

Medical Uses of Xylitol for Professionals

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Introduction *In writing this I can think of no better alternative then to follow the path I followed as I searched for why the spray I helped develop worked so well. That path is both chronological and topical, but it actually began long before we developed the spray when my wife, Jerry Bozeman, recognized that there was a connection between chronic early ear infections and these children developing learning and behavioral problems in their early school years. The stimulus that lead to the search came many years later with a granddaughter's recurrent ear infections and a wife that did not want to risk her future. The study below is the one that gave us the idea. And it worked!:*

1. Uhari, Xylitol Gum and Ear Infections (view the original article here) BMJ. 1996 Nov 9;313(7066):1180-4.

Xylitol chewing gum in prevention of acute otitis media: double blind randomised trial.

Uhari M, Kontiokari T, Koskela M, Niemelä M.

Department of Paediatrics, University of Oulu, Finland.

Comment in: BMJ. 1999 Nov 27;319(7222):1432.

Abstract OBJECTIVE: To examine whether xylitol, which reduces the growth of *Streptococcus pneumoniae*, might have clinical importance in the prevention of acute otitis media.

DESIGN: A double blind randomised trial with xylitol administered in chewing gum.

SETTING: Eleven day care nurseries in the city of Oulu. Most of the children had had problems with recurrent acute otitis media.

SUBJECTS: 306 day care children: 149 children in the sucrose group (76 boys; mean (SD) age 4.9 (1.5) years) and 157 in the xylitol group (80 boys; 5.0 (1.4) years).

INTERVENTION: Either xylitol (8.4 g a day) or sucrose (control) chewing gum for two months.

MAIN OUTCOME MEASURES: The occurrence of acute otitis media and antimicrobial treatment received during the intervention and nasopharyngeal carriage of *S pneumoniae*.

RESULTS: During the two month monitoring period at least one event of acute otitis media was experienced by 31/149 (20.8%) children who received sucrose compared with 19/157 (12.1%) of those receiving chewing gum containing xylitol (difference 8.7%; 95% confidence interval 0.4% to 17.0%; $P = 0.04$). Significantly fewer antimicrobials were prescribed among those receiving xylitol: 29/157 (18.5%) children had at least one period of treatment versus 43/149 (28.9%) (difference 10.4%; 0.9% to 19.9%; $P = 0.032$). The carriage rate of *S pneumoniae* varied from 17.4% to 28.2% with no difference between the groups. Two children in the xylitol group experienced diarrhoea, but no other adverse effects were noted among the xylitol users.

CONCLUSION: Xylitol seems to have a preventive effect against acute otitis media.

The dental benefits of xylitol are explained elsewhere. In Finland, where xylitol is widely used for its dental benefits they observed that children chewing the gum also had less ear infections. This was the study that confirmed those observations and gave us the idea of nasal administration since that is where the bacteria actually live that cause these infections.

Unfortunately the gum used to prevent tooth decay costs about a dollar a day for an effective amount, so using the gum to prevent 42% of ear infections is going to cost a little over \$70 to prevent one ear infection, which is close to what it costs to treat one. My own experience with delivering xylitol directly to the bacteria in the nose results in more than a 90% improvement in symptoms and costs less than 5\$ a month. So it costs less than \$6.00 to prevent an infection. It is also able to be used on infants, like my granddaughter, who don't yet have teeth or the ability to chew gum, where the risks for otitis are substantial.

2. The same group asked why it helps prevent ear infections (view original article here) J Antimicrob Chemother. 1998 May;41(5):563-5. Antiadhesive effects of xylitol on otopathogenic bacteria. Kontiokari T, Uhari M, Koskela M. Department of Paediatrics, University of Oulu, Finland.

Abstract The exposure of either epithelial cells or pneumococci or both to 5% xylitol reduced the adherence of pneumococci. Exposure of epithelial cells or bacteria alone to xylitol did not reduce the adherence of Haemophilus influenzae, although the exposure of both cells and bacteria to xylitol reduced the adherence significantly. The adherence of Moraxella catarrhalis remained low irrespective of the exposure.

This is an interesting study because it hints at a broader reason for working than just the effect of xylitol on the bacteria, which had been, and remains, the dominant focus of those looking at this interaction. In this study they took pathogenic strains of bacteria collected from patients and pharyngeal cell cultures from the mouths of other patients. Dividing each in half they mixed a 5% solution of xylitol with half the cells and half the bacteria. Then they mixed them together in four pots: one with no xylitol; one where the xylitol had been on the cells; another where it had been with the bacteria; and one where it was on both. After several washings to get rid of non-adherent bacteria they counted those attached to the cells.

The point about this study, besides the fact that xylitol reduces the adherence of a major pathogen, is that it works as well when mixed with the cells as with the bacteria. This suggests the action is not just on the bacteria. This sent me looking for how bacteria adhere to our cell surfaces.

But this work was triggered by the dental use of xylitol in preventing tooth decay so a detour is needed, just as it was in us, to look at how it all started. It began when dental researchers in Finland, seeing that sugar promotes decay, asked what alternative sweeteners would do. If you want to skip the dental studies the medical uses will resume below at #5.

3. The Turku Sugar Studies Acta Odontol Scand. 1976;34(4):179-216.

Turku sugar studies . V. Final report on the effect of sucrose, fructose and xylitol diets on the caries incidence in man.

Scheinin A, Mäkinen KK, Ylitalo K.

Abstract The purpose was to study differences in the caries increment rate as influenced by various sugars. The trial involved almost complete substitution of sucrose (S) by fructose (F) or xylitol (X) during a period of 2 years. There were no significant initial differences as to caries status between the prospective sugar groups; 35 subjects in the S-group, 38 in the F-group, and 52 in the X-group. During the entire study 10 subjects discontinued or were excluded. The clinical and radiographical observer error was reported and discussed. After 2 years the mean increment of decayed, missed and filled tooth surfaces was 7.2 in the S-group, 3.8 in the F-group, and 0.0 in the X-group. The weakness of the DMFS-index in not showing the development of new secondary caries and the increase in size of the lesions was overcome by expressing the caries activity in terms of indices showing the total quantitative and qualitative development. The results showed a massive reduction of the caries increment in relation to xylitol consumption. Fructose was found to be less cariogenic than sucrose. It was suggested that the non- and anticariogenic properties of xylitol principally depend on its lack of suitability for microbial metabolism and physico-chemical effects in plaque and saliva.

PMID: 795260

4. Belize studies There were two of these. In the first they looked at a variety of sugar free gums to see their impact on tooth decay on children in early school. In the first study the children chewed gum during school and were given enough for home use on the weekends. The study lasted two years and, as in the other dental studies, they looked at changes in decay for end results. There were no surprises with the first study. As with the Turkey studies xylitol only had far less decay than the other sweeteners.

But the second study did have a surprise.

J Dent Res. 1999 Mar;78(3):797-803.

The optimum time to initiate habitual xylitol gum-chewing for obtaining long-term caries prevention.

Hujoel PP1, Mäkinen KK, Bennett CA, Isotupa KP, Isokangas PJ, Allen P, Mäkinen PL.

Abstract Habitual xylitol gum-chewing may have a long-term preventive effect by reducing the caries risk for several years after the habitual chewing has ended. The goal of this report was (1) to determine if sorbitol and sorbitol/xylitol mixtures provide a long-term benefit, and (2) to determine which teeth benefit most from two-year habitual gum-chewing – those erupting before, during, or after habitual gum-chewing. Children, on average 6 years old, chewed gums sweetened with xylitol, sorbitol, or xylitol/sorbitol mixtures. There was a “no-gum” control group. Five years after the two-year program of habitual gum-chewing ended, 288 children were re-examined. Compared with the no-gum group, sorbitol gums had no significant long-term effect (relative risk [RR], 0.65; 95% confidence interval [c.i.], 0.39 to 1.07; $p < 0.18$). Xylitolgum and, to a lesser extent, xylitol/sorbitol gum had a long-term preventive effect. During the 5 years after habitual gum-chewing ended, xylitol gums reduced the caries risk 59% (RR, 0.41; 95% c.i., 0.23 to 0.75; $p < 0.0034$). Xylitol-sorbitol gums reduced the caries risk 44% (RR, 0.56; 95% c.i., 0.36 to 0.89; $p < 0.02$). The long-term caries risk reduction associated with xylitol strongly depended on when teeth erupted ($p < 0.02$). **Teeth that erupted after 1 year of gum-chewing or after the two-year habitual gum use ended had long-term caries risk reductions of 93% ($p < 0.0054$) and 88% ($p < 0.0004$), respectively.** Teeth that erupted before the gum-chewing started had no significant long-term prevention ($p < 0.30$). We concluded that for long-term caries-preventive effects to be maximized, habitual xylitol gum-chewing should be started at least one year before permanent teeth erupt.

PMID: 10096456 The finding that erupting teeth had long term protection was a surprise. These children did not have any xylitol in the five years between the first and second studies. The only way to explain the results, in the words of Philip Hujoel, is either the bacteria that make the acid that begins the cavity are no longer there, or they have stopped making the acid. As it turns out both of these are possible. In negotiating with these bacteria what xylitol seems to reiterate is a ‘shape up or ship out’, and the bacteria do both.

5. Nathan Sharon and how bacteria attach (view original article here) Essays Biochem

Lectins—proteins with a sweet tooth: functions in cell recognition.

Sharon N, Lis H.

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Abstract Lectins, non-enzymic proteins that bind mono- and oligosaccharides reversibly and with high specificity, occur widely in nature. They come in a variety of sizes and shapes, but can be grouped in families with similar structural features. The combining sites of lectins are also diverse, although they are similar in the same family. The specificities of lectins are determined by the exact shape of the binding sites and the nature of the amino acid residues to which the carbohydrate is linked. Small changes in the structure of the sites, such as the substitution of only one or two amino acids, may result in marked changes in specificity. The carbohydrate is linked to the protein mainly through hydrogen bonds, with added contributions from van der Waals contacts and hydrophobic interactions. Coordination with metal ions may occasionally play a role too. Microbial surface lectins serve as a means of adhesion to host cells of viruses (e.g. influenza virus), bacteria (e.g. E. coli) and protozoa (e.g. amoeba): a prerequisite for the initiation of infection. Blocking the adhesion by carbohydrates that mimic those to which the lectins bind prevents infection by these organisms. The way is thus open for the development of anti-adhesive therapy against microbial diseases. Lectin-carbohydrate mediated interactions between leucocytes and endothelial cells are the first step in the recirculation of lymphocytes and in the migration of neutrophils to sites of inflammation. Such interactions may also feature highly in the formation of metastases. Studies of these processes are expected to lead to the development of carbohydrate-based anti-adhesion drugs for the treatment of inflammatory diseases as well as cancer [emphasis added].

And:

6. More specifically looking at a particular condition (view original article here) FEBS Lett. 1987 Jun 15;217(2):145-57.

Bacterial lectins, cell-cell recognition and infectious disease.

Sharon N.

Abstract Numerous bacterial strains produce surface lectins, commonly in the form of fimbriae that are filamentous assemblies of protein subunits. Among the best characterized of these are the type 1 (mannose specific) fimbrial lectins of Escherichia coli that consist almost exclusively of one class of subunit with a molecular mass of 17 kDa. They possess an extended combining

site corresponding to a trisaccharide and preferentially bind carbohydrate units of oligomannose or hybrid type. Type 1 fimbriae also possess a hydrophobic region close to the carbohydrate-binding site, since aromatic alpha-mannosides inhibit strongly (up to 1000-times more than methyl alpha-mannoside) the agglutination of yeasts by the bacteria and the adherence of the latter to pig ileal epithelial cells. The combining sites of type 1 fimbriae of the salmonellae and of other enteric bacteria are different from those of *E. coli* in that they are smaller and do not possess a hydrophobic region. The various bacterial surface lectins appear to function primarily in the initiation of infection by mediating bacterial adherence to epithelial cells, e.g. in the urinary and gastrointestinal tracts. The mannose specific lectins also act as recognition molecules in lectinophagocytosis (i.e. phagocytosis of the bacteria in the absence of opsonins) by mouse, rat and human peritoneal macrophages, and human polymorphonuclear leukocytes. Affinity chromatography of membrane lysates from human polymorphonuclear leukocytes on immobilized type 1 fimbrial lectin, using methyl alpha-mannoside as eluent, showed that glycoproteins with apparent molecular masses of 70-80, 100 and 150 kDa act as receptors for the bacteria. Inhibition experiments with monoclonal antibodies suggest that the glycoprotein bands of 100 and 150 kDa may be identical with the alpha and beta subunits of leukocyte complement receptors and adhesion glycoproteins involved in complement-mediated opsonophagocytosis. The systems described serve as a fine illustration for the biological role of lectin-carbohydrate interactions. Further studies of these systems will lead to a deeper understanding of the molecular basis of infectious diseases, and perhaps also to new approaches for their prevention.

*Sharon and his colleagues have also written much on this latter subject suggesting that proper sugars could be used to inhibit bacterial adherence; mannose for example should fill the Type 1 lectins on *E. Coli* and prevent the chronic urinary infections with which these bacteria are associated. While they have written much on this the therapeutic avenue has mostly been ignored, except by the alternate medical community. It seemed reasonable that xylitol was doing the same kind of thing interfering with our nasal pathogens, an interaction that is not just on the bacteria.*

See also:

7. Bacterial Adhesion to Animal Cells and Tissues, by Itshak Ofek, Ron J. Doyle & David Hasty. Washington D.C.: ASM Press (American Society for Microbiology), 2003.

This book does a wonderful job of showing the breadth of the potential with the concept of interfering in this way with bacteria. The sugars on our cell surfaces include mannose, galactose, fucose, xylose, and three more complexed sugars. It is to these that bacteria bind with lectins specific for the particular sugar. Adding the proper sugars to this environment fills the lectin binding sites and competitively inhibits the adherence of the bacteria. The sugars in breast milk, for example, interfere with a number of pathogens. Colostrum is an even richer source and perhaps why it is so effective at preventing diarrheal complications in infants.

As these authors point out repeatedly if bacteria can't hold on they can't cause infection. That's a really important point because it ties in so well with another current biologist who is trying to get a fundamental idea across to our health care profession.

8. Paul Ewald. The Evolution of Infectious Disease. New York: Oxford Univ. Press. 1994.

*Presenting numerous examples Dr. Ewald shows that **interfering with how bacteria are transmitted from person to person** persuades them to adapt in less virulent ways. Making that transmission harder puts such pressure on them because they must live with the person they are currently infecting; killing them becomes a dead end.*

Putting this together with Sharon's idea suggests that using sugars to interfere with bacterial adhesion puts the same pressure on the bacteria to adapt in less virulent ways as does blocking their transmission.

This presents a totally new alternative in our warfare with bacteria; and since bacteria are so adept at adapting this is war we are unlikely to win. We need this alternative! And it's one we all can use without escalating the war!

*The study listed above in paragraph 2 shows how xylitol blocks nasal pathogens. The following references show it's effect on others: first on *C. difficile*;*

9. Xylitol and adherence – *C. difficile* (view original article here) FEMS Immunol Med Microbiol. 1996 Jul;14(4):205-9.

Inhibition of adhesion of *Clostridium difficile* to Caco-2 cells.

Naaber P, Lehto E, Salminen S, Mikelsaar M.

Abstract For many microorganisms, including *Clostridium difficile*, mucosal association is an important factor influencing intestinal colonisation and subsequent infection. Inhibition of adhesion of *C. difficile* to intestinal mucosa could be a new promising strategy for prevention and treatment of antibiotic-associated diarrhoea. We investigated the possibilities of influencing the adhesion of *C. difficile* by xylitol and bovine colostrum whey. Caco-2 cells and *C. difficile* cells were incubated with 1%, 5% and 10% solutions of xylitol and colostrum. Our study revealed that both xylitol and colostrum inhibited the adhesion of *C. difficile* to Caco-2 cells. Inhibition by xylitol was dose-dependent. When compared to the control, the count of adherent *C. difficile* decreased 3.4 times when treated with 1% xylitol, 12 times when 5% xylitol was applied, and 18.7 times when treated with 10% xylitol. The inhibition of adherence by colostrum was partially dose-dependent: 3.1 times in the case of 1%, and 5.5 times in the cases of 5% and 10% colostrum. Further experimental and clinical studies are needed for the application of xylitol and colostrum in the treatment and prophylaxis of pseudomembranous colitis.

*Then on *Staph. aureus*:*

10. Xylitol and adherence – *Staph. aureus* (view original article here) Chemotherapy. 2002 Jul;48(3):122-8.

Actions of farnesol and xylitol against *Staphylococcus aureus*.

Akiyama H, Oono T, Huh WK, Yamasaki O, Ogawa S, Katsuyama M, Ichikawa H, Iwatsuki K.

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Abstract BACKGROUND: Heavy colonization of atopic dermatitis (AD) with *Staphylococcus aureus* is well documented. The isolation rate of methicillin-resistant *S. aureus* is high in strains from AD in Japan. Our objective in the present study was to investigate the actions of farnesol and xylitol against *S. aureus* for the control of AD skin lesion-colonizing *S. aureus*.

METHODS: We examined the actions of farnesol on plasma coagulation and superantigenic exotoxin production by *S. aureus*, the antimicrobial activity of beta-lactam antibiotics combined with farnesol at concentrations below the minimal inhibitory concentration (MIC) and the effect of xylitol on glycocalyx production.

RESULTS: Coagulation by *S. aureus* cells was inhibited in plasma containing farnesol at a concentration of 1/12 of the MIC (100 microg/ml) after incubation for 24 h. The production of superantigenic exotoxins by *S. aureus* cells with farnesol (100 microg/ml) was about 10 times lower than that by *S. aureus* cells alone. The MICs of ampicillin and cefdinir against *S. aureus* were reduced to $< \text{or } = 0.06$ microg/ml in Mueller-Hinton agar plates with farnesol (100 microg/ml). We suggest that farnesol at concentrations above the MIC had a suppressive effect against *S. aureus* cells in the exponential and stationary phase and acted on the cell wall of *S. aureus* cells in both phases.

CONCLUSIONS: Farnesol is a promising adjuvant agent against *S. aureus* skin infections treated with beta-lactam antibiotics. Further, 5% xylitol inhibited glycocalyx production by *S. aureus* cells and consequently had a suppressive effect on the colonization of *S. aureus* on the horny cells of AD lesions.

The glycocalyx production mentioned here is a part of the biofilm these bacteria build to protect them when their colonies reach a certain size. We are increasingly recognizing that biofilms play a role in human disease and that they are difficult to treat using traditional methods that rely almost entirely on antibiotics. The amount of antibiotic needed to get into a biofilm is about 100 times the normal dose; often enough to kill the patient.

The Japanese paper, looking at farnesol and what xylitol does to this interaction has been confirmed in the aspect of wound care by a Lubbock, Texas colleague dealing with chronic and ischemic wounds. Such wounds always have a biofilm.

11. Xylitol and adherence – biofilm (view original article here) Int J Antimicrob Agents. 2009 Mar;33(3):230-6. Epub 2008 Nov 1.

In vitro susceptibility of established biofilms composed of a clinical wound isolate of *Pseudomonas aeruginosa* treated with lactoferrin and xylitol.

Ammons MC, Ward LS, Fisher ST, Wolcott RD, James GA.

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Abstract The medical impact of bacterial biofilms has increased with the recognition of biofilms as a major contributor to chronic wounds such as diabetic foot ulcers, venous leg ulcers and pressure ulcers. Traditional methods of treatment have proven ineffective, therefore this article presents in vitro evidence to support the use of novel antimicrobials in the treatment of *Pseudomonas aeruginosa* biofilm. An in vitro biofilm model with a clinical isolate of *P. aeruginosa* was subjected to treatment with either lactoferrin or xylitol alone or in combination. Combined lactoferrin and xylitol treatment disrupted the structure of the *P. aeruginosa* biofilm and resulted in a $>2\log$ reduction in viability. In situ analysis indicated that while xylitol treatment appeared to disrupt the biofilm structure, lactoferrin treatment resulted in a greater than two-fold increase in the number of permeabilised bacterial cells. The findings presented here indicated that combined treatment with lactoferrin and xylitol significantly decreases the

viability of established *P. aeruginosa* biofilms in vitro and that the antimicrobial mechanism of this treatment includes both biofilm structural disruption and permeabilisation of bacterial membranes.

While this paper reports on an in vitro study, Dr. Wolcott's practice also saw a benefit. Using this combination in his practice resulted in improved wound healing.

12. Xylitol and adherence – wound healing (view original article here) J Wound Care. 2008 Nov;17(11):502-8.

Biofilms in wounds: management strategies.

Rhoads DD, Wolcott RD, Percival SL.

Southwest Regional Wound Care Center, Lubbock, Texas, USA.

Abstract Biofilms probably induce a chronic and/or 'quiet' inflammation in the chronic wound and so delay healing. This paper reviews current strategies that can be used to suppress biofilms in chronic wounds until better options are available.

Dr. Wolcott helped to develop the Lubbock Chronic Wound Biofilm model, an experimental wound system that enables more research on wound healing. Using this model his group showed profound effects of sugar alcohols like xylitol and erythritol on biofilm formation and adherence:

13. Xylitol and biofilm formation (view original article here) J Wound Care. 2009 Dec;18(12):508, 510-12.

Effects of biofilm treatments on the multi-species Lubbock chronic wound biofilm model.

Dowd SE, Sun Y, Smith E, Kennedy JP, Jones CE, Wolcott R.

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Abstract OBJECTIVE: To evaluate the efficacy of several biofilm effectors in inhibiting biofilm formation in an in vitro multi-species chronic wound biofilm model.

METHOD: The Lubbock Chronic Wound Biofilm (LCWB) model has been described in detail elsewhere. Pathogens used in the model are *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Staphylococcus aureus*. These are three of the most important species associated with biofilms. Here, the model was exposed to the following biofilm effectors: xylitol, salicylic acid, farnesol, erythritol and two proprietary, semi-solid, wound-dressing formulations currently under development (Sanguitec gels).

RESULTS: Biofilm formation was completely inhibited in the LCWB model following treatment with 20% xylitol, 10% erythritol, 1,000 microg/ml farnesol, 20mM salicylic acid or 0.1% of either of the two Sanguitec gel formulations. Salicylic acid specifically inhibited *S. aureus* ($p<0.01$) at 10mM and 20mM, consequently increasing the ratios of *P. aeruginosa* and *E. faecalis* within the biofilm. Xylitol had an increasing inhibitory effect on *P. aeruginosa* ($p<0.01$) at all concentrations evaluated. Erythritol had an inhibitory effect on *P. aeruginosa* and *S. aureus* growth ($p<0.01$) at over 5% concentrations. The inhibitory effect of both Sanguitec gel formulations was more broadly effective, with an increasingly inhibitory effect on all LCWB species ($p<0.01$).

CONCLUSION: The LCWB model provides a multi-species format with which to evaluate the effect of biofilm effectors on wound flora in a biofilm phenotype. These results suggest that different treatments can target specific populations within a biofilm. Salicylic acid preferentially targeted *S. aureus*, xylitol preferentially targeted *P. aeruginosa*, while erythritol preferentially targeted both *P. aeruginosa* and *S. aureus*. In contrast, the two Sanguitec gel formulations provided a broad, less preferential, inhibition of biofilm development.

DECLARATION OF INTEREST: Research and Testing Laboratory is a for-profit enterprise that develops molecular methods and performs service research work on biofilms. Sanguitec gel was developed by JPK and CEJ.

I hope sanguitec is able to cross the food-drug barrier easier than xylitol has. The problem we have seen with such specifically designed agents, however, is that bacteria do adapt, and often do so rapidly. The polyvalent Strep. pneumoniae vaccine, for example, led to initial reductions in pneumococcal infections, but with time some strains adapted to fill the slots of their virulent, but targeted, cousins, and the diseases returned. Targeting bacteria in ways that are not threatening, as is done with xylitol, doesn't seem to produce increased virulence. One of the lesser referenced dental studies exemplifies this.

14. Xylitol resistant bacteria (view original article here) J Dent Res. 1987 May;66(5):982-8.

Selection for Streptococcus mutans with an altered xylitol transport capacity in chronic xylitol consumers.

Trahan L, Mouton C.

Abstract The effect of long-term consumption of refined xylitol on the natural populations of *S. mutans* in the human oral cavity has been investigated. Fifty-four *S. mutans* strains were isolated from adults and children who had been consuming commercial food products containing xylitol for a period of from 1 1/2 to 10 years. Twenty isolates were also obtained from control subjects who had never consumed xylitol-containing commercial food products. The inhibitory effect of xylitol on the isolated strains was determined by monitoring growth on glucose in the presence or absence of xylitol. This was used to define the sensitivity of each isolate to xylitol. Phosphoenolpyruvate:sugar phosphotransferase (PEP-PTS) activities were measured by means of the soluble and membrane fractions prepared from strains from both study populations. It was found that 87% of the fresh isolates from xylitol consumers were xylitol-resistant (XR), compared with only 10% of the strains isolated from the control subjects. The XR strains had low constitutive fructose PTS activity and very low xylitol-phosphorylating capacity. The xylitol-sensitive (XS) strains, however, had much higher levels of constitutive fructose PTS activity and phosphorylated xylitol 16 times more rapidly than did the XR strains. Evidence for the phosphorylation of xylitol by a fructose PEP-PTS in the XS strains was obtained. The growth inhibition by the intracellular accumulation of non-metabolizable toxic xylitol phosphate and its prevention by the presence of fructose are discussed.

This paper shows that xylitol selects for more friendly bacteria that don't cause so much tooth decay. But it also promotes their mutation [adaptation?].

15. Xylitol and mutation (view original article here) J Dent Res. 1996 Nov;75(11):1892-900.

Emergence of multiple xylitol-resistant (fructose PTS-) mutants from human isolates of mutans streptococci during growth on dietary sugars in the presence of xylitol.

Trahan L, Bourgeau G, Breton R.

Groupe de Recherche en Ecologie Buccale, Faculté de médecine dentaire, Université Laval, Québec, Canada.

Abstract The growth inhibition of mutans streptococci is one of the proposed mechanisms of action of xylitol, a caries-preventive natural carbohydrate sweetener. Xylitol is taken up and accumulated as non-metabolizable, toxic xylitol phosphate via a constitutive fructose PTS, and selects, during in vitro growth at the expense of glucose, for natural xylitol-resistant mutants that lack constitutive fructose PTS activity. Since long-term xylitol consumption leads to the emergence of xylitol-resistant mutans populations in humans in an oral environment containing sugars of dietary origin, we wanted to test the hypothesis that xylitol-resistant cells could be selected from mutans streptococci strains during in vitro growth on fructose, sucrose, or lactose. Three laboratory strains and three fresh mutans streptococcal isolates were repeatedly transferred in trypticase-yeast extract medium supplemented with glucose, fructose, sucrose, or lactose in the presence and absence of xylitol. Depending on the growth sugar, the presence of xylitol resulted in the selection of xylitol-resistant populations for several of the six strains tested, but not necessarily in the presence of all four sugars. All six strains rapidly became xylitol-resistant when grown on glucose in the presence of xylitol. All three fresh isolates became xylitol-resistant after 9 to 16 transfers in the presence of fructose or sucrose plus xylitol, while none of the laboratory strains became xylitol-resistant after 16 transfers in the presence of these sugars. The growth rates of 12 xylitol-resistant mutants in the presence of eight sugars suggested the existence of various types of xylitol-resistant mutants. The data partially explain the occurrence of xylitol-resistant mutans populations in long-term xylitol consumers and suggest a mechanism consistent with a selection process. Since various preliminary results suggest that xylitol-resistant natural mutants may be less virulent and less cariogenic than their parent strains, this selection process may alter, for the better, the mutans streptococci population of the plaque and play a role in the caries-preventive action of xylitol [emphasis added].

Thus in a manner that is completely congruent with the ideas of Paul Ewald these researchers show how xylitol applies pressure on Strep. mutans toward decreased virulence; the more virulent strains either go away, or they change into nicer bacteria. Considering that our major respiratory pathogen, Strep. pneumoniae, has the same genetic metabolism should guide us to doing the same with it in our noses.

Unfortunately it takes a while for such news to get around. The fact that xylitol is a food led to its lack of acceptance when I tried finding pharmaceutical interest in my nasal spray. Educating people to choose these less expensive avenues is not supported by regulatory agencies. Even in Finland the use of xylitol gum is not supported by the government, but is widespread because the dental profession is not aligned on making a living from repairing teeth and they take the time to educate.

Rebuilding our health care system in a comparable fashion is discussed in our book, The Boids and the Bees: Guiding Adaptation to Improve our Health, Healthcare, Schools, and Society.

Of course by the time I had found all of these references I had also found that the effect of xylitol on the bacteria was only part of the story. Allergies and asthma are, for the most part, independent of bacteria, but they too are helped by nasal xylitol. This broadened my interest.

Two outside factors helped this search. The first was from my Osteopathic training which said that the body is able to heal itself if it has the right materials; it led to looking at our nasal defenses. The second came when I was discussing the epidemiology of upper respiratory problems, specifically their increases since the early 1970's, with a local pharmacist who had lived through the period. He pointed to two events: antihistamines and decongestants were made available over the counter at this time and the passage of Medicaid and Medicare had opened the health care door to many in the nation. Add to these the ability to advertise for the new cold and allergy pills on television and a prudent person can see a connection.

The 'a-ha' behind this recognition comes from seeing the runny nose as the body trying to wash out what is bothering it. The common view is that the runny nose is a bothersome symptom that we can easily turn off. So why not? The common sense view is that rhinorrhea is a defense.

16. Rhinorrhea as a defense (view original article here) Am J Rhinol. 1998 Jan-Feb;12(1):37-43.

Nasal mucosal endorgan hyperresponsiveness.

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Abstract Nonspecific hyperresponsiveness of the upper and lower airways is a well-known characteristic of different inflammatory airway diseases but the underlying mechanisms have not yet been satisfactorily explained. In attempts to elucidate the relation of hyperresponsiveness to disease pathophysiology we have particularly examined the possibility that different airway endorgans may alter their function in allergic airway disease. The nose, in contrast to the bronchi, is an accessible part of the airways where in vivo studies of airway mucosal processes can be carried out in humans under controlled conditions. Different endorgans can be defined in the airway mucosa: subepithelial microvessels, epithelium, glands, and sensory nerves. Techniques may be applied further in the nose to determine selectively the responses/function of these endorgans. Topical challenge with methacholine will induce a glandular secretory response, and topical capsaicin activates sensory c-fibers and induces nasal smart. Topical histamine induces extravasation of plasma from the subepithelial microvessels. The plasma exudate first floods the lamina propria and then moves up between epithelial cells into the airway lumen. This occurs without any changes in the ultrastructure or barrier function of the epithelium. We have therefore forwarded the view of mucosal exudation of bulk plasma as a physiological airway tissue response with primarily a defense function. Since the exudation is specific to inflammation, we have also suggested mucosal exudation as a major inflammatory response among airway endorgan functions. Using a "nasal pool" device for concomitant provocation with histamine and lavage of the nasal mucosa we have assessed exudative responses by analyzing the levels of plasma proteins (e.g., albumin alpha 2-macroglobulin) in the returned lavage fluids. A secretory hyperresponsiveness occurs in both experimental and seasonal allergic rhinitis. This type of nasal hyperreactivity may develop already 30 minutes after allergen challenge. It is attenuated by topical steroids and oral antihistamines. We have demonstrated that exudative hyperresponsiveness develops in both seasonal allergic rhinitis and common cold, indicating significant changes of this important microvascular response in these

diseases. An attractive hypothesis to explain airway hyperresponsiveness has been increased mucosal absorption permeability due to epithelial damage, possibly secondary to the release of eosinophil products. However, neither nonspecific nor specific endorgan hyperresponsiveness in allergic airways may be explained by epithelial fragility or damage since nasal absorption permeability (measured with 51CR-EDTA and dDAVP) was decreased or unchanged in our studies of allergic and virus-induced rhinitis, respectively. Thus, the absorption barrier of the airway mucosa may become functionally tighter in chronic eosinophilic inflammation [emphases added].

A good defense helps our team to win and it's the same with the body. The idea from biology is that we evolve together with other agents in our environment with whom we interact, and the most prominent of these other agents are the bacteria. In the process we have developed defenses that come with a survival value; and they are strongest in the areas open to most of the outside world: the GI tract, the airway, and the genitourinary tract. Of concern here are the respiratory defenses (for information on the others see The Boids and the Bees).

The American Academy of Allergy, Asthma, and Immunology tells us that histamine does four things in the back of the nose:

- *opens the blood vessels so they leak more [which provides more water for the washing]*
- *makes more mucus [which holds on to more of the garbage]*
- *is a local irritant [so we sneeze more and get rid of it all]*
- *closes down the airway [to protect the more vulnerable lungs from the garbage in the upper airway. The concept of asthma being a part of this defense is totally foreign to our current way of seeing.]*

The idea was given further support from Margie Profet's look at our more common allergens:

17. Dangerous Allergens (view original article here) Q Rev Biol. 1991 Mar;66(1):23-62.

The function of allergy: immunological defense against toxins.

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Abstract This paper proposes that the mammalian immune response known as “allergy” evolved as a last line of defense against the extensive array of toxic substances that exist in the environment in the form of secondary plant compounds and venoms. Whereas nonimmunological defenses typically can target only classes of toxins, the immune system is uniquely capable of the fine-tuning required to target selectively the specific molecular configurations of individual toxins. Toxic substances are commonly allergenic. The pharmacological chemicals released by the body's mast cells during an IgE antibody-mediated allergic response typically cause vomiting diarrhea, coughing, tearing, sneezing, or scratching, which help to expel from the body the toxic substance that triggered the response; individuals frequently develop aversions to substances that have triggered such responses. A strong allergic response often includes a decrease in blood pressure, which slows the rate at which toxins circulate to target organs. The immune system identifies as toxic the following kinds of

substances: (1) those low-molecular-weight substances that bind covalently to serum proteins (e.g., many plant toxins); (2) nontoxic proteins that act as carriers of toxins with low molecular weights (e.g., plant proteins associated with plant toxins); (3) specific substances of high molecular weight that harmed individuals in ancestral mammalian populations for a span of time that was significant from the standpoint of natural selection (e.g., the toxic proteins of bee venom. Substances that bind covalently to serum proteins generally are acutely toxic, and because many of these substances also bind covalently to the DNA of target cells, they are potentially mutagenic and carcinogenic as well. Thus, by protecting against acute toxicity, allergy may also defend against mutagens and carcinogens. The toxic hypothesis explains the main phenomena of allergy; why IgE-mediated allergies usually occur within minutes of exposure to an allergen and why they are often so severe; why the manifestations of allergy include vomiting, diarrhea, coughing, sneezing, scratching, tearing, and a drop in blood pressure; why covalent binding of low-molecular-weight substances to serum proteins frequently causes allergy; why allergies occur to many foods, pollens, venoms, metals, and drugs; why allergic cross-reactivity occurs to foods and pollen from unrelated botanical families; why allergy appears to be so capricious and variable; and why allergy is more prevalent in industrial societies than it is in foraging societies. This hypothesis also has implications for the diagnosis, prevention, and treatment of allergy.

This view is consistent with the hygiene hypothesis which explains why allergies and asthma are less of a problem when there is early exposure to serious pollutants. Researchers show how such exposure guides the body's responses down a better pathway. We think that seeing the body as an adaptable organism is simpler, and that providing a better education early on allows for better choices in later adaptation.

The increases in both allergic and infectious problems all began in the early 1970's and are discussed in my article:

18. Why the Increases.

(view original article here) Med Hypotheses. 2001 Sep;57(3):378-81.

Why the increases in upper respiratory problems?

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Abstract The incidence of ear infections has roughly tripled in the last 25 years. Sinus infections and allergies also have increased. Asthma, triggered by chronic sinus infections and allergies, has paralleled the increases of otitis. These increases began in the early 1970s when antihistamines, decongestants, and combinations thereof, became available without prescription and were heavily advertised in the growing media of television. These drugs are designed to block the immune system's attempts to wash pollutants and irritants from the nasopharynx. The alternative is helping the immune system with this washing. I have used such a technique in my office for the past three years. Its rationale is discussed as well as my own experience.

This realization led to more searching for how our muco-ciliary cleaning has been handicapped over the years, both by drugs and by environmental changes.