# Therapeutics of caries prevention – Concepts and prospects

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Despite intensive research, water fluoridation and, where practiced, diet control, remain the most effective methods of preventing caries. In this paper, a number of approaches discussed appear to hold promise that they may enhance the caries preventive effect of fluoride, and others, when developed and applied, may hasten the day when dental caries will cease to be a public health problem.

*Keywords:* Fluoridation; prophylaxis

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It has been recognized for almost a century that many different therapeutic approaches may prevent dental caries. For example, W.D. Miller (67) observed that "we may counteract or limit the ravages of this disease – – – by (1) hygiene measures to secure the best possible development of the teeth; (2) by repeated, thorough systematic cleansing of the oral cavity and the teeth, to so far reduce the amount of fermentable substances as to materially diminish the production of acid as well as to rob the bacteria of the organic matter necessary to their rapid development; (3) by prohibiting or limiting the consumption of such foods or luxuries which readily undergo acid fermentation to remove the chief source of the ferment products injurious to the teeth; (4) by the proper and intelligent use of antiseptics to destroy the bacteria, or at least to limit their number and activity."

Although it has been established in principle that dental caries can be controlled in animals by means of antiseptics and antibacterial agents, this approach thus far has not been particularly successful when applied to humans (58). This lack of success may in part result from ignoring the need to insure that there is an adequate level of drug in the required area for sufficient duration to permit it to exert its maximum effect. Agents which have been effective in animals have often been added to the diet or drinking water, thereby achieving an exposure of 12–15 times daily. This frequency of exposure is effective because it comes close to realizing one of the effective attributes of chemotherapy. Few people, however, are likely to ingest chemotherapeutic substances so frequently for prolonged periods.

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## INFLUENCING THE PLAQUE FLORA

The biological interference with the plaque flora appears to be a reasonable method to prevent dental caries. The rationale behind this approach is the elimination of specific cariogenic bacteria from the flora in dental plaque. Approaches to this end could include:

1. the application of enzymes;
2. the action of antibodies;
3. antiseptics and antimicrobials;
4. the colonization of dental plaque by non-cariogenic microorganisms.

### *Enzymes*

It is implicit in the concepts listed above that a specific microorganism is responsible for the initiation of dental caries. Such a role has been attributed to several serotypes of *Streptococcus mutans.* The pertinent literature has been reviewed by Hardie and Bowden (36). There is little doubt that the presence of *Strep. mutans* in plaque is related to the development of dental caries in humans. Most of the evidence is, however, derived from the results of cross-sectional studies and is therefore circumstantial (23). Results from longitudinal studies which could provide better information are scarce and controversial (3, 66, 84, Huis in't Veld 1977 personal communication, Bowden 1977 personal communication).

*Strep. mutans* may be present as a constituent of the plaque flora at defined sites for prolonged periods without causing any changes in the underlying enamel. Furthermore, lesions have been detected in humans and animals which were covered by plaque containing low or not detectable levels of *Strep. mutans* at the time of sampling (Bowden 1977 personal communication, 41). These observations do not support the hypothesis that the development of dental caries is associated with a single species of microorganism.

In 1966 the role of sucrose in the formation of streptococcal homo-polysaccharides was described and the pertinent literature has been adequately reviewed (71, 28). Enzymes which are capable of degrading fructans and glucans were first used to elucidate the structure of these extracellular polysaccharides. It was evident that water soluble glucans produced by strains of *Strep. mutans* and *Strep. sanguis* were readily cleaved by dextranase (E.C.3.2.1.11. α-1,6 glucan 6-glucanohydrolase) from various fungi. It was furthermore demonstrated that in the presence of this glucanase the synthesis of glucans by the streptococci or cell-free glucosyltransferases was inhibited.

As a result of these promising *in vitro* effects, several laboratories carried out studies in animals to determine whether dextranase possessed cariostatic properties. In general, a caries-reducing effect was observed when the enzyme was incorporated in the diet or the drinking water. The literature up to 1969 has been reviewed by Guggenheim (28). In the following years, the glucans produced by strains of *Strep. mutans* were analyzed more critically. It could be demonstrated that these organisms produce a series of glucans with varying ratios of α-1,6 to α-1,3 links. Linear α-1,6 linked dextrans are water soluble and are cleaved by dextranase. Compounds with an approximately equal proportion of α-1,6 and α-1,3 links are gel-like and are partly susceptible to the action of dextranase. Linear water insoluble, predominantly α-1,3 linked glucans having a fibrillar appearance are highly resistant to the action of dextranase preparations (28, 14, 18). The production of water insoluble predominantly α-1,3 linked glucan (mutan) is one of the prominent characteristics of *Strep. mutans.*

Mutan has been shown to be a necessary requisite for the massive colonization of enamel by *Strep. mutans.* Mutan-negative but dextran-positive mutans lose their cariogenic properties (90, 92). This observation seems to be inconsistent with the observed

caries protective effect of dextranase. However, crude dextranases such as those used in animal experiments produced by strains of *Penicillium* contained small amounts of α-1,3 glucan 3-glucanohydrolase. A strain of fungus producing such an enzyme without dextranase activity was isolated and characterized (31). Addition of the enzyme to the diet or drinking water of rats protected them against caries, even though the enzyme was without effect on the extension of plaque (30). Plaque reduction could however be demonstrated in humans with an α-1,3 glucanase (mutanase) isolated from *Aspergillus nidulans.* Furthermore, the proportion of *Strep. mutans* in dental plaque was substantially decreased in humans who rinsed with the enzyme (47). Mutanase was found to have a beneficial effect in combination with a protease as a denture cleanser (11). Another clinical study with mutanase showed a plaque-removing effect when the crude enzyme was incorporated into chewing gum (Kelstrup 1977 personal communication). On the other hand, the results of several clinical studies with dextranase have been equivocal (55, 48, 73). In contrast to these latter findings, Murayama et. al. (70) reported that a dextranase preparation from *Spicaria violaceae* was capable of preventing dental plaque deposition in man.

Because several members of the plaque flora produce dextranase (88, 89, Guggenheim and Burckhardt 1974) and that dextran is rapidly metabolized in plaque (99, 39) the negative clinical results using dextranase are not surprising.

Another interesting enzymatic approach was reported from a Japanese group. Two enzymes produced by *Streptomyces globisporus* 1829 and named mutanolysin were found to have a lytic and/or bactericidal effect on a number of oral gram-positive bacteria (100). The enzyme has been shown to reduce plaque formation, caries and alveolar bone loss in the hamster model (76). When artificial plaque was treated with mutanolysin the addition of lysozyme and dextranase had a synergistic effect (44). Mutanolysin can also reduce plaque formation in humans (44).

Over recent years some success has been achieved using mouthrinses containing lactoperoxidase. Lactoperoxidase is a natural enzyme which, under specific conditions, is bacteriostatic; however, early observations await confirmation (40).

The possibility of using enzymes to prevent caries in humans is still viable. Enzymes specific for plaque matrix components may alter the diffusion properties in dental plaque in a manner which would allow full access of buffering components from saliva. Such a mechanism of action would only be evident in a human caries study and would not necessarily imply a concomitant plaque reduction. It must be emphasized that a reduction in plaque is *not* synonymous with reduction in disease.

### *Vaccination*

Considerable hope has been raised in the last decade that dental decay could be successfully fought by immunization. In the "lactobacilli age" caries resistance was associated with antibody or antibacterial activity in oral fluid or saliva. The pertinent literature has been critically reviewed by Sims (85, 86). Since the experiments of Wagner (95), who showed a protective effect of parenteral immunization against caries in rats monoassociated with *Strep. faecalis,* many reports have been published on this subject. It would be beyond the scope of the present paper to provide a comprehensive review of this field.

Although many regard the possibility of developing a vaccine against caries as remote, the prospect is so enthralling and the potential benefit so great that the subject is worthy of some discussion. It is well known that active immunization against bacterial diseases has been of limited value, immuni-

zation against *Corynebacterium diphteriae, Clostridium tetani* and pneumococci being exceptions. Control of bacterial diseases has been gained by the introduction of antibiotics. It has been pointed out that a mono-infection theory of dental caries is not established. Furthermore, antibodies are expected to act protectively in the oral cavity in an environment where rather small immunoglobulin concentrations are present in comparison to blood or interstitial fluid (50, 10), although it has to be recognized that 1 liter or more of saliva is secreted daily. Despite these unfavorable prospects, several independent groups have successfully immunized actively and passively in several animal model systems. Protective immunizations in rodents have been reported by Wagner (95), Tanzer et al. (91), Hayashi et al. (38), McGhee (60), and others. In monkeys effective trials have been reported by Bowen (4, 7), Lehner et al. (51). A satisfactory explanation by which mechanisms these successes were achieved is however still lacking. A lytic action of antibodies with the help of the complement system or lysozyme, or an interference with the metabolism of *Strep. mutans* is highly improbable. Increased phagocytosis of opsonized streptococci may also be excluded as a major mechanism of action. However, interference with the colonization of *Strep. mutans* on tooth surfaces by antibodies is possible. It has been shown that secretory immunoglobulin A inhibits the adherence of specific bacteria on the intestinal (24) and oral mucosa (98). The role of secretory IgA is discussed in two congress proceedings (64, 61). Antibodies may interfere with colonization by *Strep. mutans* through interacting with molecules which have been shown to participate in this process. The inhibition of glucosyltransferase has been demonstrated by Carlsson and Krasse (13), Evans and Genco (20), Fukui et al. (25), Russell et al. (80), Guggenheim and Burckhardt (33) and others. Antibodies were also shown to block receptor sites on the cell surface of *Strep. mutans* (75, 69) and on sites distant to the catalytic site on glucosyltransferases (33). Furthermore, sucrose and dextran-induced agglutination or cell adherence of *Strep. mutans* to glass surfaces has been shown to be inhibited by the action of antibodies (74, 69). It has also been implied by Evans et al. (22) that antibodies to glucan could lead to a decreased adherence of *Strep. mutans* cells to smooth surfaces.

In a number of animal experiments, immunization with whole cell vaccines of *Strep. mutans* led to a reduction of these organisms on tooth surfaces (93, 21, 8, 52, and others). Because a cross-reaction of antigens of *Strep. mutans* with human heart tissue cannot be excluded with certainty (94), a whole cell vaccine has little chance of being accepted. Therefore, many groups have tried to immunize with GTF preparations. Here, however, the results are still controversial. While Guggenheim et al. (29), Bowen (7), Russell et al. (80) could not show any effect, Hayashi et al. (38) and Smith and Taubman (87) showed caries protection in rodents.

Whether caries immunity is mediated by secretory IgA, by IgG or IgM awaits clarification. According to Lehner et al. (52) IgG and IgM antibodies transudated in the crevicular fluid are responsible for protection in primates, while others (93, 21, 59) have shown evidence for the protective role of secretory IgA antibodies in primates or rodents. Although a secretory antibody response to *Strep. mutans* in animal experiments has been evoked by antigen injection in the region of the major salivary glands (93, 59) or by retrograde parotid duct instillation (19) it is unlikely that such procedures could be applied in humans. Parenteral immunization procedures with a safe antigen, however, would be acceptable if the resulting protective effect would be of long duration as, e.g., achieved by Bowen et al. (8) in monkeys. Nevertheless, in an immunization by the oral route as reported

by Michalek et al. (65) in gnotobiotic rodents and in humans (62) could be substantiated, this would be an even more elegant way of conferring protection. Such a mechanism would, of course, imply a sensitization of the lymphocytes in gut-associated lymphoid tissue and a homing of the sensitized cells in the stroma of secretory glands. Evidence for such a mechanism has been presented recently by several authors (61).

Although the prospects of developing a successful vaccine appear good, caution is necessary. Immunization against several bacterial diseases has not been achieved. This applies in particular to a number of intestinal diseases, infection caused by pyogenic cocci and venereal diseases. The results of immunization experiments summarized above have indicated a degree of protection which was not absolute and has never been compared with other established prophylactic methods, e.g., with fluoride, although clearly the two approaches are not incompatible. In some of these studies, in which gnotobiotic animals have been used, the cariogenic challenge was extremely low by the use of a diet containing less than 10 % sucrose. Most rodent trials have not been controlled for unspecific effects, a fact which has already been very thoroughly discussed by Tanzer et al. (91). Lastly, epidemiological studies performed in the Netherlands demonstrated that antibody titers of some *Strep. mutans* antigens are not correlated with prevalence of caries. The antibody titers of serum and saliva of recruits and the proportion of *Strep. mutans* in dental plaque showed a positive correlation. However, antibody titers and active lesions could not be correlated.

### *Antiseptics and Antimicrobials*

It has been recognized for many years that the addition of antimicrobial agents to the diet of experimental animals prevents dental caries. Following the introduction of penicillin, dentifrices containing this substance were prepared and their effects determined. Smaller caries increments were observed in those who used the dentifrice than in the control subjects. However, the use of such preparations was viewed with disfavor by the American Dental Association and by the Food and Drug Administration and were soon withdrawn from U.S.A. Support for the principle of using antibiotics can also be found in the observation that subjects who received daily doses of antibiotics for the treatment and prevention of bronchiectasis develop substantially fewer carious lesions than normal siblings who were not so treated (35). Topical application of antibiotics, such as Kanamycin (57), Vancomycin and Erythromycin (56) have been shown to be effective in controlling dental plaque, few have resulted in the prevention of dental caries. Furthermore, the possibility of developing hypersensitivity and the emergence of resistant forms of bacteria is great.

Although there is a plethora of antiseptics available, some of which have been used in the mouth, none, with the exception of chlorhexidine, has shown any effect in the prevention of disease. Possible reasons for the failures are considered in the introduction.

Although chlorhexidine has substantially higher minimal inhibitory concentrations than many other antiseptics, it has considerably greater plaque restricting capacity than most other antiseptics examined. A possible explanation of this phenomenon may reside in the capacity of chlorhexidine to adsorb onto tooth surfaces and mucous membranes from which it is released slowly over several hours. Effective concentrations are therefore maintained in the mouth for considerable periods of time. Chlorhexidine is retained by binding to acidic groups in salivary glycoproteins and can be readily desorbed by rinsing with a weak solution of

a calcium salt. Chlorhexidine has yet to be shown to be an effective cariostatic agent. Chlorhexidine also stains teeth after sustained use and may affect taste sensations. Nevertheless, chlorhexidine does illustrate the type of compound which is likely to be successful in the prevention of oral disease (79).

Direct application of antiseptics to tooth surfaces appears to hold promise as a method to eliminate infection of the tooth surface by specific bacteria; for example, it has been observed that direct application of iodine to specific tooth surfaces eliminates *Strep. mutans* from those sites for several months (26). However, whether such an approach leads to a reduction in dental caries in humans has not been determined.

The use of high concentrations of antiseptics or antibiotics for short periods to control rampant caries or to reduce risks in particularly susceptible subjects is probably justified. However, if dental caries is regarded as a microbial disease associated with the presence of specific pathogens, the aim of antibiotic therapy should be the elimination or at least control of the disease-producing organisms. Furthermore, even if such therapy is successful in removing the pathogenic bacteria, unless dietary control is exercised it seems probable that there is a higher risk of re-infection.

Because the pathogenesis of caries involves the chronic interaction of microorganisms with specific dietary constituents on the tooth surface, it appears unlikely that any single preventive approach will result in the complete eradication of caries. Consideration should therefore be given to using a combination of agents which confer protection through different mechanisms, and which theoretically could be synergistic. For example, a combination of fluoride, with an appropriate antiseptic might confer more protection than could be expected from a simple additive effect. Such combinations might result in using reduced concentrations of effective agents with attendant reduction risks of toxicity.

A combination of chlorhexidine and fluoride has been found to be more effective in preventing caries in animals than either alone (68). Furthermore, it has been observed that a level of sodium phytate, combined with a concentration of sodium fluoride which, on their own, were ineffective, resulted in a significant reduction in dental caries (49). It is clear that this approach combined with new methods of delivering therapeutic agents could result in more effective use of existing methods and the development of new approaches to the prevention of dental caries.

### *Non-cariogenic Plaque*

The establishment of a non-cariogenic plaque is another conceivable way to prevent dental caries. It is well documented that the flora accompanying *Strep. mutans* has a decisive effect on the cariogenic potential of *Strep. mutans*. It has been shown that the implantation of *Strep. mutans* together with other bacteria in rats resulted in general in decreased caries scores when compared to controls infected with *Strep. mutans* only. The observed caries reduction was attributed to either a decrease of the proportion of *Strep. mutans* in plaque or a re-utilization of the acids produced. While these and other experiments describing the decreased cariogenicity of several mutants of *Strep. mutans* (90), Tanzer et al. (92), are largely of academic interest, the isolation of a lactate dehydrogenase-negative mutant by Hillman (Gibbons 1977, personal communication) opens a new horizon. This acid-negative strain competed successfully with its parent strain in rodents, a property which raises considerable hope for the future.

## SUGAR SUBSTITUTES

There is an abundance of evidence which shows the effect of frequent consumption of

sugar-containing snacks on the prevalence and incidence of dental caries (72). Exhortation to the general public to curb their frequency of ingestion of carbonhydrates is not likely to be successful, even though the benefits to be derived are apparent. In general, people do not associate the chewing of candy with the development of caries at some future date. Diet control is likely to be successful only if sweet-tasting sugar-free snacks are available as acceptable alternatives for sugar-containing snacks (7).

Considerable research is being carried out seeking low calorie non-cariogenic sweeteners and some have reached the stage for clinical testing. Saccharin is the most widely used non-caloric sweetener and is non-cariogenic. It is approximately 300 to 400 times sweeter than sucrose. Recent questions regarding its safety have intensified search for new substitues for sucrose or the re-examination of the status of previously rejected sweeteners.

Cyclamate was used extensively in the United States until 1969. It is still used widely in many countries where it is regarded as safe if used in limited amounts. It is not cariogenic and approximately 30–50 times sweeter than sucrose (96).

Aspartame is a methyl ester of two amino acids, aspartame and phenylalanine. It is almost 200 times sweeter than sucrose and is non-cariogenic (Bowen unpublished). Data pertaining to its safety is still being reviewed, and a decision is expected by mid-1978 (37).

Dihydrochalcones are a series of sweet-tasting compounds which are derived from citrus peels. Two compounds which are receiving particular attention are narginin dihydrochalcone and neohesperidine dihydrochalcone. Both substances are stable at low pH values. Hydrolysis occurs rapidly at temperatures in excess of 75–100 °C. Neohesperidin dihydrochalcone is approximately 2000 times sweeter than sucrose and narginin dihydrochalcone is almost 300 times sweeter than sucrose. It seems improbable that these substances are cariogenic. It also appears that they possess taste modifying properties because they interfere with the perception of bitterness. It is probable that dihydrochalcones would be particularly useful where long-lasting sweetness is desirable, for example, in chewing gums (43).

Stevioside is a sweetener derived from the leaves of a Paraguayan herb. It is 300 times sweeter than sugar. Although no ill effects have been reported, considerable work remains to be carried out before it will be readily available for general use in humans (43).

Monellin is a sweet-tasting material derived from serendipity berries, which are indigenous to tropical West Africa. Its commercial application is probably limited because it is heat labile (46).

Thaumatin is isolated from the fruit katemfe, found in Sudan. On a weight basis it is about 1600 times sweeter than sugar. Toxicity studies have not been completed. There appears to be considerable commercial interest in this material (43).

Tri-chlorosucrose is a synthetic derivative of sucrose. It is several hundred times sweeter than sucrose and is not apparently metabolized by oral bacteria. It has low toxicity and appears to have considerable promise.

If many of the above products were used instead of sucrose in manufactured snack foods, considerable reformulation would be needed to replace the bulk lost through removal of sugar.

The majority of the substances listed above are non-caloric and are sweet tasting. A substance, however, has been isolated from the miracle fruit which, following ingestion, causes normally sour tasting substances to be perceived as sweet. The active principle has been identified as a glycoprotein with a molecular weight of 42000. The quality of sweetness is comparable to that of sucrose. Insufficient toxicological studies have been carried out to determine

the safety of this substance, even though adverse effects have not been observed in humans who use a crude preparation extensively (42).

Sugar alcohols have been extensively used by diabetics as sugar substitutes for decades. The most commonly used have been sorbitol and mannitol and, more recently, xylitol. Apart from xylitol, they have not been widely utilized in the preparation of a large variety of snack foods. They all have approximately the same calorific value as sucrose.

Both mannitol and sorbitol appear to be minimally cariogenic in animals. It appears that sorbitol is non-cariogenic in humans. The sweetening properties of sorbitol and mannitol are substantially less than ideal and currently are usually combined with saccharin to achieve desirable taste sensations (83).

Xylitol is a pentitol which is non-cariogenic in humans. In one study, it was used in the preparation of a large variety of foods, to the complete exclusion of sucrose, and in another investigation it was used in a chewing gum at a concentration of 50 %. Results of both studies showed that xylitol is non-cariogenic; however, claims that it is cariostatic remain to be substantiated (82).

## INFLUENCING TOOTH SUSCEPTIBILITY WITH SUBSTANCES OTHER THAN FLUORINE

Approaches to enhancing the resistance of the tooth to carious attack has largely been confined to the use of sealants and fluorides, and will not be discussed here. Sufficient epidemiological research has been carried out to show that even in areas where caries attack appears to be high, the development of lesions is inexplicably low, even when little or no fluoride is present in the drinking water. Based on the results of epidemiological studies, a large number of elements appears to be associated with relative caries resistance and whether the elements act alone or in combination remains to be determined (2, 9, 16).

High levels of strontium in drinking water have been associated with low levels of caries. Furthermore, it was observed that rats given elevated levels of strontium in their drinking water developed fewer carious lesions than controls (16). Recent evidence has shown that enamel treated with strontium solutions results in reduced solubility of enamel in acid solutions. Combinations of fluoride and strontium appear to be more effective than either alone. It has also been observed that fluoride in the presence of aluminium, silicon, iron, copper, barium and strontium is associated with reduced enamel solubility (17).

Pretreatment of teeth with aluminium or titanium apparently enhanced the receptivity of enamel in rats for fluoride. However, a significant difference in the level of caries was not observed between the control and experimental animals (78). Topical application of teeth in humans with titanium tetrafluoride has led to a small reduction in the incidence of dental caries (77).

Results of epidemiological studies show an inverse association between the levels of lithium and caries. However, this observation has not yet been substantiated by experiments in animals (81).

There is also some evidence which appears to suggest that the level of hardness and conductivity of water may be inversely related to the prevalence of dental caries. Hardness may be associated with high levels of sulphate or carbonate, usually as magnesium or calcium salts (9).

It is usual to regard the use of trace elements as possible means of enhancing tooth resistance; however, it appears that some elements may promote caries, either directly by rendering the tooth enamel susceptible to caries or indirectly by interfering with the action of fluoride. Epidemio-

logical studies have shown that there is positive association between concentrations of selenium and the levels of dental caries in humans (34). Results of investigations carried out in animals have supported this observation (5). It appears that selenium interferes with the formation of enamel protein matrix. The addition of boron to drinking water of rats apparently interferes with the action of fluoride. Boron is known to combine strongly with fluoride and an insoluble complex in which ionic fluoride is not available is probably formed (54). It is debatable whether the removal of ions which interfere with the action of fluoride would be beneficial.

It appears probable that a distinction should be drawn between the possible effects of trace elements when administered pre-eruptively and post-eruptively. For example, fluoride administered pre-eruptively in sufficient concentration to raise the level in enamel significantly results in substantially less caries protective effect than when low levels of fluoride are administered continuously with only small increase in the level of fluoride in enamel. It has also been observed that, in contrast to its post-eruptive effect, strontium given pre-eruptively may be caries-promoting. The action of other elements may be similar.

From all available evidence, it is apparent that some elements alone or in combination may influence the susceptibility of enamel to caries. Research into this approach to caries prevention is difficult; however, the potential rewards as judged by results from epidemiological research are likely to be great.

## NEW APPROACHES TO CLINICAL APPLICATION OF THERAPEUTIC SUBSTANCES

In an effort to overcome the shortcomings of compounds which are ineffective as currently used, or to enhance the benefits of effective agents, several novel methods for delivery of cariostatic agents are being investigated. An investigation has been carried out to determine the effect of applying a mixture of polymyxin B, neomycin and bacitracin by means of an aerosol spray. The intention was to ensure that the aerosol powder was delivered to the precise areas where caries is likely to develop. The material adhered well and was effective in preventing caries and restricting the formation of dental caries. The prospects of this particular approach being accepted were hindered when doubts concerning the safety of fluorinated hydrocarbon propellants were raised. However, alternative methods of aerosol application may be developed (6).

The attachment of therapeutic substances to molecules which have the ability to adhere to tooth surfaces and mucous membranes is also being investigated. Some members of a group of substances termed lectins, which are proteins derived from plants, have the ability to adhere to carbohydrates and glycoproteins. Examples of such substances are concanavallin A, fucose binding protein, and wheat-germ agglutinin. Although these substances do not possess therapeutic properties, they may act on homing molecules delivering the active agent to the required site or enhancing its retention.

This approach has been used to modify the enzyme dextranase. As a result of conjugating dextranase with concanavallin A, the ability of the enzyme to adhere to hydroxyapatite, and to tooth surfaces *in vivo* was greatly enhanced (1).

In the past decade, several developments have been introduced which enhance the effect of drugs by altering their method of application or use. Controlled release formulations provide highly efficient utilization of a given drug by controlling the rate and sometimes even the site of drug release. As a result, smaller amounts of a drug may be used and agents which otherwise might be

too toxic may be utilized. By controlling the rate of release, and site of delivery, a therapeutic agent may be rendered more effective than it might otherwise be.

It is apparent that this type of technology has not been applied extensively to prevent dental caries. A substantial volume of research has recently been carried out to determine whether more effective methods to deliver fluoride can be developed. Three areas are being investigated. In the first approach, a tablet or capsule is being prepared which, when sucked or chewed, releases 10–15 % of its fluoride into the mouth; upon swallowing, the remaining fluoride is slowly released over 12–18 hours (63). Results of studies carried out in primates have shown that, following ingestion of the tablets, the levels of fluoride in the plasma rose slowly and remained elevated for 12–14 hours. Studies in humans remain to be carried out.

In a second approach, fluoride has been encapsulated in carboxy-methylcellulose and then mixed in guar gum to enhance the retention of the capsules on wet surfaces. Results of *in vitro* studies have shown that application of the microcapsules to enamel slabs results in greater uptake of fluoride than when sodium fluoride solutions are applied (97).

In addition to the approaches described above, a device has been fabricated which can be attached to tooth surfaces and release fluoride at pre-determined levels continuously over a 6-month period. The device is a trilaminate. There is a central core of fluoride containing hydroxyethyl methacrylate/methyl methacrylate copolymer encased by a copolymer membrane which controls the rate of fluoride release from the device. Results of studies carried out in dogs show that the device is effective in releasing fluoride at desired levels over prolonged periods. Toxicity studies carried out in rodents indicate that the device is harmless. It is anticipated that the effect of the device in humans will be investigated in the near future (15).

The approaches and devices discussed above represent the dawn of the application of technology to achieve optimum therapeutic effects from potentially cariostatic agents.

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