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CHEMICO-THERAPEUTIC APPROACH TO PREVENTION OF DENTAL CARIES
Final Report for Contract No. NAS 9-10566

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Submitted by Dr. Ira L. Shannon

Contracted with

University of Texas Dental Branch
University of Texas Health Science Center
P. O. Box 20068, Houston, Texas 77025
The program of chemical preventive dentistry practiced by the Astronauts and their families is based primarily upon the development of a procedure for stabilizing stannous fluoride in solution by forcing it into glycerin. This obviated the deleterious effects of hydrolysis and oxidation present when an aqueous solution was prepared and brought to this new solution an indefinitely extended shelf-life. Research under this contract brought into being new topical fluoride treatment concentrates, fluoride-containing gels and prophylaxis pastes, as well as the first completely stable stannous fluoride dentifrice. These developments were all made possible by the development of a rather complicated heat application method to force stannous fluoride into solution in glycerin.

That the stannous fluoride is clinically effective in such a preparation can be demonstrated by briefly recounting our clinical study involving orthodontic patients at the University of Texas Dental Branch.

A total of 209 patients were studied--99 on the test program and 110 controls. Oral hygiene instruction and supervision were the same for all patients and were of a relatively high order, since the patients were seen frequently by their graduate student orthodontists and were treated under the stringent requirements that would be expected in a graduate division of orthodontics.

The control group (N=110) included fifty-one boys and fifty-nine girls. Eight patients were less than 11 years old, eighty-eight were between 12 and 14, and fourteen were 15 or older. In the ninety-nine test patients, 12 were less than 11 years old, seventy-seven were
between 12 and 14, and ten were 15 or above. This group included forty-two boys and fifty-seven girls.

The program for test patients differed from that for the controls in that it included the daily use of a water-free 0.4 per cent SnF₂ gel each day at bedtime. After the evening brushing of the teeth (the third of the day), the patient rinsed his mouth well and flushed his toothbrush thoroughly with water. He then placed about 3/4 of an inch of gel on the bristles and brushed the gel onto all of the tooth surfaces. The patient then attempted by oral movements, to "force the gel into the spaces between the teeth." He then expectorated but did not rinse. No food or drink was allowed after application of the gel.

In both control and test patients an evaluation of decalcification present was made from chart records, including the report of clinical examinations, roentgenograms, black and white photographs, and color transparencies and prints. Both pretreatment and posttreatment evaluations were carried out. Completion of treatment and full band removal was not accomplished in all patients within the time limitations of this study. In all patients however, teeth were banded for at least 18 and not more than 24 months.

Decalcification was classified as localized or generalized according to the number of surfaces involved. Extent of decalcification was recorded as none; mild, with only a slight change in the enamel color; moderate, with a definite color change and increase in surface area involved; or severe, with frank enamel loss and dentinal involvement. The exact location of the decalcification on the crown was also recorded.
Each patient using the gel was required to maintain a record authenticating the frequency of its use. Every effort was made to assure daily application. At each appointment the patient was questioned as to actual frequency of use, and this was recorded to serve as a criterion for later group consideration.

Of the 110 control patients, 58% presented areas of decalcification around or under bands at the termination of the study. The test patients, gel-users, were divided into groups based upon the degree of cooperation elicited. Twenty-nine of the test patients used the gel once weekly or less (several admitted not using it at all) and the incidence of decalcification for this group did not differ significantly from the 58% level noted for the controls. Nineteen patients used the gel 2-3 times weekly and decalcification incidence was 26%. In the 51 patients who used the gel daily as directed, the incidence of decalcification was reduced to 2%. This work authenticating the effectiveness of daily self-applied treatments with this 0.4% water-free stannous fluoride gel in these high risk patients was published in the American Journal of Orthodontics (66:273-279, 1974).

There is another extremely gratifying clinical result that should be mentioned. Our 0.4% \( \text{SnF}_2 \) gel has proven highly effective in preventing the ravages of the most destructive form of dental decay that we encounter in VA patients. Patients receiving irradiation for malignancies of the head and neck develop a marked xerostomia and, if chemical intervention is not carried out, the teeth literally dissolve in a very short period time. Our clinical studies over the past 4 years have shown clearly that, in the cooperative patient who will brush with the gel once daily, this dental deterioration can be
prevented. This, of course, is a significant step in the prevention of the later development of osteoradionecrosis. For 2 years we have been collaborating with Walter Reed Army Medical Center in preventive care of post-irradiation patients. Dr. Konzelman, who is in charge of patient management at that institution, has placed 200 patients on our gel and has found that its use is highly beneficial in maintaining oral health in the post-irradiation state. In addition to preventing dental breakdown as a function of daily use, Dr. Konzelman reports that the gel is actually effective in the reparative sense. Patients who discontinued regular use of the SnF₂ gel for periods of six weeks developed softening of the tooth surface "so that an explorer could penetrate a clinically detectable depth into tooth structure. After a reinforcement visit, 18 patients resumed daily fluoride use. Three months later, most previously 'soft' cervical tooth structure appeared to be hard. Only six restorations were required in the entire group." These observations from the director of this relatively large clinical study are in complete accord with our observations in veteran patients who have received irradiation therapy. Accordingly, the use of the SnF₂ gel in similar patients is being practiced on an increasingly wide basis throughout VA Hospitals.

These results with extremely difficult problems in dental caries make it clear that this newly developed concept of daily applications of low concentrations of active stannous fluoride will indeed represent a significant step forward in the quests for methods that will eliminate this most prevalent of all human disease processes.

This entire program of chemical preventive dentistry has been
evaluated by the Prevention Committee of the University of Texas Dental Branch and is now the official program of the University. All students are now taught to employ this program in their offices after graduation.

Additional research has been accomplished and additional clinical studies are in progress that suggest that important advances will be made in clinical application of preventive dentistry in the near future. This research has been based upon the knowledge that the four most commonly employed chemicals used to treat teeth ($\text{SnF}_2$, $\text{NaF}$, $\text{Na}_2\text{PO}_3\text{F}$ and APF) are certainly not protecting by the same mechanism of action. A series of experiments was designed in an effort to take advantage of the different protective reactions of the various fluoride solutions. Inter-compound synergistic characteristics were sought by testing the solutions in various sequential applications.

Enamel solubility reduction was studied after 2-minute topical applications of the four test solutions when applied singly. This performance characteristic divided the four solutions into two distinct groups. The $\text{SnF}_2$ and APF solutions protected enamel at some five times the level found for the MFP and NaF solutions. If it is assumed at this point that the protective effect of MFP and NaF are derived entirely from the F ion, it is quite evident that the lowered pH in the APF solution tremendously increased the protective potential of the F ion solution. Each of these 2-minute topical application solutions was then tested when followed by each of the other three test compounds on the enamel surface.
Treatment with NaF alone reduced enamel solubility by 15.3%. This reduction was significantly ($P < .01$) less than that provided by NaF followed by either stannous fluoride or APF ($P < .01$) but was not significantly different from NaF followed by MFP. The additive effects of SnF$_2$ and APF did not differ from each other, but the effect of each was significantly ($P < .01$) greater than that of MFP.

MFP application alone reduced enamel solubility by 13.8%. This reduction was increased significantly ($P < .01$) by subsequent treatment with either SnF$_2$ or APF, but not by NaF. MFP followed by SnF$_2$ gave protection indistinguishable from that furnished by MFP followed by APF, but each of these treatments was significantly ($P < .01$) more effective than MFP followed by NaF.

The topical application of SnF$_2$ alone reduced enamel solubility by 74.6%. Following such treatment by topical application of APF reduced this protection level significantly ($P < .05$) to 70.2%. ESR by SnF$_2$ was also reduced significantly ($P < .01$) by subsequent application of either NaF or MFP. SnF$_2$ followed by APF was significantly ($P < .01$) more effective than the tin compound followed by either NaF or MFP. There was no significant difference when SnF$_2$ was followed by NaF or by MFP.

It was thus evident that if any of these four treatment solutions was to serve as an effective pretreatment, it certainly was not NaF, MFP, or SnF$_2$.

Topical treatment with APF provided an ESR of 71.1%. Adding a subsequent SnF$_2$ treatment increased the protective effect
significantly (P < .01) above that provided by APF alone. Treatment with NaF added significantly (P < .01) to the effect, but MFP did not increase the APF effect significantly. The ESR provided by APF followed by SnF$_2$ was significantly (P < .01) greater than that for APF followed by either NaF or MFP. Of the latter two NaF was significantly the more effective (P < .01).

The finding of most significance in this primary experiment was the remarkably high, 95.7%, enamel solubility reduction produced by treatment with APF followed by SnF$_2$. This suggested the possibility of combined treatment in the dental office. Since 0.5% SnF$_2$ is currently employed as a topical application by many dentists, preceding this with APF solution as a topical or in a prophylaxis paste would not be difficult. Also, since the protection results from at least two separate mechanisms of action, it might be expected that this protection would be of a more resistant type than that provided by either single application. This is particularly true if the products of the reactions are viewed as a heavy formation of CaF$_2$ imparted by APF treatment and a highly insoluble outer layer of Sn$_3$F$_3$PO$_4$ deposited thereon by treatment with SnF$_2$.

An experiment was then designed to ascertain the durability of the protective layer produced by sequential application of APF and SnF$_2$. A total of 120 extracted human teeth were employed in testing three topical application procedures. The first group of 40 teeth received a 2-minute treatment with freshly prepared APF solution containing 1.23% fluoride. Ten teeth were used to measure ESR by this compound in the routine fashion. The remaining 30 teeth were placed in rapidly flowing tap water and, at intervals
of 24 hours, ten teeth were moved and processed through the second lactic acid exposure. ESR was thus measured after no exposure to running water as well as after 24, 48, and 72 hours of exposure. The flowing tap water was intended to simulate somewhat the washing effect of saliva.

The second group of 40 teeth was processed in an identical fashion except that the test preparation was a fresh 0.5% aqueous solution of SnF$_2$. The third group of 40 teeth received a 2-minute application with APF and a subsequent treatment with SnF$_2$.

ESR was calculated in the routine fashion by subtracting the amount of phosphorus by the second (post-treatment) acid exposure from that of the first (pretreatment), dividing this figure by the latter, and multiplying the results by 100.

Enamel solubility results after treatment with APF alone or with SnF$_2$ alone were evaluated. A routine topical application of 0.5% SnF$_2$ provided significantly ($P < .01$) more protection than did APF solution. Treatment with APF alone reduced enamel solubility by 69.2%. Washing for 24 hours reversed this effect significantly ($P < .01$) but no additional significant loss of protection was noted after the 48 and 72 hour washing periods. Treatment with SnF$_2$ reduced enamel solubility by 79.6%. This protection decreased significantly ($P < .01$) during the first 24 hours of washing but, as was the case with APF. Further washing did not decrease the protection significantly.

Thus, with APF treatment alone, washing for 24 hours reduced the initial protection by 52%. With SnF$_2$, the same amount of washing decreased its effectiveness by 57%.
With APF followed by SnF$_2$, the initial level of protection was 94.0%. Washing for 24 hours reversed this effect significantly ($P<.01$), but only to 83.1%. Once again, additional washing over 48 and 72 hour periods did not diminish the protection significantly.

Not only was the reduction in solubility much greater with the combined treatment, but the protection that was provided was of a much more resistant type. Washing for 24 hours after APF-SnF$_2$ treatment reduced the high initial protection by only 12%.

It was thus clear that sequential treatment with APF and SnF$_2$ significantly increased the resistance of enamel to acid dissolution. This protection was significantly ($P<.01$) higher than that provided by either treatment procedure alone.

These experiments, along with several others in the same multiple treatment area (please see dual, multiple and sequential treatment titles in publications listing) have substantiated the validity of the use of more than one fluoride in providing both a high level of protection as well as a more durable effect. This concept is already under clinical trial in our program with orthodontic patients and soon may be brought into widespread use as another step forward in clinical preventive dentistry.

**Xerostomia, Saliva Biochemistry and Salivary Gland Physiology**

Since xerostomia is almost invariably associated with deleterious changes in the teeth, it is a prime subject for consideration in any overall program of caries prevention. As a primary step in developing a better understanding of some of the underlying causes of xerostomia, a disorder that is highly destructive in the dental sense, we have investigated several influences that we considered as possibly
associated with alterations in glandular function. We have precisely determined the contributions of the individual salivary glands to whole saliva volume and have pointed out that increased levels of resting flow are significantly associated with increased resistance to caries but that such is not the case with periodontal status. We isolated a significant effect of systemic dehydration and hyperhydration on gland function, and reported that smoking brought about profuse salivation. An individual's blood pressure was found not to be significantly correlated with his rate of salivary flow, but body position and sleep were highly significant influences. Body weight was not related to saliva flow, and mental exercise was likewise not an influence. The sight of and discussion of food or drink did not affect flow rate but olfactory stimulation (smelling a cut lemon) induced a very high rate of flow.

An exciting development has been our observation of the fact that light deprivation exerts a highly significant depressive effect on the rate of human parotid saliva. When subjects were blindfolded the rate of resting flow fell from 0.057 ml/min (S.D. = 0.027) to only 0.014 ml/min (S.D. = 0.010). For each individual as well as for all as a group, there was a highly significant decrease in rate of function induced by blindfolding.

A second experiment in this series substantiated this result when room darkening was utilized rather than blindfolding. We later established that light deprivation exerted a proportionally depressant effect on rate of function of the human submandibular gland, that there appeared to be no accommodation to darkness during a series of samplings, and that a light intensity of only 0.1 foot
candle is sufficient to maintain the usual level of resting parotid flow. Increasing intensity up to 150 foot candles did not significantly increase this rate of flow.

Light deprivation was also utilized to test our concept of salivary gland electrolyte management in the human that we had established utilizing a potent anticholinergic drug. We had previously established that atropine administration in the human brings about a significant decrease in resting parotid flow and significant increases in concentrations of virtually all of the biochemical constituents of this fluid. A notable exception, however, was sodium which remained constant despite the great decrease in rate of flow. Light deprivation produced biochemical effects similar to those induced by atropine on concentrations of constituents of saliva. These responses in constituent concentrations were in accord with the concept that, at very low levels of gland function, there is a proportionate reabsorption of water from the luminal fluid (or fluid being transferred through the secretory cells) that is initiated by the reabsorption of sodium or by active transport of sodium toward the interstitial compartment.

As a result of the flow rate depression brought about by darkness, we suggested that photic stimulation of retinal receptors is responsible for a component of sympathetic neuronal activity that plays a part in control of human salivary secretion, and that this activity may play a dominant role in maintaining the resting secretion of the gland. There are two major reasons for this suggestion. First, specific sympathetic pathways are known to exist from the retina to the parotid
gland by way of the superior cervical ganglion. Secondly, there are several striking similarities in the innervation and light-induced cyclic changes between the parotid and the pineal gland. Both the pineal and the parotid receive sympathetic postganglionic neurons from the superior cervical ganglion. There are also highly suggestive similarities in biochemical responses and electrophysiology between the pineal and parotid glands under various environmental situations.

Since resting flow is the primary flow with which we are interested in the xerostomic patient, applications for information such as the foregoing will be sought in dealing with the clinical problems associated with such decreased salivary gland function.

We are concerned with xerostomia no matter what its etiology might be, but our primary emphasis in dental prevention with xerostomies continues to be the patients whose depressed salivary gland function is a result of irradiation therapy for malignancy of the head and neck. The measuring of flow as it relates to amount of irradiation, the provisions of a substitute for saliva when flow virtually ceases, the provision of effective chemical protection to the tooth surfaces, and the prevention of osteoradionecrosis by the obviation of tooth disintegration -- all of these are our interests with the xerostomic irradiated patient.


Saliva Biochemistry and Salivary Gland Physiology


Addendum to Final Report on Contract NAS 9-10566, National Aeronautics and Space Administration, Johnson Manned Spacecraft Center, Houston, Texas

In response to the specific requirement for a system by which isolated human subjects could easily collect samples of their own parotid fluid, without technical assistance of any sort, devices have been developed that make this possible. Individualized collectors have been fabricated for American and Russian members of the Apollo-Soyuz teams. Plastic bite blocks have been constructed intraorally to fit the occlusal surfaces of the maxillary and mandibular posterior teeth adjacent to the orifice of the parotid ducts. Subjects can position the collectors simply by fitting their teeth into the impressions in the bite block. Negative pressure is then induced in the outer suction ring of the collector by squeezing and releasing a rubber bulb that is attached by tubing to the suction ring. A second section of flexible plastic tubing leads from the collection chamber in the center of the device to the graduated sample receiving tube. Copious flow is elicited by the simple expedient of sucking on a specially made sour candy drop.

These devices will be employed by participants in the Apollo-Soyuz program for the collection of parotid fluid. Primary analyses of the fluid will be measurements of Secretory IgA and Lysozyme.

Modification of the collection device to meet the Apollo-Soyuz mission requirements has been carried out under this contract.