "diet" may be used on the labels of foods for use in the diets of persons with diabetes.
The American Diabetes Association emphasizes that the basic nutritional requirements for persons with diabetes mellitus are generally the same as those for normal individuals and suggests that the National Research Council's Recommended Dietary Allowances can be used as a basic nutritional guide. However, certain special nutritional requirements of diabetic patients must be observed, such as the use of complex carbohydrates in place of the rapidly absorbed simple sugars, and substitution of some fat calories by starches. These dietary principles can be followed conveniently, at minimum expense, through the proper choices of commonly available food items. Thus, for practical purposes, even if foods for special dietary use intended specifically for diabetic individuals could be devised, they are not necessary for adequate dietary management. It appears that such foods, with the exception of the artificially sweetened soft drinks and the water-packed fruits, cannot be delineated or defined on rational nutritional grounds.

Some experts believe that there may be a need for a low-calorie, low-sweetness drink using regular sweeteners; however, the possible acceptability of such a product is unknown. While foods with low or reduced calories may be useful in the dietary management of diabetes because they provide a means for reducing caloric intake and avoiding rapidly absorbable simple sugars, special foods for persons with diabetes mellitus, except the artificially sweetened soft drinks and the water-packed fruits, are unnecessary.
VI. SUGGESTIONS FOR FUTURE CONSIDERATION

• More data are needed on the metabolic effects of substitute nutritive sweeteners such as fructose, xylitol and sorbitol in foods as they are consumed in regular diets. For instance, prospective studies are needed on 24-hour and 30-day effects on blood sugar, insulin response and other parameters as a result of administering varying amounts of fructose, sucrose, sorbitol, and xylitol in different combinations in the diets of (1) persons with mild cases of adult-onset diabetes where fasting blood sugars are normal but glucose tolerance tests are abnormal; (2) mild or moderately severe maturity-onset diabetes patients with persistent fasting hyperglycemia; and (3) juvenile-onset, lean, insulin-dependent diabetic individuals. The effects of controlling blood glucose during the 24-hour period as well as from minute-to-minute are not well defined. The results of such studies would suggest a series of other important avenues of research.

• More clinical and metabolic data are needed on the effects of foods sweetened with fructose and other sucrose substitutes used as parts of the main meals versus between-meal snacks and drinks in the acute management of patients with insulin-dependent diabetes.

• Certain studies of the effects on blood glucose levels and urinary glucose losses of substituting fructose or sorbitol for sucrose in prescribed diabetic breakfast meals suggest that fructose or sorbitol has little, if any, advantage over sucrose in well-regulated patients with maturity-onset diabetes mellitus. It appears unnecessary to have specially sweetened foods designed for adult individuals with this type of diabetes. The differences between these results and other studies showing metabolic advantages for fructose, sorbitol, or xylitol in the dietary management of diabetes should be resolved using both insulin-dependent and insulin-independent diabetic subjects.

• More animal and prospective clinical and epidemiological studies are needed to determine what elements of the diet are crucial in terms of the debilitating concomitants of diabetes; for example, neuropathy, retinopathy, and coronary artery disease.

• Additional investigation of fructose metabolism in normal and diabetic animals and human subjects is needed. Examples of pertinent questions include the effects on blood lipids when substantial amounts of fructose such as 100 to 150 g per day are consumed; the long-term effects of reducing sucrose intake by 50 percent and replacing this with fructose; whether or not the cariogenic bacteria may become fructose- rather than glucose-dependent; the long-term
effects on glycoproteins; and whether or not toxic metabolites may result from the more rapid formation of Schiff-bases with fructose compared with glucose.

- Additional studies are required on the effects of fructose, xylitol and sorbitol on glycoproteins in relation to atherosclerosis, particularly in human subjects.

- The possible carcinogenicity of orally administered xylitol requires concerted attention if this nutritive non-glucose sweetener is to have a greater role in dietary management of diabetes mellitus.

- The effects of fructose, sorbitol, and xylitol on weight reduction and weight maintenance in obese diabetic patients should be investigated. In addition, their ability to support weight gain in the juvenile-onset diabetic patient requires investigation.

- More comparative data are desirable on the relative sweetness of products prepared with fructose as they might be consumed in typical American diets.

- There is insufficient scientific information on the influence of dietary fiber on the absorption and metabolism of carbohydrates to determine its possible beneficial or adverse effects. The absence of hyperglycemia that has been reported in subjects taking certain types of dietary fiber with their diets may be a result of interference with carbohydrate absorption. The influence of the level and type of dietary fiber on carbohydrate absorption needs clarification.

- Uncertainties about the long-term effects of large amounts of unsaturated fats in the diet on the course of diabetes mellitus require further investigation.

- Additional investigations are advisable on the influence of certain environmental factors on the prevention and amelioration of diabetes complications, for example, small molecular weight compounds such as inositol in relation to neuropathy.

- Although difficult to obtain, more information is needed on the comparative risks of disturbed carbohydrate metabolism and development of complications in diabetic patients who consume refined sugar versus those who avoid it, and how much refined sugar is allowable particularly for persons with insulin-dependent diabetes. Similarly, there are unanswered questions about the advisability of a liberal carbohydrate diet for individuals with moderately to poorly controlled diabetes.
VII. LITERATURE CITED


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