Chemotherapeutic agents for controlling plaque and gingivitis


Abstract. There has been a vigorous search for many years for chemical agents that could supplement or even supplant patient-dependent mechanical plaque control and thus reduce or prevent oral disease. 5 categories of agents or approaches have been considered: (1) broad spectrum antiseptics; (2) antibiotics aimed at specific bacteria; (3) single or combinations of enzymes that could modify plaque structure or activity; (4) non-enzymatic dispersing or modifying agents; and (5) agents that could affect bacterial attachment. The success of these approaches can be evaluated clinically by the use of standard scoring methods for measuring plaque and gingivitis and their safety established by soft tissue and microbiologic examination. Antiseptic agents have received the bulk of the attention over the years. At present, only 2 antiseptics, the big-biuguanide, chlorhexidine gluconate (Peridex) and a combination of phenol related essential oils (Listerine), have developed sufficient supporting data in 6-month (or longer) studies to gain the approval of the Council On Dental Therapeutics of the American Dental Association. On the basis of short-term studies, cetylpyridinium chloride, zinc and copper salts, sanguinarine and octenidine warrant continued study as does stannous fluoride at an appropriate concentration. On the basis of current research, a new generation of more specific antibacterial agents that interfere with attachment to pellicle can be developed. It is hard to predict, however, that they will affect gingivitis, at least until there is more information on what specific organisms should be targeted.

Key words: plaque; gingivitis; microbiota; antiseptics; antibiotics; enzymes; modifying agents.

Long before we had any glimmer of the nature of plaque and its relation to oral disease, people recognized the value of mouth hygiene. In tombs of the Sumerians dating to 3000 B.C., archeologists have uncovered toilet sets of gold that included tooth picks. Plaque control in the hereafter—that’s motivation, and confidence. The most popular oral hygiene device worldwide has been the tooth stick or chewing stick. Often oral hygiene was closely intertwined with religion and ritual practices, especially in Western countries, where toothsticks were called miswaks or swaks. Mohammed commanded his followers to clean their teeth with the swak as a way of praising God.

One of Mohammed’s biographers wrote: “Even the approach of death did not keep the prophet from demanding the swak because it is the most elegant thing that one can use and the most fitting to be found beautiful, for it makes the teeth white, clarifies the understanding, makes the breath fragrant, extinguishes the gall, dries up the phlegm, strengthens the gums around the teeth, makes the glance clear, sharpen’s the power of the vision, opens the bowels and whets the appetite” (Proskauer 1946). What a wonderful commercial.

The first reference to mouthwashing as a formal practice has been credited to Chinese medicine. about 3700 B.C., for treatment of diseases of the gums. The recommendation was rinsing with the urine of a child. Apparently rinsing with urine as a part of mouth hygiene became widespread over the centuries with descriptions in many countries. Especially popular among the Romans, Spaniards and other Europeans, it persisted as a practice until the early 18th century (Weinberger 1948). Urine was considered as an effective aid in curing many diseased parts of the body because of the comparability of its salt content to that of blood. The possible value of urea and ammonia was not considered.

Mouthwashing as an adjunct to mechanical cleansing became popular with the upper classes in the Roman period with Pliny recommending salty water, used in an uneven number of mouthfuls (1, 2, 3 or 7) – an oddity of unknown rationale – and Hippocrates advocating a mixture of salt, alum and vinegar. Other old favorites included a mixture of honey, oil and beer and a combination of dill, anise seed, myrrh and pure white wine. These may be the antecedents of California style cuisine.

Mouthwashing also had a religious connection. The Talmud contains instructions for rinsing the mouth between meals to remove food remnants and prevent admixing of meat and milk products, a violation of the dietary laws. Although bathing was not very popular, both mechanical tooth cleaning and mouthwashing were established practices by the 16th century. The Zene Artemey (Medicines for the Teeth), published in Germany in 1530, the first printed work devoted exclusively to dental therapeutics, contained a section on How to save the teeth. The recommendations included washing the mouth with burnt
Antiplaque, anti-gingivitis agents

...mixed with vinegar or myrrh in wine. The final suggestion was always after eating, wash the mouth with wine or beer, in order to wash away all that might adhere to the teeth and make them decay, produce bad odor, and destroy them. This very popular book underwent 15 separate editions between 1530 and 1576, without the benefit of television talk shows. A tribute to word of mouth.

It would not be inappropriate to consider Joseph Lister as one of the major progenitors of chemotherapeutics. As a surgeon and researcher he became interested in surgical sepsis, which accounted for about 50% of the deaths from surgical procedures. He postulated that it was caused by a pollen-like dust. Initially he had no inkling that the sepsis might be caused by living matter but quickly recognized the possibility when he became acquainted with the early work of Pasteur on fermentation and the later studies on the relationship between germs and disease. Lister and Pasteur became good friends and this intellectual collaboration became the basis for surgical antisepsis when Lister introduced the use of carbolic acid. Between 1865 and 1869, surgical deaths dropped to 15% among those who adopted the practice.

Over the next 20 years, the specific micro-organisms of many disorders were discovered but little was accomplished therapeutically. This was a great disappointment to the researchers of the day, including W. D. Miller who was actively involved in studying the use of antisepsics in the prophylactic treatment of decay. I quote his plaintiff prose: The fact that decay of the teeth is parasitic origin having been once established, the thought suggests itself that we ought to be able by means of properly chosen antisepctic materials not only to arrest decay, but to prevent its appearance. This is, indeed, the avowed object of the very many antisepctic mouth-washes now in the market. As a matter of fact, however, there is no evidence that anything has as yet been accomplished in the prophylactic treatment of the teeth through the use of antisepctic mouth-washes (Miller 1890).

I think it would be profitable to review some of Miller’s other observations and his own studies to give us perspective as to why its been such a difficult problem. Miller pointed out that there are places around every dentition which will remain untouched by even the most thorough application of the antiseptic, or the antiseptic will reach them in such a dilution that it possesses little or no action. He went on to note that many antiseptics cannot be used orally because they are injurious to general health, can injure the mucous membranes and teeth or have to be excluded because of bad taste or smell. He concluded with the statement that the preparation of a mouthwash which possesses an antiseptic action of any importance is accompanied by the greatest difficulties. This statement is still valid today.

But Miller did more than enunciate the problems. As a trained researcher in bacteriology (he had been a disciple of Robert Koch), he compared a large series of antiseptics, at varying dilutions, for their ability to prevent the growth or kill oral bacteria. Recognizing the limitation imposed by time of contact between the antiseptic and the oral bacteria, he went on to determine the minimum time required to kill the organisms. Not only did he appreciate the difference between a bacteriostatic and a bactericidal effect, but he also recognized the value of using an antiseptic mouthrinse after toothbrushing had removed oral debris and reduced the bacterial burden. In short, he established many of the ground rules that the dental research community followed for the next half of the 20th century. The search for oral antibacterial agents was, in a sense, a continuation of Miller’s efforts.

The post-Miller involvement with oral antiseptics generated a plethora of germicidal claims and implications of value in preventing and treating oral disease and mouth odor but essentially no valid clinical data. Most of the studies were in vitro testing or single episode reductions in oral bacterial counts. With the advent of antacids and the 1950s examination for changes in lactobacilli counts became popular. Counting of Streptococcus mutans did not begin until much later.

Beginning in the 1960s, the preventive and therapeutic studies of oral antimicrobials began to shift from caries, which was beginning to respond dramatically to fluorides, to gingivitis and periodontitis. When calculus was considered the dominant etiologic factor in the periodontal diseases, the mineralized deposit was the target and a number of anticalculus agents were examined (for review see Weinstein and Mann 1964). Even when the chemical agent was effective, however, as with disodium etidronate, the very significant reduction in supragingival calculus formation did not result in an impact on gingivitis (Suomi et al. 1974).

For the past 25 years (as Dr. Lister revealed so graphically described), plaque has been the designated enemy in the periodontal diseases (as well as in caries). Despite the proven efficacy of adequate mechanical removal of plaque (Frandsen 1985), the level of patient involvement is so demanding that only about 30% of the population in the developed countries, and a small fraction of that in the undeveloped countries, can be expected to practice adequate plaque removal. Clearly, the availability of chemical agents that supplement or even supplant the purely patient-dependent mechanical regimen are essential (Mandel 1972) if the plaque diseases are to be dealt with on a population basis. How have we been proceeding towards this goal and how close are we to fulfillment?

It should be noted at the outset of this status report that thanks to the efforts of the preventive dentistry-industrial complex and to the support of the National Institute of Dental Research, as well as to many academic institutions in various countries, there is a very extensive literature on chemical plaque control. There is a large and rapidly growing body of literature on the effect of antiplaque agents on gingivitis. There are now numerous reviews on chemotherapeutic agents (Mandel 1972, Parson 1974, Lesche 1976, Hull 1989, Korman 1985, 1987, Newbrun 1985, Mandel & Kleinberg 1985, Adly 1986, Ciancio 1987). Clearly, chemotherapeutic control of plaque and gingivitis is a growth industry.

According to Korman (1985, 1987) chemical plaque control could prevent or reverse gingivitis if: (1) eliminated all plaque; (2) reduced plaque below an individual’s threshold for disease; (3) altered the bacterial composition of plaque in such a way that health would not convert to disease. A 4th pathway might also be considered, namely the ability to modify the pathogenicity of a plaque, that is to detoxify it by removing or altering toxic products such as endotoxin or butyrate. Chemotherapeutic agents could also affect gingivitis directly if they possessed anti-inflammator or prostaglandin synthetase inhibitory activity (Goodson 1985).
Reviewing the various agents and approaches that have been used for chemical plaque control it would appear that they fall into 5 general categories: (1) antiseptic agents aimed at killing or preventing the proliferation of all the plaque organisms; (2) antibiotics capable of inhibiting or killing a specific group of bacteria; (3) single enzymes or combinations of enzymes that can break up or disperse the gel-like matrix which holds the plaque together, or modify plaque activity; (4) non-enzymatic dispersing, denaturing or modifying agents that can alter the structure of the plaque or the metabolic activity of the plaque bacteria; (5) agents that can interfere with the attachment of all or some of the oral bacteria to the pellicle surface.

**Antiseptic Agents**

Table 1 lists the antiseptic agents that have been clinically tested for prevention or reduction of plaque. In general they have been shown to exhibit little or no oral or systemic toxicity (in the concentration used), virtually no induced drug resistance and in most instances, a broad antimicrobial spectrum.

**Phenolic compounds**

Historically the agents that have been in clinical use the longest are the phenolic compounds and the longest running product is Listerine antiseptic, a combination of the phenol-related essential oils, thymol and eucalyptol, mixed with menthol and methyl salicylate in a 26.9% hydroalcoholic vehicle. The original Listerine formulation was among the antiseptic agents W. D. Miller studied (in 1884) for efficacy against oral bacteria. In his book on the Microorganisms of the human mouth (1890), he noted that Listerine has proved to be a very useful and active antiseptic.

In the modern era the interest in Listerine antiseptic goes beyond the Miller testimonial and rests on an extensive series of clinical studies. The earlier studies were short term, ranging in duration from 7–60 days and indicated statistically significant reductions in plaque accumulation and level of gingivitis when used in conjunction with, or in the absence of, daily oral hygiene (Kennedy et al. 1970, Gomer et al. 1972, Lusk et al. 1974, Fornell et al. 1975, Menaker et al. 1979). The more recent studies, in compliance with the guidelines of the Council on Dental Therapeutics have been 6 months in duration. In the study by Lams et al. (1983) on existing plaque and gingivitis, twice daily supervised rinsing resulted in a reduction of 20.8% in plaque and 27.7% in gingivitis scores when compared to the vehicle control and 22.2% and 28.2% respectively when compared to a water control. In a 6-month combined clinical microbiologic study on developing plaque and gingivitis (De Paola et al. 1986), there was a 34% reduction in both plaque and gingivitis when compared to a 5% hydroalcoholic control. In another study of 9 months duration on inhibition of development of plaque and gingivitis, following multiple prophylaxes, there was a significant but more modest retardation of 19.5% in plaque scores and a significant reduction of 23.9% in gingivitis (Gordon et al. 1985).

At the end of the nine month period, the plaque that remained on the teeth was physically removed in a standard manner and examined for wet weight, dry weight and protein content and its overall toxic potential measured by the limulus lysate assay for endotoxin activity. Reductions of greater than 50% were found in wet and dry weight as well as total plaque protein when the Listerine antiseptic rinse group was compared to controls. There was a reduction of nearly 80% in plaque toxic activity (Fine et al. 1985).

These findings suggest that the plaque area score may minimize the actual effect on plaque mass and that Listerine antiseptic exerts a protective effect that goes beyond its impact on the proliferation of plaque bacteria. The phenolic compound may be capable of extracting the lipopolysaccharide derived endotoxin from plaque.

Goodson (1985) has recently pointed out that most phenolic compounds have anti-inflammatory and prostaglandin synthetase inhibitor activity which can occur at concentration lower than that for antibacterial activity. Phenolic compounds are also known to act as scavengers of oxygen-free radicals (Kuclik et al. 1977) and hence should have an effect on leukocyte activity. Azuma et al. (1986) showed that this was indeed so. They demonstrated a marked suppression of superoxide anion generation in neutrophils as well as a comparable reduction in neutrophil chemotaxis for a series of phenolic agents. Thymol was particularly effective.

The totality of clinical and laboratory evidence supports the value of Listerine antiseptic as an adjunctive means of reducing plaque accumulation and toxic potential, and at the same time dampening gingival inflammation. Twice daily, a desirable combination in managing gingivitis rinsing is as effective as more frequent use (Markodi et al. 1987). Some patients find an initial burning sensation and bitter taste. Accommodation, however, usually occurs in a few days. Occasional staining of a minimal nature has been reported, but overall side-effects are minimal and safety has been established by a hundred years of wide-scale use. As befitting such a venerable product, it has become the first over-the-counter mouthrinse to be accepted by the Council of Dental Therapeutics for its help in controlling plaque and gingivitis.

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* Adapted from Newbrun (1985).
tertiary ammonium compounds

Genetically, this group of cationic surface active agents consists of many members whose physical and germicidal properties have been studied for more than 30 years. Their ability to interact with the bacterial cell membrane affects permeability with subsequent loss of cell content. Although they are bactericidal to both gram-positive and negative bacteria, the evidence suggests that they are more effective against the former. 2 of the groups, cetylpyridinium chloride (CPC) usually at 0.05%, with and without domphen bromide and benzenthionium chloride, at similar concentrations, have been used in mouthwashes for many years. A number of short-term studies with both commercial rinses and preparations at higher concentrations have shown plaque reductions of 25-35% and equivocal effects on gingivitis (Sturzenburger & Leonard 1969, Volpe et al. 1969, Carter & Barnes 1975, Holbeche et al. 1975, Cianco et al. 1975, Compon & Beagrie 1975, Barnes et al. 1976, Lobene et al. 1979, Ashley et al. 1984). In the only 6-month study reported (Lobene et al. 1977) there was a 14% reduction in plaque and a 24% reduction in gingivitis. A number of adverse effects have been reported such as tooth staining, burning sensation, and increased calculus formation. At higher concentrations, such as 0.2% benzenthionium chloride, oral desquamative lesions have been reported (Gjermo et al. 1970).

According to Kornman (1985), there appears to be agreement among investigators that the quaternary ammonium compounds have a moderate degree of efficacy as antiplaque agents but that their potential is limited by the rapidity by which they are absorbed from oral tissue sites (Jonesval & Gjermo 1978). Apparently they adsorb well initially but do not have sufficient substantivity to maintain an antibacterial effect. Use of higher concentrations or more frequent rinsing increases efficacy but also accentuates the undesirable side effects of staining, burning and soft tissue irritation.

Bi-biguanides

Described in 1954 to provide a polyvalent with a very broad antimicrobial spectrum, chlorhexidine gluconate, a cationic bi-biguanide, was introduced into human use in 1957 in Great Britain as an antiseptic cream for skin wounds. In the United States, it made its appearance as Hibiciens, a 4% solution used as an antimicrobial skin cleanser. Loe & Schiott (1970) captured the interest of the dental world when they introduced it as a 0.2% mouth rinse in an experimental gingivitis study in which they showed that 5, 2 or even 1 daily rinse virtually prevented plaque accumulation or development of gingivitis over a 21-day period of no oral hygiene. The first test of the use of chlorhexidine as a supplement to brushing was a four month, twice daily rinsing in a group of soldiers (Fiorla et al. 1972). There was a 66% reduction in plaque and a 24% reduction in gingivitis. Its use as a supplement to regular brushing was then tested over a 2-year period in a group of 150 medical students. The results on plaque scores and gingival index were modest. It was also noted that the calculus scores were significantly higher in the chlorhexidine group and many participants formed stain on the teeth and around plastic and synthetic porcelain fillings. A bitter taste was also noted. These side-effects have been consistent in subsequent studies over the years. There have also been occasional reports of mucous membrane irritation and desquamation.

The more recent studies with chlorhexidine as an adjunct to normal oral hygiene have been shorter, usually 6 months in duration. Lang et al. (1982) conducted a supervised study of a 0.12% and a placebo rinse 5 times weekly in a group of children and found a modest decrease in plaque scores (1.54 versus 1.24) but a substantial decrease in gingival index (0.74 versus 0.15). Results with a 0.12% chlorhexidine rinse were similar to 0.2% with less staining.

Despite its wide use in many European countries, acceptance of chlorhexidine in the United States was delayed because of the concern over its side effects. Since one way to reduce the problem was to reduce the concentration, an additional study was initiated to compare a 1.0% rinse with a 0.2% rinse. Segreto et al. (1986) conducted a 3-month clinical trial in San Antonio, Texas on 600 adults. 3 groups used either 0.12% or 0.2% chlorhexidine, or a placebo, twice daily. The 2 chlorhexidine groups exhibited comparable results, about 30% less gingivitis and 35% less plaque than the placebo group.

The major study in the United States was recently conducted by Grossman et al. (1986) on 430 adults in a 6-month clinical trial comparing twice-daily rinsing with 0.12% chlorhexidine and a placebo. Gingivitis was 34-41% lower (2 different examiners) and plaque 61% lower in the chlorhexidine group. The authors noted that “as expected, accumulation of dental calculus and extrinsic dental stain increased in the chlorhexidine group”. Although no comparisons were made, the amount of stain and calculus was possibly less than with the 0.2% rinses, but still very discernible.

Based on the published clinical studies and additional as yet unpublished studies, chlorhexidine was accepted (under the trade name, Peridex) by the FDA and the Council on Dental Therapeutics for sale on a prescription basis.

The antibacterial effects per se of chlorhexidine are not unique. It binds strongly to bacterial cell membranes, increases permeability, initiates leakage and/or precipitates intracellular components (Kornman 1985). Many cationic agents function this way. What gives chlorhexidine its advantage over many other agents is its ability to bind strongly to many sites in the oral cavity. It is this substantivity which enables it to function as a form of slow release device and maintain an ongoing rather than an intermittent antibacterial presence that can restrict bacterial proliferation. Chlorhexidine binds most strongly to amionic groups (sulfates, phosphates, carboxy) groups and hence can interact with amionic glycoproteins and phosphoproteins on the buccal, palatal, and labial mucosa and the tooth home pellicle. The soft tissues provide a much greater area for binding (Gjermo et al. 1974, Waller & Rolla, 1985). This same binding property enables chlorhexidine to bind to bacterial surfaces and affect adherence, as well as to initiate bacterial destruction.

Another related positive attribute of chlorhexidine is its lack of activity against specific bacterial enzymes or receptors. By acting by a generalized perturbation of the bacterial membrane rather than in the antibiotic mode, there is much less opportunity for development of bacterial resistance (Baker et al. 1987).

The most disquieting characteristic of chlorhexidine has been the formation of a yellowish-brown stain on the teeth and tongue, on plastic and composite restorations and on artificial teeth. In non-brushing studies, it is noted within
a few days and in brushing studies its onset is later and the intensity is less but it is experienced by many people. Most observers agree that the acquired pellicle with the adsorbed chlorhexidine, rather than the plaque, is the site of stain formation. 3 mechanisms have been proposed for this staining (Erikson et al. 1985): (1) a non-enzymatic brown- ing reaction (Maillard reaction) leading to the formation of brown pigmented substances known as melanoidins, a re- action that can be catalyzed by a high pH substance such as chlorhexidine; (2) formation of pigmented metal (iron, tin) sulfides as a result of denaturation of pellicle proteins by chlorhexidine, with subsequent generation of sulfhydryl groups which react with the metals introduced into the oral cavity; (3) surface precipitation by chlorhexidine of dietary chromogens contained in a variety of food stuffs, particularly beverages. In vitro experiments by Addy et al. (1985) favors the third mechanism as the most likely and foods such as tea, coffee, fruit juices, sauces are most frequently involved. Since some individuals consistently show greater staining than others, dietary patterns can be important. High concentrations of sulphur containing pellicle proteins in some individuals might also be significant.

The mechanism for the increased propensity for calculus formation has not been established. However, it appears likely to be due in part, at least, to local elevations in pH as a result of adsorption of the cationic agent per se and to the marked impact on bacterial integrity. The affected bacteria cannot metabolize sugars and no acids are produced. In vitro studies have shown that dead bacteria calcify more rapidly than live organisms (Wasserman et al. 1958).

Alexidine

Both animal and short-term clinical tests indicated that alexidine, a bis-higua- minide structurally related to chlorhex- idine, exhibited a potential for reduc- tion of plaque and gingivitis. In a 6- month study on 207 adults, the 2 groups rinsed twice daily with 0.35% alexidine or a placebo as an addition to their regular oral hygiene. In the alexidine group, there was a significant reduction in plaque throughout the study. Gingi- vitis was significantly less at 30 and 90 days but not at 180 days. Staining was frequent. There was some instances of taste disturbance (Weathered, Finn and Jamison 1977). In a subsequent study over a 60-day period (Formicola et al. 1978), there was a significant reduction in plaque but not in gingivitis.

Alexidine did not appear to offer any advantage over chlorhexidine and there have been no further published studies.

Bis-pyridines

Ocetenidine has been examined in one 7- day no brushing study (Patterson et al. 1983) and in a 21-day experimental gingivitis study (Patterson et al. 1986). In the latter study of 88 subjects, 0.1% octeni- dene used twice or three times per day was compared with a mouthwash veh- icle. In an additional cell, subjects used the octenidine in water, but this was stopped due to mucosal irritation. Both octenedine groups had significantly less plaque and gingivitis than placebo at 7, 14 and 21 days. There was no difference between the two or three times per day groups. Stain was observed in 26 of the 44 subjects at the end of the study. In all but 5 subjects it was removed following a single brushing with a commercial dentifrice. A few subjects had minor taste complaints. This appears to be a promising agent.

Herbal extract – sanguinarine

Sanguinarine, currently being employed as an antiplaque, antigingivitis agent in both a mouthrinse and toothpaste, is an alkaloid extract from the blood root plant, Sanguinaria Canadensis. It is interesting to note that a structurally similar compound, fagonarine, is found in a Nigerian chewing stick with purported benefits in oral hygiene (Obebiyi & So- fowara 1979). In vitro studies (Dzink & Socransky 1985) established the ability of sanguinarine to inhibit growth of 98% of oral isolates at a relatively low concentration of 16 micrograms per milliliter. Several early short term clinical studies in private dental offices evaluated a combination of an oral rinse and toothpaste containing 0.03% sanguinarine chloride and 0.2% zinc chloride and showed a variable, but usually significant reduction in plaque (Greenfield & Cuchel 1984, Nyygaard-Østby & Persson 1984, Klewansky & Vernier 1984).

In a 14-day experimental gingivitis study with a cross-over design, 14 dental students rinsed twice daily with 0.03% sanguinarine extract (equivalent to 0.01% sanguinarine) or a placebo. There was a reduction of nearly 40% in plaque and 20% in gingivitis scores with the active rinse (Wennström & Lindhe 1985). The same researchers also exam- ined the effect of the mouthwash on established and developing plaque and periodontal disease in a 6-week study in 21 adult subjects who maintained nor- mal oral hygiene (Wennström & Lindhe 1986). They found that sanguinarine had a significant effect on established plaque and an inhibitory effect on new plaque formation. In these subjects with moderately advanced periodontal disease, there was no effect on gingivitis. However, neither did chlorhexidine, which was also examined.

Negative results with both 0.03% and 0.1% sanguinarine (with 0.2% zinc chloride) in a 4-day no brushing trial have been reported by Etemadzadeh & Amarni (1987). In a 1-month dentifrice study, there was no significant difference in plaque between the sanguinaria-containing dentifrice and a conven- tional product (Schonfeld et al. 1986).

There have been two 6-month studies published to date. In one study with orthodontic patients, 9 subjects brushed twice daily with sanguinaria toothpaste and used the oral rinse after brushing. While ten subjects used placebo prepara- tions. Plaque and gingivitis scores were significantly better in the sanguinaria group (Palcans et al. 1986). In the second study, 100 subjects brushed twice daily with a sanguinaria or a con- trol toothpaste using the Bass technique which was taught to the subjects at a screening visit (Lobene, Soparkar & Newman 1986). There was no signifikan- cent difference in plaque scores between the groups. Although gingivitis scores were lower in the sanguinaria group, both groups ended with higher scores than at baseline. In view of the instruc- tioned oral hygiene this is difficult to ex- plain.

Clearly additional long-term studies are required before we can have any confidence in the efficacy of sanguinarine, either as a rinse or toothpaste (or in combination) against plaque and gingi- vitis.

Heavy metal salts

It has long been recognized that salts of heavy metals are effective antibacterial agents. Silver nitrate, bichloride of mer- cury and zinc chloride were among the agents tested against oral bacterial by Miller in 1884. Because of tooth stain-
ing, soft tissue and systemic effects. Silver and mercury have limited oral use. Zinc has persisted over the years in a variety of oral products. Antiplaque interest dates to studies by Fishman et al. (1973) on a combination of 5% zinc citrate and 0.125% zinc tri bromsalen. Since then there have been a number of studies employing a variety of zinc salts at different concentrations (Adely et al. 1979, Compton & Beague 1975, Skjorland et al. 1978) with varying results. Harrap et al. (1983) noted that efficacy was dependent on concentration and frequency (as might be expected) and that heavy plaque formers benefited to a greater extent than light formers. In a mouthrinse, 0.5% zinc citrate or zinc chloride can have an impact by binding to the surface of oral bacteria and affecting adherence and altering muta bloc activity and reducing growth rate. Recent studies support the role of zinc in reducing plaque growth (Saxton et al. 1986).

All of the mouthrinse studies to date with zinc salts have been short term. Interest has shifted commercially to their incorporation in dentifrices and there are now several studies on plaque ginvititis of a combination of 1% citrate and a germicide. Iclodesan, at either 0.5%, or 0.2% concentration. In a 28-day study, there was a reduction in plaque of 50% and improvement in gingival health (Saxton et al. 1987). In a 6-month study the dentifrice successfully maintained the gingival health established by professional cleaning and oral hygiene instruction (Svatus et al. 1987). Staining is not a problem with zinc salts. At appropriate concentrations they have anti-calculus properties (Lobene et al. 1987) but taste acceptance limits the level that can be used.

Zinc chloride at a level of 0.2% is also incorporated in the sanguinaria products. When used in a mouthrinse at a level of 0.03%, sanguinaria with the zinc chloride did not have a significantly greater effect on plaque and ginvititis than sanguinaria alone (Southard 1987).

Several studies indicated that copper sulfate at a concentration as low as 0.035% was effective at reducing plaque and ginvititis (Water & Rolla 1982, Waterhaug et al. 1984). It produces some staining but not as much as chlorhexidine. Copper has a greater affinity for the binding than does zinc and appears to be more effective in depressing acid production (Assiet et al. 1983, Assiet 1983). Further studies on copper would appear to be warranted.

A number of short term studies have indicated that stannous fluoride is a more effective antiplaque agent than sodium fluoride (Birkenland et al. 1973, Tinnanoff et al. 1976, 1983), suggesting the importance of the tin ion per se. Binding of the metal to the bacterial surface impedes colonization and intracellular accumulation affects metabolic activity (Camosci & Tinnanoff 1984). A 28-month study in children aged 12-15 who daily rinsed with either 0.05% sodium fluoride or 0.1% stannous fluoride confirmed the earlier clinical study. The stannous fluoride group had less plaque accumulation at the end of four months. No difference, however, was apparent at 16 and 28 months (Leverett et al. 1984). At what point between four and sixteen months the difference disappeared is not known. Ginvititis in the stannous fluoride group was less severe throughout the study but the difference was not significant. Since there was no placebo rinse group the impact of fluoride per se on plaque could not be measured, but the assumption is that it was very modest.

Once daily rinsing with stannous fluoride at 0.1% may be inadequate for a sustained anti-plaque effect. As with zinc, dose and frequency are very important. In an experimental ginvititis model with 0.3% stannous fluoride a reduction comparable to chlorhexidine (about 80%), was achieved (Svatus et al. 1977). In a limited two year study of twice daily rinsing with 0.1% stannous fluoride versus phos-flur, there was significantly less ginvititis with the stannous fluoride at the end of one year, but not at 2 years (Klock et al. 1984). The appropriate schedule for an antiplaque, anti-ginvititis effect remains to be established. Stannous salts do cause staining, an effect widely noted in past years with the original Crest dentifrice.

Miscellaneous Agents

A number of antibacterial agents have shown promise in screening or short-term clinical studies for antiplaque, antiginvititis use but there has been no sustained interest as evidenced by continued supporting data. These include pexidone and perborates (Gomes et al. 1984, Winnestrom & Lindhe 1979) and heveldine (Bergenholtz & Hanström 1974).

Antibiotics

Table 2 lists the large number of antibiotics that have been the subject of at least screening or animal trials for antiplaque activity. The criteria recommended by regulatory agencies for oral topical use of antibiotics are rather stringent: (1) not currently used for medical purposes in man and death situations; (2) no cross-sensitization; (3) active at low dosage; (4) non-sensitizing, allergenic or irritating to oral tissues; (5) does not produce resistance or alter oral ecology; (6) no significant absorption. It is not surprising that only 3 antibiotics have been the subject of any appreciable clinical study against plaque and ginvititis-niddamy cin, vancomycin and kanamycin.

Niddamy cin (CC 10232), a macrolide antibiotic effective against Gram-positive organisms, has been employed as a mouthrinse twice daily at a concentration of 0.1%. Reductions in plaque accumulations have been reported in the range of 11-77%, and ginvititis 50-70% in studies ranging from 1-9 months (Stallard et al. 1969, Volpe et al. 1969). Its clinical use was not pursued, however, because of cross-sensitization to erythromycin.

Vancomycin, an antibiotic also effective against Gram-positive bacteria, has been examined in a variety of formulations with very variable results. Greatest success was noted with an institutionalized group where the vancomycin was applied as an ointment on a daily basis (Mitchell & Holmes 1965).

Kanamycin, which has a broad range of activity, would appear to be more appropriate for antiplaque antiginvititis use than the narrow range antibiotics. Indeed a 5% concentration in Orabase emollient, an adhesive paste, did have an effect on plaque weight and ginvititis in a mentally handicapped group with poor oral hygiene (Loesche et al. 1971, Loesche & Nafe 1973).

In general, the prevailing view is that for antiplaque, antiginvititis use the concerns with antibiotics overshadow

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th><em>Adapted from Newbrun (1985)</em></th>
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<tbody>
<tr>
<td>Bactracin</td>
<td></td>
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<tr>
<td>Erythromycin</td>
<td></td>
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<tr>
<td>Penicillin</td>
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<tr>
<td>Vancomycin</td>
<td></td>
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<tr>
<td>Gramicin</td>
<td></td>
</tr>
<tr>
<td>Spectramycin</td>
<td></td>
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<tr>
<td>Polymyxin B</td>
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</table>
the potential benefits and there has been virtually no interest for the past decade.

Enzymes

Table 3 lists the enzymes that have been employed to alter plaque integrity or more recently, to generate products that can affect the metabolic activity of plaque organisms. The early studies with mucinasas, pancreatin (a mixture of amylase, lipase and protease) and fungal enzymes examined their effect on calculus formation rather than on plaque per se (see Weinstein & Mandel (1964) for a review).

Perhaps the first enzyme to be considered for plaque per se was pepsin, the active ingredient in the toothpaste Pepsodent. Despite the enthusiastic advertisements at the time (1917), given the characteristics of the enzyme or the product, there was no real possibility of efficacy. The first bonafide study of an enzyme preparation on plaque was a mixture of amylase and several proteases from B. subtilis. A 3-week dentifrice study claimed a 50% reduction in plaque accumulation while a seven week mouthwash study indicated a 34% reduction (Shater & Schiff 1970). There are no further reports.

In the early 1970's, considerable excitement was generated over the clinical use of dextranase in reducing plaque by means of disrupting the extracellular glucans. The clinical findings were very disappointing (Caldwell et al. 1971; Lo bene 1971). As the studies were in progress it became apparent that the dextranases affected only water-soluble glucans and that the insoluble glucans were the important ones in the plaque architecture and adherence. These "mutans" can be cleaved by the enzyme mutanase. Kelstrup et al. (1977, 1987) have conducted two clinical studies with a crude mutanase. In one study, only a slight effect was noted. In the second study, a significant reduction in plaque and gingivitis was achieved with the enzyme administered in chewing gum. Some local side-effects were observed, however, including soreness of the tongue, localized ulceration and taste disturbances.

Apparantly crude enzyme preparations contain a variety of undesirables which can have effects on the soft tissues as well as the plaque. This is clearly a limitation with this approach. Very pure enzymes with limited specificity are required.

A new approach is to employ enzymes to generate an antibacterial product that could affect plaque and gingivitis as well as caries. A current example is the use of the enzymes amylglucosidase and glucosidase.

The rationale behind this combination is the step-wise production of hydrogen peroxide in situ by dint of splitting starch remanias in the oral cavity to glucose (by amylglucosidase) and hydrolysis of the glucose to gluconic acid and hydrogen peroxide (by the glucose oxidase). The peroxide, in turn, reacts with thiocyanate ions in the oral cavity in a reaction that is catalyzed by the naturally occurring salivary peroxidase, to form hypohiociacian. This ion is a powerful oxidizing agent and can oxidize the thiol groups in the bacterial enzymes responsible for acid production. Initially, a mouthrinse and then a dentifrice containing amylglucosidase and glucose oxidase were used, with mixed results in several animal and human studies.

Koch et al. (1973) and Hugoson et al. (1974) reported a reduction in plaque and gingivitis. The recent studies have been with a dentifrice. Meskin et al. (1983) reported superiority to a rival toothpaste when plaque and gingivitis was studied in a 14-day trial. In a 12-week study there was no difference in plaque but a very modest but statistically significant improvement in gingivitis (Medda & Cooksey 1986). Negative results have been reported by Muller et al. (1981) and Asfahl & Rolla (1983). Additional long term studies are required before we can have confidence in the efficacy of this approach.

Plaque Modifying Agents

As noted in Table 4, a few products have been developed that combine several agents to provide both antibacterial and plaque disruptive properties. A product (also called Ascral T) was introduced as a "mucolytic" agent based on its content of ascorbic acid. percarbonate (an oxygen liberating agent) and copper sulfate. In several published studies, in only one was there a significant reduction in plaque scores (over a four week period), but no reduction in gingivitis (Johansson et al. 1970). There are no further studies published.

Another combination that has been

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Table 3. Antiplaque enzymes

<table>
<thead>
<tr>
<th>Enzyme Type</th>
<th>Enzyme Name</th>
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<tbody>
<tr>
<td>mucinasas</td>
<td>dextranase</td>
</tr>
<tr>
<td>pancreatin</td>
<td>mutanase</td>
</tr>
<tr>
<td>fungal enzymes</td>
<td>zymamidase</td>
</tr>
<tr>
<td>protease - amylase</td>
<td>amylglucosidase, glucose oxidase</td>
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</table>
Table 4. Plaque modifying agents

<table>
<thead>
<tr>
<th>Type</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascendal</td>
<td>Ascorbic acid, peccarbonate, copper sulfate</td>
</tr>
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</table>

examined for an antiplaque, antigingivitis effect is ura peroxide. 11% in an anhydrous glycerin gel. This is a more stable form of hydrogen peroxide which combines its antibacterial and debride-ment properties with the protein denaturing property of urea. In two clinical studies, a short-term reduction in plaque scores but not in gingivitis was noted (Shipman et al. 1971, Chilton & Didio 1971). One study reported a positive effect on both (Zipper et al. 1970).

The use of combinations of agents is perfectly reasonable but the proper mix has not as yet been introduced.

Interference with Attachment

Early attempts to form repellent coatings on tooth surfaces (silicones, polystyrene membranes) as a means of interfering with bacterial colonization were mostly ineffective (see Weinstein & Abel (1964)). With the increasing knowledge about the molecular nature of the interactions between bacterial surface lectins and pellicle receptors as well as some of the biochemical details of co-aggregation, design of specific agents to interfere with attachment seems possible. Passive immunization with specific antibodies, competitive food lectins, various sugars, enzyme etc. have been mentioned as possibilities. Development of a magic bullet is highly possible. There is only one little problem. What should be the target?

Conclusions

Chemotherapeutic mouthwashes can be characterized as solutions that have finally found their problems. For years they have been treated with disdain or at best, tolerance, by the profession and regulatory agencies. The conventional wisdom was that their effect on the oral flora was so transitory or modest that given the rapid regeneration time of the mouth bacteria, their impact was negligible and hence they were no more significant.

In recent years, several changes have occurred that have resulted in a reconsideration. One, and especially seminal.
Zusammenfassung

Chemotherapeutische Mittel zur Kontrolle der Plaque und der Gingivitis

Seit vielen Jahren hat man mit intensiver Forschung nach dynamischen Agenzien gesucht, die im Sinne des Patienten abhängige mechanische Plaquekontrolle zu vervollständigen oder sogar zu ersetzen, um durch die ursprüngliche Krankung zu reduzieren oder ihr vorzubeugen. 5 Kategorien wirksamer Mittel oder therapeutischer Ansätze sind in Betracht gezogen worden: (1) Antiseptika mit breitem Spektrum; (2) Antibiotika gegen spezifische Bakterien; (3) Einzelmischungen oder Enzymkombinationen, die imstande sind, die Struktur oder die Aktivität der Plaque zu beeinflussen; (4) Nicht-enzymatische, plaquemöbilierte oder modifizierende Agenzien; (5) Agenzien, die die bakterielle Hafthaltigkeit beeinflussen können. Der Erfolg dieser Ansätze kann klinisch und durch den Handel bestätigt werden.

LITERATUR


durch die Anwendung standardisierter Messverfahren (Scoring) bei der Messung des Plaquebelag und der Entwicklung der Gingivitis berufen und ihre Verlaufsge

rkeit durch die Untersuchung der Weichgewe

be und der Mikrobiologie gesichert werden. Die hauptsächlichsten Ausmaßmerkmale sind im Laufe der Jahre den anasthasenischen Agenzie

nenteilige Daten zusammen, die die Akkumulation des Anschusses zur anasthasenischen Therapie (Council On Dental Therapies) der zahnärztlichen Gesellschaft Amerikas (American Dental Association) erbracht können. Von der ihren Ergebnissen ausgehend, berechnet Cariogenicitätsindex, Zink und Kupfersalze. Sanguinum und Oceum, wie auch Zinkfluo

ride in geeigneten Konzentrationen, zu weiteren Studien. Auf der Basis der laufenden Forschungstätigkeit könnte eine neue Generation spezifischer antikariöser Substanzen, die das Haftvermogen an das Pellicel beeinflussen, entwickelt werden. Es ist jedoch schwer vorzusagen ob sie auch die Gingivitis beeinflussen können — zunächst bis weitere Informationen darüber verfügbar sind, welche Organ-

ter vorläufighin beeinflussen werden


Resumé

*Agens antiplaque* are agents against the plaque and gingivitis

Depuis bien des années, les efforts ont été menés pour trouver des agents chimiques pouvant aider ou même remplacer le contrôle mécanique de la plaque dentaire par le patient, et donc de réduire ou prévenir la maladie buccale. Cinq catégories d'agents ont été proposés : 1) l'antiseptique à large spectre, 2) antibiotiques dirigés contre certaines bactéries spécifiques, 3) enzymes simples ou combinés pouvant modifier la structure ou l'activité de la plaque, 4) agents non-enzymatiques dispensaires ou modificateurs, 5) agents pouvant modifier l'attaque bactérienne. Le succès de ces approches peut être évalué cliniquement en utilisant des méthodes standard de mesure pour estimer la quantité de plaque et de gingivite, et leur survie en examinant les tissus mou et la microbiologie. Les agents antiplaque ont reçu le plus d'attention. Il n'y a que deux antiplaque qui ont effectuee de données convaincantes lors d'études longitudinales pour obtenir l'appréciation de l'association dentaire européenne: le bis-biguinazide, gluconate de chlorure d'antiseptique et une combinaison d'huiles essentielles (Listerine). Sur la base de ces résultats, d'autres agents proposent une certaine valeur: le chlorure de cetylpyridinium, les sels de zinc et de cuivre, la sanguinarine, l'octenidine et le flavonol de...
tambien a bonne concentration. Actuellement,
une nouvelle génération d'agents antibacte-
riens plus spécifiques est à l'étude, interve-
nant sur l'attaque des microorganismes a la
récouvrement de surface. Il est cependant diffi-
cile de prédire s'ils vont affecter la gingivite,
du moins jusqu'à plus ample information in-
diquant quels organismes sont à viser.

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