Saccharin

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Saccharin, a nonnutritive sweetener discovered in 1879, has been the subject of controversy concerning its effect on public health on several occasions during this century. Over this period, the substance has come to be regarded as a useful commodity in the dietary management of diabetes mellitus. We review the historical and scientific background on the subject and propose a new approach in making public-health decisions on unique foods that serve a special dietary purpose. *Diabetes Care* 12:75–80, 1989

Saccharin and diabetes mellitus are a substance and a pathologic condition whose association was described in Funk and Wagnall's *New Standard Encyclopedia* in the 1930s: "Saccharin . . . finds use as a sweetening agent, especially for persons who should not eat sugar, owing to disease, as diabetes." Saccharin, the oldest nonnutritive sweetener in the American food supply, has a colorful and intriguing history, the details of which are difficult to cover fully here. Given that the focus of this symposium is on the need for, or usefulness of, sweeteners in the diets of individuals with diabetes mellitus, we recount some of the pertinent historical events dealing with saccharin while concentrating on the conclusions and recommendations of public-health and other professional organizations on the use of saccharin by diabetic subjects.

In 1879, saccharin, a coal tar derivative, was synthesized accidentally by an American chemist, Constantin Fahlberg, who worked in the laboratory of Ira Remsen at the Johns Hopkins University. Their work was reported that same year in the German scientific literature with an article titled *On the Oxidation of Orthotoluenesulphamide* (1) and the following year in the *American Chemical Journal* (2). Initially, saccharin was intended to be used as an antiseptic agent in the treatment of urinary tract infections. However, its potential as a sweetening agent was readily apparent, and it soon came to be used as a substitute for sugar in canned vegetables and beverages that were subject to heat damage due to lack of refrigeration. Shortly after its discovery in 1879 until the beginning of World War I, saccharin was at the center of international commercial intrigue and a major controversy concerning food safety and quality. We review some of the history surrounding saccharin for interest, amusement, and pertinence to this discussion.

Throughout the last two decades of the 19th century, commercially produced saccharin was manufactured only in Germany. Marketing of the sweetener was rigidly controlled by a powerful cartel of six German firms, known as the Dye Trust. By 1901, John Francis Queeny, a purchasing agent for a pharmaceutical house in St. Louis, Missouri, became impressed with the commercial potential of the synthetic sweetener by its increase in sales to a growing list of customers (3). Queeny became convinced that an American enterprise could profit by producing the substance in the United States and selling it to the major commercial users of sugar, including those involved in the production of soft drinks, candy, tobacco products, and other commodities. The arithmetic was simple, sugar sold for $0.06/lb and saccharin for $4.50/lb. However, because of its intense sweetening capacity, the equivalent cost of saccharin was less than $0.01/lb. Having arranged with the Sandoz Company in Switzerland to provide a proficient chemist along

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with a supply of the key intermediate chemical needed in the synthesis of saccharin, Queeny filed papers of incorporation in 1901 for Monsanto Chemical Works, Monsanto being his wife's maiden name. The early years of the new company were very precarious because the only commodity produced was saccharin and it did not take long for the Dye Trust to take notice of an upstart American firm daring to compete with what was considered to be their proprietary product. The cartel's method in dealing with such fledgling outfits was merciless and almost always effective in stifling competition before it grew big enough to become bothersome. They simply dropped the market price of saccharin from $4.50 to 1.00/lb in anticipation of driving the struggling competitor into bankruptcy, at which point the price would be raised to whatever level the market would bear. The tactic almost succeeded, but Monsanto survived to become a giant in the chemical industry. Monsanto's birth was based squarely on saccharin, and its founder was a participant in a larger drama that occurred before World War I concerning the pros and cons of the sweetening substance.

At the beginning of this century, a struggle ensued to establish the basis for the safety and quality of food and drugs in the United States. The preeminent champion of this endeavor was Harvey W. Wiley, who was driven by a moral responsibility, one might even say a religious conviction, to establish a national law that would guarantee the purity and wholesomeness of food and drugs. This milestone was achieved in 1906 when President Theodore Roosevelt signed the Food and Drugs Act into law. In the words of Wiley, "I am sure I may be pardoned for feeling that the thirtieth of June 1906 marks an important date in history; certainly it is important in the long and proud record of legislation seeking to guard the well-being of men, women, and children" (4). With enactment of this law, the storm clouds of controversy had begun to form. A feeling of deja vu arises, considering that some of the contentious issues of the day dealt with the addition of such substances as sulfites, caffeine, and saccharin to foods. Wiley was convinced that the replacement of sugar by saccharin in a food constituted adulteration under the new law on two counts. *1*) He felt that saccharin consumption led to health injury, and 2) such substitution debased the quality of a product. In 1908, a meeting was scheduled at the White House to arrive at resolutions on the use of several additives, including saccharin, in foods. The subject was broached by Congressman James Sherman of New York who told President Roosevelt that his firm of food packers had saved $4000 the previous year by using saccharin instead of sugar in sweet corn. At that point, Wiley interjected, "Yes, Mr. President, and everybody who ate that corn thought they were eating sugar, whereas they were eating a substance which was highly injurious to health." Whereon, in Wiley's words, the President turned toward him and, with clenched fists, hissed angrily through his teeth, "You say saccharin is injurious to health? Why, Dr. Rixey gives it to me every day. Anybody who says saccharin is injurious to health is an idiot!" (4,5).

His decision made, Roosevelt recruited a five-man Referee Board of Consulting Scientific Experts headed by the President of Johns Hopkins and codiscoverer of saccharin Ira Remsen. The board was charged to rule on saccharin and other substances to determine if their addition would either render a food injurious to health or reduce, lower, or injuriously affect quality. Some accounts of these events conclude that the Referee Board gave saccharin a clean bill of health. This is not quite true. From 1911 to 1912, four Food Inspection Decisions were issued with regard to the use of saccharin in food (6–9). It was concluded that in a normal diet, daily ingestion of saccharin was not likely to exceed 0.3 g, an amount considered to be harmless. Consumption of a greater amount was considered liable to impair digestion. In addition, because saccharin had no food value, substitution of it for sugar lowered the quality of a food. On this basis, foods sweetened with saccharin were considered adulterated under the law. Two Food Inspection Decisions came to an additional conclusion (8,9). It was recognized that "persons suffering from diseases may be directed by their physicians to abstain from the use of sugar. In cases of this kind, saccharin is often prescribed as a substitute sweetening agent." It was stated further that any substance intended to be used for the prevention, cure, or mitigation of disease was a drug under the Food and Drugs Act. A product containing saccharin and plainly labeled to show that the intended use was for individuals who, on account of disease, must abstain from the use of sugar fell within the class of drugs. Although not mentioned by name, at least one disease or medical condition to which this conclusion certainly applied was diabetes mellitus.

Trying to bring these various pieces together, mention was made of Queeny, the founder of Monsanto, who in 1911 was having difficulty acquiring data in support of the safety of saccharin. Accordingly, he inquired gingerly into the personal sweetening proclivities of then former President Teddy Roosevelt. In a letter dated 7 July 1911, the following reply was received: "I always completely disagreed about saccharin, both as to the label and as to its being deleterious. . . . I have used it myself for many years as a substitute for sugar in tea and coffee without feeling the slightest bad effects. I am continuing to use it now. Faithfully yours, T. Roosevelt" (5). As testimonials go, clearly this must be considered a heavyweight.

The Food and Drugs Act of 1906 was superseded by the Federal Food, Drug, and Cosmetic Act of 1938. Under this law, a new category of "foods for special dietary uses" was created for which "special dietary uses" were defined, in part, as those for "supplying particular dietary needs which exist by reason of a physical, physiological, pathological, or other condition, including, but not limited to, the conditions of disease." Among the findings from the hearing conducted for the promulga-

tion of regulations on label statements for foods for special dietary uses were the following (10): *1*) Saccharin, alone or in combination in a saccharin salt, is a nonnutritive sweetening substance sometimes used to satisfy the psychological desire for sweets in the diets of people who must restrict their intake of carbohydrates. It has no other use as a food and is not utilized in normal metabolism. *2*) Information necessary to inform the purchaser of the value of a food for special dietary use by reason of its saccharin content is a statement that it contains a specified percent by weight of saccharin, a nonnutritive artificial sweetener that should be used only by people who must restrict their intake of ordinary sweets.

There were other labeling requirements, but the important point to be made was the recognition of an appropriateness for use of a nonnutritive sweetener to satisfy a psychological desire for a sweet taste. Two of the regulations promulgated in 1941 were superseded in 1979 by two other regulations, currently in effect, that generalized the class of special dietary foods sweetened with saccharin and identified two categories of food that are distinct but not necessarily exclusive of each other (11). One of the two regulations provides definitions and label statements for special dietary foods used in reducing or maintaining body weight or calorie intake. This regulation is commonly referred to as the one dealing with low-calorie and reduced-calorie foods. The second regulation provides for a label statement to identify special dietary food useful in the diet of diabetic subjects.

In April 1977, the Food and Drug Administration (FDA) proposed a ban on saccharin because the agency had accumulated sufficient information from chronic bioassay tests indicating that saccharin may cause cancer (12).

As to the biology and toxicology of saccharin, saccharin is stable at physiological pH and temperature and is well absorbed in the body. It does not accumulate in body tissues and is excreted unchanged in the urine and feces. It is not metabolized in species, including the rat, humans, and rhesus monkey, in which it has been studied, and there is no known metabolite in mammals. In addition, saccharin is not electrophilic and does not bind covalently with DNA in the liver or bladder of rats, nor does it produce other cellular effects considered traditionally to be part of the process of carcinogenesis.

In terms of mutagenicity and carcinogenicity, saccharin has been extensively studied, but the data have been extremely difficult to interpret (13). The compound is nucleophilic and therefore unlikely to be attracted to, or react with, DNA. With minor exceptions, saccharin is consistently negative in the Ames test, with or without metabolic activation or under host-mediated conditions. The results of in vitro mammalian tests for gene mutation appear to be negative, with only a few positive results at very high doses. Saccharin is therefore unlikely to affect DNA directly and probably does not cause gene mutations. It does not appear to cause chromosomal effects, except at very high doses and with inconsistency. One hypothesis argues that it interferes with DNA repair by an as yet undefined mechanism. As a result, it is not clear whether the effects of saccharin reflect specific gene toxicity or nonspecific toxicity.

Numerous chronic toxicity tests extending over several generations with laboratory rats have consistently indicated that saccharin causes a dose-related increase in the number of bladder tumors (14). This is particularly true in studies where the fetus is exposed in utero and exposure continues after birth. A recent study by the International Research and Development Corporation produced results that were consistent with earlier studies in the United States and Canada and at the FDA.

Several human epidemiological studies have been conducted in the search for an association between bladder cancer and artificial sweeteners (15). These studies support the generally accepted conclusion that users of saccharin or cyclamate do not have a measurably increased risk of bladder cancer. However, most of the studies have one or more limitations to their usefulness. In part, these revolve around the patterns of consumption and the forms of saccharin available through the 1960s.

Several recent animal studies have raised additional questions concerning the mechanism of action of saccharin. There is widespread agreement that saccharin is probably not an initiator but acts as a promoter of carcinogenesis in the bladder. Work done in several laboratories, including the National Center for Toxicological Research of the FDA, supports the idea that saccharin may indeed be acting as a promoter, particularly at levels >0.1% of the diet. Other studies have recently argued that the effects of saccharin salts are not those of saccharin itself but rather of Na^+. Ashby (13) has suggested that the profile of genotoxic activities associated with NaCl is almost identical to that of sodium saccharin. He suggests that the reported genotoxic and cancer-promoting activities of both sodium saccharin and NaCl only become apparent at elevated dose levels that make them significant contributors to the biological medium. Further complicating the issue have been the various risk assessments done on saccharin. Depending on the model chosen, the data can vary by as much as three orders of magnitude, from 1/10,000 to 1/10,000,000. There is a great deal of controversy over which model best suits the data.

Although there appears to be no question that saccharin is a weak carcinogenic substance in animals, the controversy concerning its mechanism and the level of human risk it actually poses has led to confusion on the part of the public concerning the hazards associated with the consumption of saccharin. As a result of this confusion, and in response to the 1977 proposal, the 95th Congress reacted by passing the Saccharin Study and Labeling Act (Public Law 95-203) that prohibited the FDA from banning saccharin based on the information then available. The congressional moratorium has been extended several times and is currently sched-

uled to expire on 1 May 1992. The Saccharin Study mandated in 1977 assessed not only the risks but also the benefits attributed to saccharin (16). Part 1 of the study, released in November 1978, stated that the data on the efficacy of saccharin in dietary management of health problems were scarce and in many cases inadequate. Regarding the benefits to physical health, it was concluded that the scientific evidence did not permit assessment of the role that saccharin plays in weight control or dietary compliance, both key factors in the prevention or treatment of obesity and diabetes. Another conclusion was that, as for other sweeteners, information on the efficacy of saccharin in health maintenance, e.g., the dietary management of health problems, was sparse and usually inadequate. Another conclusion was that diabetic individuals, particularly the young, would be subjected to psychological stresses if artificially sweetened foods and beverages that permit a more normal life-style were removed without a suitable replacement. Nevertheless, the committee was unable to evaluate the implications of such psychological reliance on saccharin.

Several recommendations or statements have been made within the past 10 yr by professional health organizations that deal directly or indirectly with diabetes mellitus. Reacting to the FDA's proposed ban, the American Diabetes Association (ADA) issued a policy statement in 1979 that more research was needed to solve the saccharin controversy and there was little justification for placing further governmental restrictions on the use of saccharin by the American public (17). In a 1985 update of that statement, the major benefits of saccharin were identifed as an improvement in quality of life, low cost, and stability at warm temperatures (18). Three alternative sweeteners mentioned in the statement are saccharin, aspartame, and cyclamate. The suggestion is made that such sweeteners be used in a prudent way by children, pregnant women, and women in their childbearing years. Finally, it is said that combined use of artificial sweeteners should be encouraged to minimize the risk from any one sweetener, and continued research into the possible risks of long-term use of saccharin and other sweeteners, either alone or in combination, should continue. In 1986, ADA developed another policy statement on nutritional recommendations and principles for individuals with diabetes mellitus (19). With regard to alternative sweeteners, it is stated that the use of such sweeteners of both the noncaloric (e.g., aspartame and saccharin) and the caloric (e.g., fructose and sorbitol) varieties is acceptable in the management of diabetes. It is also said that, if sweeteners are used, the use of various sweeteners, each with its particular advantages, is recommended to distribute any potential risks. On two other points, it was mentioned that excessive intake of any sweetener requires nutritional counseling and that better labeling is needed to inform consumers about the sweeteners contained in food. It was said again that continued research is needed to identify the risks and metabolic effects of long-term use of individual sweeteners and combinations of sweeteners in humans, particularly in individuals with diabetes. Because their intake as a group may be greater than that of the general population, specific studies on children, adolescents, and adults were necessary. Finally, a need was stated for more information about the diabetic palate and the preference for sweeteners in children and adults to determine actual needs for alternative sweeteners.

In 1979, the American Dietetic Association issued a statement on saccharin that considered the benefits and risks of its use (20). Noting that even though it is sometimes difficult to assess risk, it is usually possible to describe the benefits. A question was raised as to an appropriate approach to measure the benefits of a nonnutritive sweetener in relation to obesity and diabetes when there may only be psychological benefits. Nevertheless, it was also stated that there was no scientific evidence available at the time either in support of or against a substantial benefit of saccharin. Accordingly, among the various conclusions of the American Dietetic Association was one in support of the need for continuing research on the dietary uses of saccharin and other nonnutritive sweeteners. This was identified to include clinical studies to gather evidence on the use of nonnutritive sweeteners to characterize user groups and to determine the impact of such use on the simultaneous intake of nutritive sweeteners and total calories. In addition, there was support for studies to identify benefits, whether psychologic or physiologic, in the prevention or control of disease.

In 1985, a study was performed by the Committee on Nutrition of the American Academy of Pediatrics on children with insulin-dependent diabetes mellitus (IDDM) (21). This study provides information on dietary practices and diet composition for patients with a chronic illness that is the third most common in children and adolescents <18 yr of age. Three recommendations were made regarding nonnutritive sweeteners. *1*) The use of cyclamate and saccharin by children with IDDM should be limited pending further review. Although most researchers agree that any carcinogenic effects are weak, the availability of aspartame, an alternate sweetener without significant calories and with no apparent risks, justifies the caution. *2*) Aspartame is a satisfactory nonnutritive sweetener and can be a useful part of a diabetes meal plan. However, its use is limited by its instability during extended cooking and its rapid deterioration in neutral or alkaline solutions. In addition, consumption of large amounts of granulated aspartame, which contains a lactose or dextrose carrier, could affect blood glucose levels. *3*) Use of combinations of artificial sweeteners is reasonable to limit any risks with any one sweetener.

The Juvenile Diabetes Foundation (22) stated

> Artifically sweetened beverages and desserts have offered an acceptable alternative to the life of restrictions forced on a diabetic child. Parents of diabetics are concerned that in a world without an artificial sweetener for medicines, for cooking and baking the

all important birthday cakes and holiday treats, for sodas and snacks, our children will now have an even more difficult medical, social, and emotional adjustment.

This statement was presumably made at a time when saccharin was the only available sweetener in the U.S. marketplace. A more recent article by Grummon (23) addressed the subject of sugar substitutes of both the nutritive (e.g., fructose, sorbitol, and xylitol) and nonnutritive (e.g., saccharin, cyclamate, and aspartame) types. According to Grummon, there are acceptable alternatives to sugar that will satisfy the diabetic person's desire for sweets without wreaking havoc on the delicate balance between glucose levels and insulin. She also said that, although aspartame has limitations, particularly regarding its limited stability and inability to function as a bulking agent in foods, it appears to be the safest sugar substitute available, offering to the diabetic patient the sweetness desired and the control (for blood glucose levels) and safety required.

As a final item in this review of recommendations from professional societies, a position statement was issued in 1981 by the American Association of Diabetes Educators (24). This statement declares that people with diabetes should be assured of a level of nutritional status that allows them to achieve maximum quality of life. To achieve adequate nutritional status, people with diabetes require meal plans that have been individualized to their needs. Regarding nutritive and nonnutritive sweeteners, "the use of nutritive sweeteners in the meal plan must be accurately and authoritatively addressed. Patients with gestational diabetes may be advised to restrict saccharin-containing foods, but need to know the types and amounts of other sweeteners which are allowed in their meal plan." The main thrust of this statement is that the professionals best qualified to individualize a meal plan for the person with diabetes mellitus are nutritionists/dietitians. With such professional support, it is concluded that a diabetic person will understand and feel responsible for his/her own individualized meal plan and will be motivated to comply with the food requirements necessary for good diabetes management.

Although there is some level of concern regarding the possible risk related to the consumption of saccharin, the general consensus among the statements that have been reviewed is a desire for continued availability of the artificial sweetener. The urgency for this abated considerably after aspartame was approved for use. As noted previously, the current congressional moratorium of FDA's proposed ban on saccharin will expire in 1992. In April 1985, during the congressional hearings for the moratorium before the current one, the Department of Health and Human Services, FDA's parent department, expressed no objection to continuation of the moratorium. In his testimony, Frank E. Young, commissioner of FDA, noted that "the actual risk, if any, of saccharin to humans still appears to be slight" and that "research to date has allayed many of our fears" but not resolved all of the uncertainties and questions that gave rise to the 1977 legislation (25). FDA is reviewing the results of research about saccharin that have become available since the moratorium was last extended to determine if our past position needs modification.

Saccharin is a unique compound whose regulation is instructive to those attempting to understand the problems regulatory agencies, e.g., FDA, have in acting as gatekeepers of contemporary technology. FDA's mandate to ensure the safety of substances added to, or present in, the food supply is often extraordinarily difficult to fulfill. The agency is constantly being faced with a choice whose selection requires developing information at the forefront of contemporary science. FDA does not have the luxury of delaying action to do more research. At some point, the agency must make a decision. The problem is that the scientific community expects that decision to be based on the highest level of experimental science. On the other hand, the public as a whole often argues that there are other reasons that FDA should consider in making decisions. These include economic and social forces as well as issues of culture and traditional practice. In the case of saccharin, these views have often come into sharp conflict. Saccharin is a weakly potent carcinogen that causes dose-related increases in bladder tumors in the rat. Many questions need to be resolved in translating animal data to human risk. These range from the question of whether the rat is unique to whether the actual active substance is the sodium salt rather than the saccharin itself. A substance that does not exhibit traditional carcinogenic initiator properties yet produces the effect that saccharin does is difficult to evaluate. From the public health point of view, the issues become even more complicated. At what point does the public-health scientist say the data are sufficient to make a regulatory decision even though those data may not be sufficient by strict experimental science standards. The work with saccharin has been made even more complicated by the difficulty of demonstrating the efficacy of saccharin. The objective studies that have attempted to show a special role for artificial sweeteners, such as saccharin, in the regulation of body weight or in the therapy of diabetes have been largely unsuccessful, and yet practitioners in the field argue that the psychological and social support offered by these products is immeasurable. For example, saccharin and other artificial sweeteners have permitted diabetic adolescents to live relatively normal lives. The public supported this view when FDA proposed in 1977 to remove saccharin, which was then the last remaining artificial sweetener. The flood of letters in support of saccharin generated by this action was a reflection of strong public feeling.

What all this work suggests is that we need a new science, one where we can begin to quantify the social and psychological benefits of food products. FDA must always be cognizant of the impact of its decisions on the public. Although its mandate specifically alludes to the safety of food, it also has a responsibility to ensure that the food supply remains abundant and easily avail-

able. To do this properly, we must not only refine our traditional scientific knowledge of biologic and chemical events but must also consider how we can make more objective evaluations of those components of the decision process that up to now have been considered primarily subjective. We need at least the support, if not the understanding, of the scientific community to accomplish both of these tasks.

REFERENCES

1. Fahlberg C, Remsen I: On the oxidation of orthotoluenesulphamide. *Chem Ber* 12:469–73, 1879
2. Remsen I, Fahlberg C: On the oxidation of substitution products of aromatic hydrocarbons. IV. On the oxidation of orthotoluenesulphamide. *Am Chem J* 1:426–38, 1880
3. Forrestal DJ: How it all began. In *Faith, Hope, and $5,000.* New York, Simon & Schuster, 1977, p. 11–24
4. Wiley HW: *Harvey W. Wiley: An Autobiography.* Indianapolis, IN, Bobbs-Merrill, 1930, p. 231–46
5. Anderson OE: The struggle to set enforcement policy. In *The Health of a Nation.* Chicago, IL, Univ. of Chicago Press, 1958, p. 197–223
6. U.S. Department of Agriculture: *Saccharin in Food.* Washington, DC, Food Inspection Decision 135, 29 April 1911
7. U.S. Department of Agriculture: *Saccharin in Food.* Washington, DC, Food Inspection Decision 138, 12 July 1911
8. U.S. Department of Agriculture: *Saccharin in Food.* Washington, DC, Food Inspection Decision 142, 11 March 1912
9. U.S. Department of Agriculture: *On the use of Saccharin in Foods.* Washington, DC, Food Inspection Decision 146, 9 July 1912
10. Food and Drug Administration: Part 125—Label statements concerning dietary properties of food purporting to be represented for special dietary uses. *Fed Reg* 6:5921–26, 1941
11. Food and Drug Administration: Part 105—Food for special dietary use, label statements. *Fed Reg* 43:43248–260, 1978
12. Food and Drug Administration: Saccharin and its salts. *Fed Reg* 42:19996—20010, 1977
13. Ashby J: The genotoxicity of sodium saccharin and sodium chloride in relation to their cancer-promoting properties. *Food Chem Toxicol* 23:507–19, 1985
14. Scientific Review Group: Saccharin—current status: report of an expert panel. *Food Chem Toxicol* 23:543–46, 1985
15. Hoover R, Hartge P: Non-nutritive sweeteners and bladder cancer. *Am J Public Health* 72:382–83, 1982
16. National Research Council: *Saccharin: Technical Assessment of Risks and Benefits. Report no. 1. Committee for a Study on Saccharin and Food Safety Policy.* Washington DC, Food and Drug Admin., no. 223-78-2145, 1978
17. American Diabetes Association, Select Committee on Sugar Substitutes: Policy statement: saccharin. *Diabetes Care* 1:209–10, 1978
18. American Diabetes Association, Council on Nutrition and Food Science: ADA 1985 position statement: saccharin. *News & Notes* 2:4–9, 1985
19. American Diabetes Association: Nutritional recommendations and principles for individuals with diabetes mellitus: 1986. *Diabetes Care* 10:126–32, 1987
20. American Dietetic Association: The saccharin question re-examined: an A.D.A. statement. *J Am Diet Assoc* 74:574–81, 1979
21. American Academy of Pediatrics, Report of the Committee on Nutrition: *Nutritional Management of Children and Adolescents With Insulin Dependent Diabetes Mellitus.* Washington, DC, Food and Drug Admin., no. 223-82-2393, 1985
22. Juvenile Diabetes Foundation International: *Testimony Presented by Sheila Hennessy at a Hearing on Saccharin and Food Safety Before the Subcommittee on Labor and Human Resources,* U.S. Senate, 9 May 1979
23. Grummon P: Sugar and its substitutes. *Diabetes Countdown* 5:6–7, 1984
24. American Association of Diabetes Educators: Individualized meal plans for patients with diabetes mellitus. *Diabetes Educ* 7:44, 1981
25. Young FE: *Testimony Presented at a Hearing on Saccharin Study and Labeling Act, Amendments of 1985 Before the Committee on Labor and Human Resources,* U.S. Senate, 2 April 1985