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# The Rocky Road of Xylitol to its Clinical Application

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## “DISCOVERY” OF XYLITOL

In September, 1890, the German chemistry professor Emil Herman Fischer and his assistant, Rudolf Stahel, separated from beech chips a new compound which was named Xylit, the German word for xylitol (Fischer and Stahel, 1891). Later, in 1902, owing to his versatile chemical achievements, Dr. Fischer was awarded the Nobel Prize in chemistry.

Almost simultaneously with Fischer, the French chemist M.G. Bertrand had managed to isolate xylitol syrup by processing wheat and oat straw (Bertrand, 1891). The “discovery” of xylitol must therefore be credited to two groups of researchers.

During the next five decades, xylitol received little attention. During the 1950s, however, Dr. Oscar Touster, who worked at that time in Nashville, Tennessee, found by accident that the metabolism of xylitol in humans is associated with pentosuria.

That the history of xylitol was indeed quite “eventless” for the first 50 to 60 years after its first description in 1891 is reflected, for example, by an early statement that “these compounds [pentitols] have never been studied physiologically” (Carr and Krantz, 1945). Dr. Touster’s work was to change that situation remarkably. By the mid-1950s, he and his co-workers had concluded that xylitol is formed in the human body. This discovery stemmed from investigations on L-xylulose, the characteristic urinary sugar in essential pentosuria. This is a harmless, rare, recessive genetic disorder initially found in Jews and Arabs. Dr. Touster reasoned that essential pentosuria involved the accumulation and excretion of a metabolite which is readily disposed of in normal, but not in pentosuric, individuals. Eventually, the product was isolated and characterized as xylitol (Touster and Shaw, 1962).

## THE DAWN OF THE CARIOLOGIC INSIGHT

To me as a biochemist, the most intriguing chemical characteristics of the xylitol molecule are its “polyol properties”. These include the ability of xylitol to form complexes with certain cations, such as Ca(II), Cu(II), and Fe(II) (Angyal *et al.*, 1974). Another interesting feature of the xylitol molecule is its capacity to displace water molecules from the hydration layer of proteins and also from that of the above-mentioned cations (Lewin, 1974; Gekko and Satake, 1981). In 1969, xylitol was introduced to me as a possible sugar substitute. There was no clinical information on the possible effects of xylitol on dental caries, however. In 1965, I had joined the new Dental School at the University of Turku

(Finland) and there met Dr. Arje Scheinin, then Professor of Cariology at the Dental School. He was to become my most important co-worker (second only to my biochemist wife, Lisa). In 1970, we teamed up to form a two-man group that attracted other interested members from the surrounding scientific community. What followed was a long-time collaborative oral biologic and clinical research program that is still in full swing in Turku, and that has expanded to other oral biology laboratories all over the world.

The first project in 1970 was to test the effect of xylitol on the growth of dental plaque. The results showed that four-day use of xylitol-containing caramels, sweet rolls, and beverages was associated with a 45 to 50% reduction in the mass of dental plaque compared with that after the use of sucrose or glucose (Scheinin and Mäkinen, 1971). When another similar experiment of five days also resulted in a 50% reduction of dental plaque (Scheinin and Mäkinen, 1972), we began to design clinical trials which were to be named the Turku Sugar Studies (Scheinin and Mäkinen, 1975). In this research effort, adult subjects were assigned to experimental groups which consumed either sucrose, fructose, or xylitol diets over a period of two years. Never before had human subjects been provided a virtually complete and an exceptionally versatile fructose or xylitol diet over such a long time. Although the organization and implementation of this feeding trial were exciting and logistically challenging, the results of the study were also interesting: Those who consumed the xylitol diet registered an impressive reduction (> 85%) in dental caries incidence compared with the sucrose group. Owing to the encouraging preliminary results, a one-year chewing gum study was speedily set up while the feeding trial was still ongoing. Although the consumption levels of xylitol in these two studies were about 67 g and 6.7 g *per* day and subject, respectively, both studies showed similar caries prevention rates, *i.e.*, at least 80 to 85%, compared with the sucrose-using groups.

Following the publication of the first results, the dental circles immediately, and perhaps understandably, divided into two schools; Some colleagues readily accepted the “xylitol concept”, while others were more reserved. We perused virtually all published manuscripts on the physicochemistry of the sugar alcohols, hoping that the effect of xylitol on caries could be delineated from the existing literature. It was evident that the five-carbon structure of xylitol and its “extra” hydrogen atoms had to play a role in the clinical effects we had observed. On the basis of the results of the Turku study, several other trials (Table 1) and a large number of laboratory studies ensued.

The results of the Turku studies were soon recognized, first in the then-Soviet Union, where xylitol had been routinely used in the diets of diabetic subjects. A two-year study conducted in the state of Kazakhstan demonstrated a > 70% reduction in the overall caries incidence in the xylitol group compared with the sucrose group. The next trials were those conducted under the auspices of the World Health Organization. Two WHO studies were successfully completed: one in French Polynesia (1981-84), and another in Hungary, in the early 1980s. The former trial involved a 32-month consumption of various xylitol confectioneries and resulted in a nearly 40% reduction in caries compared with subjects receiving the basic prevention only. Both groups received the same basic prevention, which included the use of fluoridated toothpaste. Xylitol still significantly increased the protection against caries. The Hungarian studies resulted in a 45% lower incidence of caries in the xylitol group than in the control group. Again, the xylitol program performed better than the basic programs involving use of fluoride in various forms. A simultaneously performed Canadian xylitol trial showed that even quite low levels of xylitol were associated with significant caries reduction (Table 1). Further information was obtained from a school study in the small rural town of Ylivieska in Finland. This was a Finnish Government study approved by the National Board of Health and conducted at a provincial Public Health Center employing government dentists and personnel. The xylitol level in the gum tested was 64.7%. The control group did not receive gum as part of the study, but both groups did receive the basic caries prevention implemented at Public Health Centers in Finland. Consumption of three and two pieces of gum *per* day resulted in 60% and 30% reductions in caries, respectively. A separate study was carried out in subjects who were considered to be at high risk with regard to caries. This study resulted in 50% to 80% reduction in the incidence of caries. One aspect of the Ylivieska trial was especially exciting: the long-term protection. The trials were originally planned to include re-examinations several years after the discontinuation of the gum program. The re-examinations were conducted 2 to 5 years following the end of the treatment period and demonstrated that a significant caries-preventive

effect was still observable, even though habitual xylitol use had been discontinued several years earlier (Isokangas *et al.*, 1993).

In the mid-1980s, I contacted the Pan-American Health Organization (PAHO) for information about suitable new study venues. PAHO recommended Belize, where the next clinical studies were conducted. The purpose was to make direct comparisons of the effects of xylitol and sorbitol chewing gums. Children chewing xylitol gum had a significantly lower caries increment after 40 months than those using sorbitol gum, supporting the view that xylitol has an active anti-caries effect above that of a mere sugar substitute (Mäkinen *et al.*, 1995). Chewing gum as a vehicle for xylitol has been found both to be convenient and to provide an effective salivary stimulus (Birkhed, 1994; Tanzer, 1995; Edgar, 1998). True epidemiologists also recognized the utility value of xylitol programs in caries prevention: Dr. Pentti Alanen and his co-workers have shown that it is economically feasible to include xylitol in school-based prevention programs (Alanen *et al.*, 2000).

### CONVINCING THE FDA AND REWARDING ENDORSEMENTS

A few reminiscences are appropriate in this connection. The first proposal for the special dietary use of xylitol in foods in the United States was published by the Food and Drug Administration in 1963. It permitted the addition of xylitol to marmalade and jams for special dietary uses. However, reports on adverse effects of intravenous administration of xylitol in 1971 led to a proposed revocation of the regulation. In 1978, when the revocation was still pending, the Life Sciences Research Office of the Federation of American Societies for Experimental Biology published a report on xylitol, stating that the Turku Sugar Studies had provided evidence that "xylitol is without adverse effects when consumed at an average level of 53 g *per* day over a 2-year period". Additional studies on the metabolism and pharmacodynamics of ingested xylitol were suggested, however. Owing to these developments, the then-National Caries Program canceled its plans to carry out a xylitol chewing gum trial at Stony Brook, NY. The FDA subsequently hesitated to approve the

**Table 1.** Human Caries Studies on Xylitol

	Duration (yrs)	Dose (g/day)	Caries Reduction (%)	References
1. Turku Xylitol Studies, Finland	2	67	> 85	Scheinin and Mäkinen, 1975
	1	6.7	> 82	
2. Soviet Study	2	30	73	Galiullin, 1981
3. WHO Studies				
Polynesia	3	up to 20	58-62	Kandelman <i>et al.</i> , 1988
Hungary	2-3	14-20	37-45	Scheinin <i>et al.</i> , 1985
4. Canadian Study	1-2	1-3.9	52	Kandelman <i>et al.</i> , 1990
5. Ylivieska Study, Finland	2	7-10	30-57	Isokangas <i>et al.</i> , 1988 <sup>a</sup>
	3	7-10	59-84	
6. Belize Studies	3.3	up to 10.7	up to 73	Mäkinen <i>et al.</i> , 1995
	2	up to 10.7	up to 65	Mäkinen <i>et al.</i> , 1996a
7. Dayton VAMC <sup>b</sup>	1.8	up to 8.5	80 (root caries)	Mäkinen <i>et al.</i> , 1996b
8. Estonia Study	2-3	5	50-60	Alanen <i>et al.</i> , 2000

<sup>a</sup> Long-term effects described in Isokangas *et al.*, 1993.

<sup>b</sup> Dayton, Ohio, Veterans Administration Medical Center.

commencement of new studies on xylitol. At the same time, xylitol usage continued—for example, in Europe—and the New Jersey-based Finnfoods Inc. (a sales organization of the only significant xylitol gum manufacturer at the time, Hellas, in Turku, Finland) continued its regular marketing and sale of xylitol gum in the United States. The health authorities in many other countries did not take the negative xylitol news seriously.

About the same time, a far-seeing scientist in the United States shared the same positive expectations about xylitol as the Finnish researchers and fought persistently to get an approval from the FDA for his own xylitol gum studies. This person was Dr. Walter J. Loesche at the University of Michigan. Being unable to comprehend the obvious disregard of the FDA in this matter, he started a xylitol chewing gum study at Ann Arbor. The results were encouraging: Dr. Loesche found that xylitol significantly reduced the salivary *Streptococcus mutans* levels compared with fluoride alone or placebo alone, and stated that “the plaque levels of *S. mutans* were significantly reduced compared to values obtained by chewing either sorbitol- or fructose-sweetened gum” (Loesche *et al.*, 1984). Eventually, the FDA completed another review, this time ingeniously focusing in the same report on the “health aspects of sugar alcohols and lactose”. The report was published in 1986, and on its basis, the manufacturers of xylitol could justifiably claim that xylitol was safe for human use.

Some consequences of the strong public commitment to the caries-preventive efficacy of xylitol have been almost moving, even droll. In Finland, the public health evaluation of xylitol led to interesting uses of xylitol, of which three examples will be mentioned here: The Finnish Army included xylitol gum in its combat field rations, the Students Health Service tested xylitol gum as part of refectory meals; and thousands of public school pupils have been involved in special “Smart Habit” campaigns at schools under supervision. In the school campaigns, xylitol gum is used at public junior high schools, the objective of the drive being the development of a new health education model, to disseminate more information concerning xylitol, and to promote cooperation between dental care professionals and schools. Similar programs, featuring Yxi-the-Rabbit (a sharp-toothed Bugs Bunny-like character), have been implemented in

many Finnish day nurseries. In one special campaign aimed at elementary school pupils, the figurehead is the Montreal Canadiens’ Finnish ice hockey star, Saku Koivu.

## EXPLOITATION OF THE EXTRA HYDROGEN ATOMS

The versatile medical uses of xylitol may help us understand the basis of the effects of xylitol in the oral cavity. Xylitol has been routinely used in infusion therapy as a source of energy (Georgieff *et al.*, 1985). This is based on the non-involvement of insulin in the initial metabolism of administered xylitol. Xylitol administration also reduced middle ear infections in young children at a day-care center (Uhari *et al.*, 1996, 1998). The biochemical rationale behind all these applications of xylitol lies in the pentitol nature of the xylitol molecule. Although some of the proposed applications of xylitol will need validation in the form of controlled clinical trials, it may be interesting to mention a few other potential uses of xylitol (Table 2). The use of xylitol in the therapy of adenosine deaminase deficiency (Table 2) is interesting: Both D-ribose and xylitol increase the phosphoribosyl pyrophosphate content of cells, leading to increased salvage and *de novo* synthesis of purine nucleotides, with a concomitant increase in *de novo* protein synthesis, and in the formation of the required enzyme. Such biochemical reactions may explain the earlier finding according to which the consumption of xylitol—under certain conditions—increases the protein content of saliva, and the activity or concentration levels of some salivary enzymes (Mäkinen *et al.*, 1976, 1978; Bird *et al.*, 1977).

The multifaceted nature of the effects of xylitol may be surprising but receives a chemical explanation when one examines the chemical profile of the xylitol molecule. Xylitol is a substance that can produce abundant NADH and NADPH. These molecules can in turn affect the cellular redox potential. The altered redox potential of the cellular environment in turn regulates the levels of coenzymes and hormones. Consequently, to me the xylitol molecule is a reservoir of “extra” hydrogen atoms which can be enzymatically deposited onto other molecules, eventually generating reduced forms of the above coenzymes. At the same time, the metal-complexing (Angyal *et*

**Table 2.** Selected Medical Uses and Effects of Xylitol<sup>a</sup>

- Therapy of glucose 6-phosphate dehydrogenase deficiency of red blood cells. Xylitol works as a therapeutic agent because the red cells metabolize xylitol, generating NADPH.
- Anti-ulcer activity of hypertonic solutions of xylitol (and of D-glucitol).
- Prevention of adrenocortical suppression during steroid therapy (Georgieff *et al.*, 1985).
- Increasing of the auditory threshold values of patients with Menière’s disease.
- Therapy of adenosine deaminase deficiency in a form of adult myopathy. Both D-ribose and xylitol work similarly (Bruyland and Ebinger, 1994). Xylitol can act as an anabolic dietary substance.
- Restoration of heart muscle adenine nucleotide levels.
- Increasing the levels of retinol-binding proteins (Georgieff *et al.*, 1985).
- Reducing the incidence of liver and bile duct disturbances.
- Stimulation of mixed-function oxidase.
- Prevention of experimental osteoporosis and improvement of the properties of bones and collagen molecules (Svanberg and Knuutila, 1994; Mattila *et al.*, 1995; Mäkinen, 2000).
- Use of xylitol as a protein-sparing and vitamin-B-sparing agent.
- Preservation of red blood cells.
- Prevention of acute middle ear infections in children (Uhari *et al.*, 1996, 1998).

<sup>a</sup> Additional literature references regarding statements shown can be found in review articles (Mäkinen, 2000) or obtained from the author.

al., 1974) and water-displacing capacities (Lewin, 1974) of xylitol are in full force. The question is of a concerted action of all properties of the molecule. It is conceivable that such effects also play a role in the effects of xylitol on dental caries.

Currently, scientific research of xylitol's dental benefits continues on several fronts. To me, the most captivating new achievements are perhaps Dr. Luc Trahan's microbiologic insights regarding the development of so-called xylitol-resistant and xylitol-tolerant cell populations of mutans streptococci, and the cellular pattern of bacterial stress- and/or heat-shock proteins as affected by xylitol (Trahan and Mouton, 1987; Trahan, 1995). Also, I expect interesting results from several ongoing trials related to the mother-child transmission of mutans streptococci and caries as affected by xylitol (Söderling *et al.*, 2000). Personally, at the current phase of my life, I may be equally curious about the grandfather-grandchild transmissions.

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