

TETRADECYCLAMINE DENTIFRICE

The possibility of using salts or other substances to protect tooth enamel against decalcification has long been recognised. Many compounds have been studied for their power of reducing enamel solubility, and this trend in dental research is well exemplified by the work of Muhler & associates (1948)⁹⁸ and Manly & Bibby (1949).⁹⁹

This method of protection appears to operate by reaction of the applied material with the calcium phosphate of the tooth surface, either by adsorption or by ion exchange, to convert it into a new substance of lower solubility. The data of the latter authors suggest that the most effective reagents may be fluorides or salts of some of the rare elements.

A less radical way of protecting the tooth surface is suggested by several reports of reduction of caries resulting from diets with a high fat content. Rosebury & Karshan (1939)¹⁰⁰ found that the addition of various fats and oils to the diet of the cotton rat gave decreasing levels of fissure caries.

Schweigert et al (1946),¹⁰¹ also working with the cotton rat, found that the diets to which lard was added at the expense of sucrose gave much greater protection than could be accounted for merely by the sucrose reduction. Similar views have been expressed by Box (1942),¹⁰² and by

McCullum et al (1939)¹⁰³, who considered that fat might waterproof the tooth surface so that acid was prevented from coming in contact with the enamel. Box also showed that both whole teeth and powdered enamel could be markedly protected by oleic acid against decalcification in vitro.

IN VITRO STUDIES

In the study by Walsh & Green (1950)¹⁰⁴, application of the natural and mineral oils were studied, measurable protection was observed for only two compounds, namely oleic acid and solution of long chain aliphatic amines in paraffin oil. Over a 2-hr. period, a single application cetylamine in paraffin to the wet tooth afforded 70 to 80% protection against saliva at pH 4.0. When the action of acid was prolonged to 24 hours, the protection was still of the order of 50%.

It seems probable that the NH_2 groups of the amine are adsorbed at the enamel surface and the hydrocarbon radicals of the cetylamine then act as a bridge between the enamel and the paraffin oil, which is enabled to form a more or less stable film. This affinity between enamel and amine is sufficient to permit the displacement of saliva from the tooth surface, a process which is facilitated by brushing, and once established the more viscous oils are less easily removed. Since it is generally agreed that decalcification of tooth surfaces by acid is the initial lesion in dental caries, the application of oily adsorbed films suggests itself as a possible prophylactic measure.

These results prompted a more detailed study of other aliphatic amines in solution (Green & Walsh, 1951).¹⁰⁵ The most effective of these compounds was found to be tetradecylamine. Under the conditions of their experiments they found that 1% solution of this amine in medicinal paraffin produced a degree of protection of 86%. The protective effect was enhanced by thorough cleansing of the tooth surface before wetting with saliva. From these experiments, it appeared that a solution of tetradecylamine in medicinal paraffin oil was the most suitable agent for a clinical investigation.

Toxicity test was then carried out by Malcolm, Keaker & Bell.¹⁰⁶ They found that the daily administration of 4 drops of tetradecylamine in paraffin to white rats produced no toxic symptoms. This dosage was greatly in excess of that which could be swallowed by a human being using this compound in a dentifrice.

CLINICAL TRIALS

Preliminary clinical work was undertaken by King (1951)¹⁰⁷, who found that when 1% tetradecylamine was used as a dentifrice, the formation of bacterial plaques on teeth was significantly reduced and that there were no undesirable side effects.

Nevin, Walsh & King (1953)¹⁰⁸ then began a clinical

trial of a tetradecyclamine dentifrice used by a group of school boys aged 13-14½ years. This preliminary trial was of 14-month duration. The preparation was used under the same uncontrolled conditions as applied to the ordinary use of commercial products. 131 boys were divided into 3 groups. The experimental group used 1% free tetradecyclamine dentifrice; the control used a paste which differed in that it contained no tetradecyclamine, and the sub-control group used the ordinary commercial dentifrices.

The result was that 37% less new caries developed in the experimental group than in the control group, and 34% less than in the sub-control group. The result was surprisingly good because a number of factors was discovered which reduced the effectiveness of the experimental paste. The taste was unpleasant, some of the paraffin oil separated out on standing and some of the amine became absorbed on to the calcium carbonate which was used as a filter. Finally, one of the flavouring agents, oil of cinnamon, reduced the effectiveness of the amine by oxidation. Tests carried out on the oil from the experimental paste at the conclusion of the trial showed that its protective effect had been reduced from 25.9 to 15.3%.

In an attempt to overcome some of these difficulties, Irwin & Walsh (1953)¹⁰⁹ prepared a gel containing the amine in bentonite (a colloidal clay) and ethanol. This gel gave approximately 60% protection to the enamel of extracted teeth when they were exposed for 24 hours to saliva buffered at pH 3.92.

Unfortunately, this gel was unpleasant to use in the mouth. Consequently, Irwin, Leaver & Walsh (1955)¹¹⁰ prepared an emulsion in which the taste was improved with oil of peppermint and sucaryl. This emulsion was subjected to a one-year preliminary clinical trial by Ludwig & Taylor (1957).¹¹¹ There was a 44% reduction in dental caries in the experimental group.

The results of the investigation indicated that the use of a dentifrice consisting tetradecyclamine gives considerable protection against caries. It is of particular interest that this protection was given despite no supervision on use. Experiment covered one year and subjects participating were only of a limited number.

However, the participants in this study had two main objections to the experimental dentifrice. Some of them found the taste unpleasant, others objected to the absence of an abrasive and the resultant discolouration of the teeth. In addition, it is found that tetradecyclamine was unstable in this preparation. In the course of time the free amine liberated ammonia and some of its protective action was lost.

Further work was done in an attempt to overcome these objections before subjecting the dentifrice to a large scale clinical trial.

The latest study was carried out by Ludwig (1963)¹¹² on 316 children for two years. The result was negative in reducing dental caries. It seems likely that the failure of

the test dentifrice was due to fairly rapid loss of its protective capacity. Laboratory tests of the tetradecyclamine dentifrice showed its protective rating in vitro fell to about 10-20% which is not high enough to exert a favourable effect in reducing the caries rate in the mouth under the normal condition.

CONCLUSION

From the above evidence, it is obvious that tetradecyclamine is rather unstable. Further work is necessary to improve its availability, before the final assessment of its value in the prevention of dental caries is feasible.

FLUORIDE DENTIFRICES

The addition of fluoride compounds to dentifrices is not a recent innovation, for fluorides were being added to a variety of toothpastes and mouthwashes at the close of the nineteenth century according to Volker.¹¹³ Any useful effect that these preparations might have had was not detected, because the testing of dentifrices in controlled clinical trials had not been developed. In consequence, fluoride dentifrices were neglected until Bibby (1942) tested one containing sodium fluoride. Since that time, there has been renewed interest in fluoride dentifrices, particularly in those containing stannous fluoride.

The value of the fluoride ion in the prevention of caries is well recognised, but the mechanisms of its action are not fully understood.

A number of fluoride compounds has been incorporated into dentifrices: sodium fluoride, sodium monofluorophosphate, various organic fluorides, and stannous fluoride.

SODIUM FLUORIDE

Epidemiological findings in areas where fluoride occurs naturally in the water, indicate that not only is fluoride necessary during the pre-eruptive phase of tooth formation, but also during the post-eruptive phase, if the maximum inhibition of dental caries is to be obtained. This

fact is illustrated by the findings of Dean and co-workers in Bauxite, United States. Children who were exposed to pre-eruptive effects of fluoride had less caries, even though they had no post-eruptive fluoride, but the degree of inhibition was not as great as comparable children, who were continuously exposed to fluoride.

In communities where the drinking water contains the optimal concentration of fluoride, the post-eruptive and pre-eruptive effects of fluoride are acquired by continued consumption of the drinking water. However, in those communities where fluoridation is not possible, alternative methods of bringing fluoride into contact with the tooth have been devised in order to utilize the caries-preventive effect of fluoride. The usual method is "topical application" of a relatively concentrated fluoride solution onto the tooth surface. Up to now nearly 100 study groups embracing many thousands of subjects have been described, and in the great majority of these studies, a positive reduction in caries has been demonstrated. Various dietary supplements of fluoride such as sodium fluoride tablets, fluoride added to milk and to table salt have been tried. Dentifrices with incorporation of sodium fluoride were also used as a means of supplying fluoride to the tooth surface. Furthermore, the choice of dentifrice as a vehicle for anticaries agent is suitable from the view point of its availability to all classes of people.

In 1942, a clinical test, under the direction of Bibby was conducted among orphanage children, 4-16 years of age and among dental students. In all of these studies the group was divided approximately in halves, half using the fluoride dentifrice and half using a control dentifrice. During the first year, 69 children using a dentifrice (Teel) containing 0.01 NaF showed a 23% increase in caries. During the second year, the concentration of NaF was raised to 0.1% and the group showed a 17% reduction in caries. ^{114, 115}

The 48 dental students using a 0.01% NaF toothpaste during the first year showed an 8% increase in dental caries. When they used a 0.1% concentration during the second year, they showed a 20% increase in caries. Another group of dental students using NaF in Teel showed a 12% increase in caries the first year and 14% increase in caries in the second year.

In 1946, a second test was started under the direction of Bibby & Wellock among school children, 9 to 14 years of age. At the end of one year, 122 who used a 0.1% NaF toothpaste showed a 23% reduction in dental caries and at the end of the second year showed a 6% reduction. None of these results, ranging from a 23% reduction to 23% increase in caries, were statistically significant. Then a proposed large scale of testing was undertaken in 1948, under the direction of Wellock with about 2,000 school children, 7-13 years of age. At the end of one year, 946 children who used a 0.1% NaF

toothpaste showed a 9% increase caries as compared to the caries of 969 children who used a control paste.

Smith & Shaner (1946)¹¹⁶ using a powdered dentifrice containing CaCO_3 , and 0.1% NaF, twice daily, reported reduction of Lactobacillus counts.

In 1947, McClendon & Foster¹¹⁷ carried out a clinical trial with powdered rock phosphate (containing 3.77% iron and 7% silica) and synthetic apatite, total fluorine content was 0.25%, as a dentifrice. The study was on 150 young adults, ranging 18-22 years old, with no supervision, for one year. A reduction of 60% was noted. Bibby & Brudevold (1954)¹¹⁵ stated that "in view of negligible ionization of the compounds used, the results are somewhat surprising and point out the need of more specific information on the nature of the fluoride reactions with the tooth surface."

The most recent study of the effectiveness of a sodium fluoride dentifrice was reported by Muhler & associates (1955),¹¹⁸ when they compared the anti-cariogenic effect of dentifrices containing both stannous and sodium fluoride. The conclusions which they reached after conducting the test for a period of one year was that the sodium fluoride dentifrice (containing 0.22% NaF) had no significant effect when used by school children following their usual tooth brushing habits.

The cause of the ineffectiveness of the dentifrice is presumed that the fluoride was incompatible with the abrasive,

and the formation of sparingly soluble calcium fluoride. Ericsson (1961)¹¹⁹ shows that soap, glycerol and sorbitol all reduce the uptake of fluoride from monofluorophosphate and sodium fluoride. This may partly explain the failure of sodium fluoride in preventing formation of dental caries.

STANNOUS FLUORIDE DENTIFRICES

The sodium compound is usually considered first when a soluble salt is required, but Muhler and his associates at Indiana University screened other soluble fluorides for possible caries-inhibitory action. Tests were made upon enamel in the laboratory to measure the protection afforded by different compounds against acid decalcification. The uptake of fluorides was measured. The compounds which showed some promise of the effectiveness were tested on experimental animals before being put to clinical trials.

Muhler & Van Huysen (1947)¹²⁰ showed that stannous fluoride was more effective than sodium fluoride in protecting enamel against acid decalcification, and recently this has been supported by Segreto,¹²¹ and Francis,¹²² but enamel does not accept more fluoride from solutions of the stannous salt than from the sodium salt. Hatton, Nebergall, and Muhler (1955)¹²³ reported that more fluoride was lost from solutions of stannous fluoride than from solutions of sodium fluoride when both were exposed to powdered enamel. However, Smith et al (1957)¹²⁴ showed that this was not due to preferential uptake, but due to the precipitation of fluoride following a change in pH. The stannous fluoride which reacts with enamel probably forms a mixture of a tin phosphate, tin oxide, and calcium fluoride at the surface and fluorapatite within the superficial layers of the enamel.

The results of tests upon experimental animals have been variable. Muhler and associates (1953)¹²⁷ showed stannous fluoride to be more effective than sodium fluoride in reducing the incidence of dental caries in rats and hamsters, but Pindborg (1958)¹²⁶ failed to confirm this.

In a recent review by Muhler et al. (1961)¹²⁵ it was shown that 8% stannous fluoride solution in topical application is more effective than 2% sodium fluoride, and independent work from McLaren & Brown¹²⁸ confirmed this work. However, Nettitt et al. (1958)¹²⁹ were unable to show a significant difference in the caries-preventive effect of the two fluoride compounds.

Thus much of the evidence obtained in chemical, animal, and human experiments indicates that stannous fluoride confers upon enamel a degree of protection which is superior to that of sodium fluoride. However, it should be noted that most of the data upon which this is based have been supplied by Muhler & associates and as yet this evidence has received scanty independent corroboration.

As a result of Muhler's work on stannous fluoride dentifrices, this has led to the marketing of Crest (The Procter & Gamble Company, Cincinnati, U.S.A.) which was first on sale in the United States in 1956.

CLINICAL TRIALS OF STANNOUS FLUORIDE DENTIFRICE

At present there is no method available for estimating the effectiveness of any dentifrice in the prevention of dental caries, therefore, the ultimate proof must depend upon the results achieved in clinical trials. The results of 21 trials of dentifrices containing stannous fluoride are now available. 17 of these trials have been carried out with Crest or a dentifrice of slightly different composition used during the development of the present formula (Table 8). Muhler et al. initiated these trials and their findings appear in a series of reports published since 1954. A trial of Crest by independent workers has been reported by 4 groups of workers. The results of all the clinical trials of Crest and of a dentifrice differing from Crest in pH and binder (Hill, 1959)¹³⁶ are summarized in Table 9.

The first study was conducted by Muhler (1955)¹³⁰ on children without supervision for 1 year with pre-Crest dentifrice. The composition of the dentifrice is shown in Table 8. After 6 months, the total DMFS reduction was 72%, a figure which was never exceeded by the subsequent studies using the Crest formulation. At the end of that year, the caries reduction was 49%. When the control and experimental groups were compared for the 6 to 12 month interval, the reduction in average new DMFS was estimated to be only 9.3%.

The marked difference in the results of the two intervals poses a problem of interpretation. The large

COMPOSITION OF FREE-CREST DENTIFRICE

Stannous fluoride	0.4%
Heat-treated Ca orthophosphate	42%
Detergent (non-soap)	2%
Humectant	25%
Binder	1.4%
Water	29.2%

COMPOSITION OF CREST DENTIFRICE

Stannous fluoride	0.4%
Calcium pyrophosphate (polishing agent)	59%
Stannous pyrophosphate	1%
Monoglycero sulphonate and alkyl sulphate (detergent)	1.51%
Glycerin (humectant)	30%
Carboxymethyl cellulose & veo gum (binder)	15%
Water	24.97%
Minor ingredients (flavour, etc.)	1.62%

TABLE 3. COMPOSITIONS OF FREE-CREST AND
CREST DENTIFRICES.

Date	Authors	Age Group	Duration in years	Super-vision	% Reduction in New DMFS at the end of the year		
					1 yr.	2 yr.	3 yr.
1955	Muhler et al. ¹³⁰	5-15	1	No	49%		
1955	Muhler et al. ¹¹⁸	5-15	1	No	56%		
1957	Muhler et al. ¹³²	17-36	2	No	41	34	
1959	Jordan & Peterson ¹³⁵	8-11	2	1/ day	34	20	
1959	Jordan & Peterson ¹³⁵	8-11	2	No		12 (not significant)	
1959	Hilli ¹³⁶	9-16	2	No	14	15 (not significant)	
1960	Muhler ¹³⁴	6-16	2	No	23	25	
1960	Poffley & Muhler ¹³⁵	10-19	2	3/ day	58 (10 mon.) 47	46	
1961	Keyes et al. ¹³⁷	17-24	2	No	0.5	14 (not significant)	
1961	Muhler ¹³⁹	6-17	3	No	58	55	65
1962	Muhler ¹³⁸	6-18	3	No	24	24	25
1962	Gish & Muhler ¹⁴⁰		2	No		32	
1964	Zacherl ¹⁴¹		1½	No		40 (18 mon.)	
	Weinstein ¹⁴⁴		2	1/ day		12	
	Bixler & Muhler ¹⁴²		2	3/ day		32	
	Muhler & Bixler ¹⁴²		2	5/ day		54	

TABLE 9. Stannous fluoride dentifrices - Clinical Trials.

initial reduction in DMFS noted during the 6 months could so influence the number of DMFS noted at the end of 1 year that a severe loss of effectiveness in the second 6 months would be masked. Maintenance of effectiveness of the stannous fluoride dentifrice has not been demonstrated in this study.

In the second of these trials (Muhler et al, 1955)¹³¹ comparisons were made also with a dentifrice containing sodium fluoride. Unlike the stannous fluoride dentifrice the use of one containing sodium fluoride produced no significant reduction in new DMFS when compared with the control.

In the first three trials tested a dentifrice of similar formula to that given above, but with minor changes in the concentration of some ingredients and without stannous pyrophosphate. In each case the effect of the test dentifrice was compared with the effect of a control dentifrice of similar composition, but without stannous fluoride and the pH is close to neutrality.

In the seventh of these trials (Peffley & Muhler, 1960)¹³⁵, the maintenance of effectiveness of stannous fluoride dentifrice was indicated. 58% reduction in DMFS was noted after 10 months, and 46% at the end of the experimental period. The result indicated the benefit, which may be derived from Crest under carefully supervised conditions.

The topical application of a fresh, 8% aqueous solution of stannous fluoride to children 6 to 17 years of age appears to enhance the benefits derived from an oral hygiene programme

which includes the unsupervised use of Crest dentifrice (Muhler, 1960).¹³⁴ The reduction in caries incidence under these conditions was 63% at the end of 3 years. In a study conducted simultaneously on a similar group which received no topical applications of stannous fluoride solutions, there was a 21% reduction in the incidence of caries. Two unpublished reports show the similar trend. (Scola, and Muhler & Bixler).¹⁴²

The study by Kyes et al.¹³⁷ on a stannous fluoride dentifrice (Crest), a sodium fluoride dentifrice containing the enzyme inhibitor sodium lauryl sarcosinate, and a non-medicated control dentifrice, were compared. These workers were unable to demonstrate any significant differences in the caries-reducing effects of test and control dentifrices, but lack of a measurable effect in this trial, which was carried out on young adults, may have been related to a lower caries rate in these older subjects. However, Muhler & Radike (1957)¹³² using subjects of similar mean age, were able to demonstrate a reduction in caries increment.

The polishing agent in the original formula for Crest was calcium orthophosphate (Table 8). Later calcium pyrophosphate was used as the abrasive, and stannous pyrophosphate was added to provide additional stannous ions to increase the stability of the dentifrice.

The experimental conditions varied widely among the clinical trials with stannous fluoride dentifrices. For instance, the studies were either unsupervised or supervised to varying degrees, three different experimental dentifrice formulae were used, the control dentifrices were not standardized from study to study, and prophylaxis was used in some studies and not in the others. In evaluating the data of these clinical trials four aspects must be considered: 199

1. Does the stannous fluoride dentifrice produce an initial and immediate reduction in caries?
2. Is the effect maintained or altered in the continued use?
3. What are the age group or age groups affected?
4. Do the results reported depend on the toothbrushing technique and frequency?

With such a wide variation in the experimental conditions, however, trends can only be deduced from the clinical studies (published reports only).

Seven of the studies showed positive, but widely varying degrees of initial effect. There was no initial effect with Hill's stannous fluoride dentifrice formulation. These results indicate a trend towards some degree of initial effectiveness.

Of the seven clinical trials where some degree of initial effectiveness was demonstrated, only three showed

convincing evidence of continued effectiveness. Failure of stannous fluoride dentifrice to maintain the initial level of response even over as short a period as one or two years points the need for further investigation of this possible deficiency in their action. Among explanations for the loss of effectiveness may be included the possibility of development of acquired bacterial resistance to the action of stannous fluoride or the relative instability of the action chemical components in the dentifrice.

It is not possible at present to evaluate the effect of stannous fluoride on adults since only two of the ten trials involved adults. The study by Nubler et al. (1957)¹³² showed a substantial reduction of caries in adults using the pre-Crest formula, but in the study by Eyles reported that there was no reduction of caries in adults who used the Crest dentifrice. The age range used in both of these studies was too restricted (college freshmen) to allow conclusions to be drawn for the adult population in general.

The results of these studies may be summarized arranging the percentage reduction in caries and the degree of brushing supervision as follows :

<u>Conditions of Use</u>	<u>Reduction of DMFS in % after 1 year</u>
Unsupervised brushing	23
Once a day brushing (supervised)	34
Three times a day brushing (supervised)	58
Unsupervised brushing in addition to an 8% SnF ₂ topical every 6 months	58 (after 10 mon.) 47

The statement of the Council on Dental Therapeutics of the American Dental Association made on June 15, 1959,¹⁴³ after analysis of the data of these clinical trials, indicate that a stannous fluoride containing dentifrice (Crest) is an effective anti-caries agent, and that the effectiveness, although it is demonstrable under normal conditions of use, is greater when used more frequently, that is, three times a day in a supervised brushing programme. Crest was classified as Group B in Accepted Dental Remedies, which states "Group B consists of products which lack sufficient evidence to justify present acceptance, but for which there is reasonable evidence of usefulness and of safety. These products meet the other qualifications and standards established by the Council on Dental Therapeutics. It is the Council's opinion that Group B products may be promoted for special use and study."

In August, 1964,¹⁴⁴ the Council on Dental Therapeutics has reclassified Crest from Group B to Group A with the following statement :

"Crest has been shown to be an effective decay preventive dentifrice that can be of significant value when used in a conscientiously applied programme of oral hygiene and regular professional care."

According to the Council, "Group A consists of accepted products which will be listed in ACCEPTED DENTAL REMEDIES and may use the Seal of Acceptance, unless otherwise provided."

In August, 1960,¹⁴³ when the Council first classified the product in Group B, seven clinical studies had been submitted by the Manufacturer for evaluation by the Council. Since that time 8 additional clinical studies have been conducted. Six of these have not yet been published.

A clinical investigation of 18 months' duration was conducted by Zacherl¹⁴¹ in Canada, on children who brushed their teeth at home as usual, and in this study, the reduction observed was approximately 40%.

A 2-year study by Weisenstein¹⁴⁴ involving the normal home use of the product plus supervised brushing once a day resulted in reduction of caries by 12%.

Gish & Muhler (1962)¹⁴⁰ conducted one clinical study with children, who had lived all their lives in a community in which the water supply contained fluoride at a level of approximately 0.9 ppm. In this instance, the investigation found that after 2 years, the test subjects averaged 32% fewer new caries lesions than the controls.

Another 2-year study by Lihler & Bixler with supervision of brushing three times a day showed 32% and 54% reduction in DMFS.¹⁴²

In a number of clinical studies a group using Crest was compared with a control group. Other groups were also included to determine whether it was possible to obtain additional benefit by the topical application of concentrated stannous fluoride solutions and/or by the use of a prophylactic paste containing stannous fluoride. Although the data from each of these studies do not always indicate an added effect, they do suggest that the additional procedures generally complement each other. (Table 10).

In August 1964, the Council on Dental Therapeutics announces: "Cue toothpaste (product of Colgate-Palmolive Company) as an agent for home use in the partial prevention of dental caries, has been classified as the product in Group B". It further states that: "Cue has been shown to be an effective decay-preventive (anti-carries) dentifrice that can be of significant value when used in a conscientiously applied programme of oral hygiene and regular professional care."¹⁴⁵

The active ingredient in the product is stannous fluoride. The Cue formula contains :

Technique

1/2 Reduction in DMFS 142
Fixler & Muhler Seola et al. (1963)
(1964)

Technique	1 yr.	6 months
Prophylaxis SnF ₂	54.5	40
Prophylaxis + SnF ₂ dentifrice	34.8	61
Prophylaxis + topical SnF ₂ (8%)	44.7	
Prophylaxis + topical SnF ₂ + SnF ₂ dentifrice	66.5	74

TABLE 10. Clinical trials of stannous fluoride dentifrices with combination of paste, and solution.

Stannous fluoride	0.4%
Insoluble Na metaphosphate	40.6%
Anhydrous dicalcium phosphate	5%
Glycerin	27%
Water	22.35%
Miscellaneous, including binder, foaming agents, and flavour	4.65%

The manufacturer has submitted data from laboratory and animal studies and three clinical studies, each of which was of 2-years' duration. These studies were conducted under varying conditions; one involved the use of children ranging in age from 7 to 16. In this study, the brushing was supervised 3 times a day, and the subjects received a dental prophylaxis every 6 months. The data indicate a DMFS reduction in caries incidence of approximately 37%. (Thomas.)

A second study by Mergelle et al. conducted in a community in which water was fluoridated at a level of 1 ppm, involved the use of children ranging in age from 8 to 15 whose brushing was supervised twice a day. In this study, the reduction in caries incidence was approximately 16%.

The subjects in the third study (Henriques et al.) were between 5 and 12 years of age, and they received no brushing supervision or prophylaxis. In this instance, caries reduction was about 17%.

Although the results of each of these studies were not statistically significant at the same level of confidence, each did show a positive reduction in caries incidence for the test group when compared with the control. In each of these studies the product was also compared with another stannous fluoride dentifrice which has been shown to be effective in clinical studies. In each instance, the products were found to produce similar degree of caries reductions.

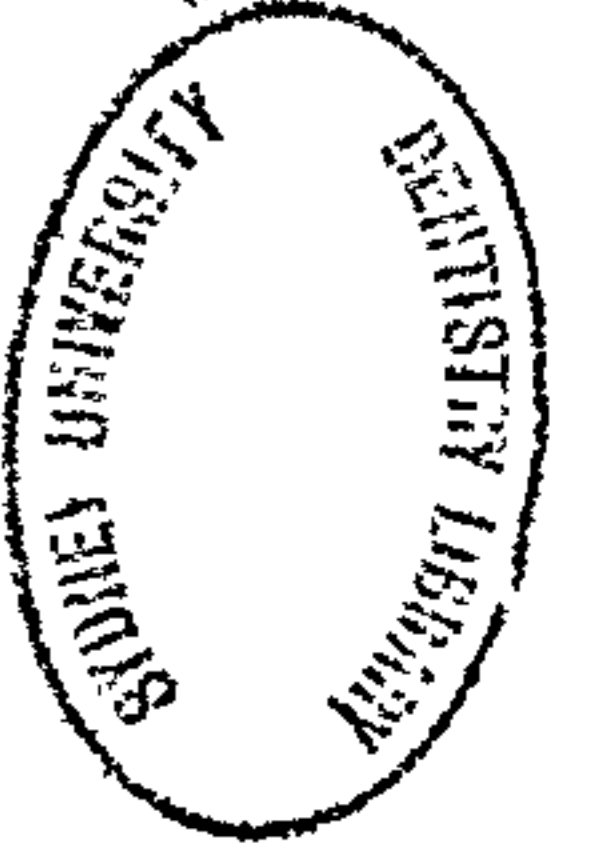
AUSTRALIAN FLUORIDE DENTIFRICES

Although there is a number of fluoride dentifrices available in Australia containing both stannous and sodium fluoride, there are, as yet, no clinical trials either conducted or published which would enable their effectiveness to be evaluated.

Chong¹⁴⁶ (Commonwealth Bureau of Dental Standards) has carried out laboratory testing of fluoride toothpastes. She estimated the percentage reduction in solubility of enamel from deciduous teeth after treatment with the fluoride toothpastes. The results are so variable, that it is impossible to quote quantitative values for the degree of protection. However, they do give a general picture of the efficiency of the dentifrices. With one exception, none of the sodium fluoride dentifrices showed any improvement, but those containing stannous fluoride, namely Colgate, Floran and Gibbs stannous fluoride dentifrices and the U.S. product

Crest (not available in Australia) exhibited a definite protection against acid attack. The sodium fluoride dentifrice showing similar protection was Nyal Fluoride. Similar work has been reported by Gillings & Broadhurst (1963) on the enamel solubility reduction by 10-30% with local sodium and stannous fluoride dentifrices.

As mentioned previously, at present there is no method of assessing the effectiveness of a dentifrice by laboratory means, and clinical trials of two or three years of testing are required to confirm their therapeutic value. However, these dentifrices, which have been mentioned, can be used with perhaps a reasonable possibility of some protection.



MONOFLUOROPHOSPHATE

Monofluorophosphate is a complex fluoride, which does not yield fluoride ions in aqueous solution. It is soluble to the extent of about 25 gm in 100 gm of water at room temperature yielding a solution with pH 7 to 7.5. The salts yield the PO_3F^- ion which is stable at ordinary temperature in neutral or slightly alkaline solution. In acid solution the complex slowly hydrolyzes to orthophosphate and fluoride.

Shourie et al. (1950)¹⁴⁷ showed that when monofluorophosphate was administered at a level of 400 ppm of fluoride in the drinking water of Syrian hamsters, monofluorophosphate and sodium fluoride caused comparable and nearly maximal reductions in the destruction of tooth surfaces of dental decay. Monofluorophosphate was found to be 7 to 8 times less toxic in 200 to 300 gm to rats than was sodium fluoride. When it was calculated on the basis of fluoride content the complex fluoride is 2.5 to 3 times less toxic than the free ionic form.

Haydon and associates (1951)¹⁴⁸ found that fluorides as $\text{Na}_2\text{PO}_3\text{F}$ was approximately twice as effective as fluoride in sodium fluoride in inhibiting acid production in saliva-glucose mixture. It was also shown that while increasing the amounts of calcium ions progressively decreased the effectiveness of sodium fluoride against salivary acid production. No such decrease observed for $\text{Na}_2\text{PO}_3\text{F}$. Samples of hydroxyl apatite

were treated with $\text{Na}_2\text{PO}_3\text{F}$ and sodium fluoride at levels of 20, 40, 80, 160 and 320 ppm fluoride. The apatite treated with $\text{Na}_2\text{PO}_3\text{F}$ at the lower levels of fluoride showed a greater solubility than that treated with sodium fluoride. At the higher levels of fluoride the situation was reversed.

Fluoride analyses of sodium fluoride treated apatite showed an increase to a saturation between the 80 and 160 ppm levels, while the fluoride content of $\text{Na}_2\text{PO}_3\text{F}$ treated apatite increases at each successive level. The fluoride content of $\text{Na}_2\text{PO}_3\text{F}$ treated apatite was always below, being about half at the 80 ppm level.

Haves et al. (1951)¹⁴⁹ conducted topical application of 15% solution of monofluorophosphate every 4 months for one year, on 150 boys and girls whose average age was 12.1 years. At the end of one year, 20% fewer new decayed and filled surfaces among the treated teeth continuously present and 30% fewer new decayed and filled surfaces among teeth erupted during the year in which there were one or two treatments.

Santesson (1957)¹⁵⁰ showed that fluoride was taken up by enamel from solutions of sodium monofluorophosphate. Ericsson (1961)¹¹⁹ in his radioactive fluoride study, it appears that the uptake of fluoride by powdered enamel and intact enamel surfaces is considerably lower from solutions of sodium monofluorophosphate than from comparable solutions of sodium

fluoride, especially at pH values below 6. A notable exception is the uptake from the liquid phase of the dentifrices by homologous tooth surfaces, which was about the same from both compounds.

The quantities of calcium and phosphate that were liberated from the enamel on treatment with sodium monofluorophosphate were less than with sodium fluoride. This may be due either to a lower reaction rate with the monofluorophosphate ion or a special mode of reaction of this ion with the enamel phosphate. It may be mentioned in this connection that treatment of powdered enamel or enamel surfaces with sodium monofluorophosphate results in an uptake of phosphate simultaneously with fluoride, although to a less extent, this was found in experiments with P^{32} & F^{18} labelled sodium monofluorophosphate. This, however, still does not answer the question of the mode of action of the monofluorophosphate ion.

CLINICAL TRIAL

Finn and Jamison (1963)¹⁵¹ tested the effectiveness of monofluorophosphate dentifrices on 600 children brushing the teeth 3 times a day under supervision. Three types of dentifrice were used with the following ingredients :

1. A 0.76% sodium monofluorophosphate tooth-paste formulated in a compatible base of insoluble sodium metaphosphate as the polishing agent, and a mixture of sodium lauryl sulphate and sodium N-lauroyl

sarcosinate to the desired taste and foam characteristics (pH about 5.5)

2. A 0.4% stannous fluoride toothpaste formulated in a compatible base with calcium pyrophosphate as the polishing agent (pH 4.5 to 4.8)

3. A 2.0% sodium N-lauroyl sarcosinate toothpaste compounded in a compatible base containing dicalcium phosphate dihydrate as the principal polishing agent (pH about 7).

At the end of 2 years, the 0.76% sodium monofluorophosphate dentifrice permitted approximately 25% fewer new DF surfaces than a dentifrice containing 0.4% stannous fluoride with calcium pyrophosphate or one containing 2.0% sodium lauroyl sarcosinate with dicalcium phosphate dihydrate. The difference is significant statistically. This study also indicates that there is no significant difference between the effects on caries incidence of stannous fluoride and 2% sarcosinate dentifrice. This study does not imply that either the sarcosinate or stannous dentifrice will not produce a reduction to dental caries; they may well do so. However, if a reduction is achieved it is similar in both the stannous fluoride and sarcosinate dentifrice, with significantly less caries reduction than found for the sodium monofluorophosphate dentifrices tested.

This is the only clinical test that has been conducted so far on sodium monofluorophosphate dentifrice. Its effectiveness in the control of dental caries can only be evaluated when further work is carried out.

AMINE FLUORIDE DENTIFRICE

Dentifrices containing organic fluoride compounds have been developed from laboratory work which showed that aliphatic mono-amines protect enamel against decalcification (Irwin, Nevin & Walsh, 1957)¹⁹⁸. This action, which was explained by the formation of a mono-molecular water-repellent layer at the enamel surface, led Muhlemann, Schmid & Konig (1957)¹⁵² to test the hypothesis that if the detergent action of these organic compounds could be combined with the action of fluoride an increased protection of the tooth should result.

In vitro studies with amine fluorides and preliminary animal experiments have shown some of these compounds to be superior to inorganic fluoride in several respects. Anti-bacterial, physico-chemical and anti-solubility properties as well as low toxicity were promising enough to justify an investigation into their effectiveness in a therapeutic dentifrice. In vitro tests of the compatibility of amine fluorides with different abrasives and other abrasives and other basic dentifrice constituents were also carried out.

Konig & Muhlemann (1961)¹⁵² tested the caries-inhibiting effect of amine fluoride containing dentifrices in animal experiment. Applications of 5 different amine dentifrice pastes were done twice daily for 3 days and once daily for another subsequent 17 days with rather soft hair

pencil, slightly brushing the molars for about 15 seconds. Superfluous toothpaste from around the animals' mouths was wiped off with a clean cloth. Food cups were not accessible for 2 hours after each application. For the last time toothpastes were applied 24 hours before the experiment ended. The tooth surface solubility was then measured. A caries inhibiting action of amine fluoride dentifrices and superiority of insoluble metaphosphate incorporated as abrasive were found in the animal study and as well by Marthalar in the clinical study.

Marthalar in the same year used 5 types of dentifrices, as shown in Table II, to study the effectiveness of amine fluoride dentifrice in the control of dental caries. The study was on 800 children, aged 7 to 12 years, in Zurich. The amine dentifrices showed significant reduction in the dental caries. In contrast to the stannous fluoride dentifrices, the study indicates no fluoride effect at all during the first 6 months and a significant effect during the following 12 months. This can only be in part explained by the slight inactivation of the dentifrices in the metal tubes used during the first three months of the study. It is assumed, therefore, that in the case of amine fluorides the cariostatic effect shows a time lag after the onset of the fluoride application. A clearer answer to this problem is only possible after a longer duration of the study.

In the animal studies, with respect to initial

carious lesions, the 3 amine fluoride dentifrices, whether containing metaphosphate or barium sulphate as abrasives, were identical in cariostatic effectiveness. With respect to the more progressed lesions, the amine fluoride dentifrice containing metaphosphate was superior in the animal experiment to the corresponding barium sulphate dentifrice. In the clinical study, it was found that when insoluble metaphosphate was used as abrasive, greater reduction of dental caries was noted.

From the limited evidence available, it is impossible to evaluate the effectiveness of amine fluoride in the prevention of dental caries.

DENTIFRICH

	A	B	C	D	E
Sodium lauryl sulphate	1.00	1.51	1.00	1.51	1.89
Compound 2971	"	0.41	"	0.40	"
Compound 242"	"	25.00	35.00	35.00	35.00
Mucilage	12.00	12.00	12.00	12.00	12.00
Sorbitol					
Insoluble metaphosphate	55.00	35.00	"	"	"
Barium sulphate	"	"	30.00	30.00	30.00
Titanium dioxide	1.00	1.00	"	"	"
Ground resin	5.00	5.00	"	"	"
Water (with saccharin and aromatics)	21.00	20.09	22.00	21.09	21.11
Total	100.00	100.00	100.00	100.00	100.00

† Diethanol aminopropyl-N-ethanol octadecylamine dihydrofluoride.
 1.51% compound = 0.1% fluoride
 1.89% compound = 0.125% fluoride.

" Cetylamin hydrofluoride, 0.40 compound 0.025% fluoride.

TABLE 10. Composition of the dentifrices used in the Marthaler study.

COMPATABILITY OF FLUORIDE WITH DETERGENTS & ABRASIVES

It is well known that the effectiveness of sodium fluoride dentifrice was lost through the reaction of fluoride with the abrasive agent, calcium phosphate, with the formation of calcium fluoride. In the experiments reported by Ericsson (1961)¹¹⁹ have further shown that soap, glycerol and sorbitol all reduce the uptake of fluoride from sodium fluoride and stannous fluoride and sodium monofluorophosphate. This finding may help to explain some of the negative results in previous clinical tests with fluoride-containing dentifrices. There was little or no reduction of the fluoride uptake with sodium lauryl sulphate and carboxymethyl cellulose.

Much work has been spent by Muhler and collaborators in the search for suitable abrasives for a dentifrice containing stannous fluoride. From Ericsson's tests, it is evident even with calcium pyrophosphate, regarded by the Muhler group as the most suitable abrasive for a stannous fluoride toothpaste, may rapidly bind the greater part of the fluoride in stannous fluoride, if the pyrophosphate is not of the ideal quality. In spite of the great loss of fluoride from stannous fluoride to the abrasive used in the toothpaste tests, the fluoride uptake by the enamel was notably high from this compound. Still more remarkable was the low liberation of phosphate from the enamel by treatment with stannous fluoride, probably owing to the low solubility of tin phosphate as tin is known to be taken up at the same time as fluorine.

In addition to calcium pyrophosphate other abrasives seem to deserve testing in combination with stannous fluoride. Silica was suggested by Segreto et al. (1959).¹³¹

Ericsson (1963)¹⁵³ found that several aluminium compounds appear suitable as abrasives in dentifrices owing to their moderate degree of hardness and their consistency when incorporated in paste. The compatibility of the fluoride compounds, NaF , SnF_2 , ZrF_4 , and $\text{Na}_2\text{PO}_3\text{F}$ with some aluminium compounds, which might be employed as abrasives in toothpaste and dental polishing agents was tested using F^{18} as a label. Aluminium oxide and synthetic aluminium hydroxide and kaolin could be used in different pH ranges with different compounds. The F^{18} uptake by powdered dental enamel from the labelled fluoride was greater than previously found by the author when testing the same fluoride in combination with other abrasives.

The variations of the results obtained with SnF_2 might be explained by the lability of this substance: minor changes in the experiment conditions will cause notable variations in the degree of oxidation and tin hydroxide precipitations. The relative insensitiveness of the sodium monofluorophosphate to pH changes and the probable difference in the mode of reaction of this salt with the enamel, as compared with the simple fluoride ions, may possibly be utilized to obtain a combined effect of the two ions.

STABILITY OF STANNOUS FLUORIDE IN DENTIFRICE

The instability of stannous fluoride in solution was reported by Muhler & associates in 1952. Loss of almost half the activity of a solution containing 100 ppm was reported to take place in 5 days, during which time the pH changed in proportion to the amount of stannous hydroxide precipitated.¹⁵⁴

In 1954, animal studies confirmed the influences of pH and aging, in that lessened effect on animal caries was observed for solutions with changing pH or with one week's aging of a stannous fluoride solution.¹⁵⁵

In 1955, Hatton, Nebergall & Muhler¹⁵⁶ reported that freshly prepared stannous fluoride solution hydrolyzes within a short time, and that further dilution produced more precipitate. The ease of oxidation of stannous fluoride solution was confirmed by Muhler & Day¹⁵⁷ in a study showing that solution of stannous fluoride in oxygen-free water will enhance the effectiveness of stannous fluoride in reducing dental caries initiation and extension. A change in pH of the drinking water containing stannous fluoride from 2 to 4 weeks was observed to decrease the cariostatic action by about 50%.¹⁵⁶

The influence of change in pH was reported by Walsh et al. (1957), it was observed that tin in neutral solution is quantitatively removed from the solution as the insoluble hydroxide.¹⁵⁸

During most of the topical application studies the need for precautions has been recognised, as for example one in 1958,¹⁵⁹ wherein the solutions were prepared and used immediately.

In the formulation of stannous fluoride dentifrices an attempt is made to minimize the loss of the effective agent by acidifying the preparation to a pH of about 4.5. In addition, new abrasives have been employed, or specially developed, to reduce the loss of fluoride by precipitation as calcium fluoride.

Calcium pyrophosphate is used as polishing agent in the Crest dentifrice, and is prepared by heat treating calcium orthophosphate. This polishing agent is to be compatible with stannous fluoride. Stannous pyrophosphate, not present in the original formula, was added in an attempt to maintain the level of available stannous ion. Other manufacturers are using insoluble sodium metaphosphate, either alone or together with small amounts of calcium compounds, as the polishing agent in their dentifrices.

Two studies have been reported, in which there has been an attempt to assess the availability of these ions and to measure the loss in availability which occurs as the dentifrice ages during storage.

In the first, Manly (1961)¹⁶⁰ analysed two commercial

preparations and showed a surprising variation in the amount of available fluoride in the dentifrice. The half life for stannous tin, or the amount at which 50% of tin is available in an aqueous extract, seems to differ for the two products. It appears 5 to 6 weeks for one product and perhaps 30 to 40 weeks for the other. There is a definite correlation between age of a dentifrice and the availability of tin present in the dentifrice. The availability of fluoride does not show such a good correlation with age of dentifrice. In general there is a correlation of availability of fluorine and stannous tin in one brand of dentifrice only. As soon as the availability of either tin or fluoride goes below 56% there appears to be no longer any correlation between the two parameters. It was further found that the % of available tin seemed to be a better index of protective action of the enamel against dissolution in acid, than was the % of available fluoride.

In the second study, Duckworth (1962)¹⁶¹ measured the available fluoride in three dentifrices that were on sale in U.K. The fluoride extracted by both water and saliva was estimated. There was a decrease in available fluoride with time, but a possibly more important finding was that the amount of fluoride released to saliva was less than the amount released to water. It is not known for certain why there is less available fluoride when the dentifrice is extracted with saliva; the fluoride may react with salivary calcium and be precipitated as calcium fluoride or become bound to protein in the saliva (Hall, 1962).

These analytical data suggest that the shelf life of a stannous fluoride dentifrice could have an important bearing upon its effectiveness, and that for maximum effect the manufacturer should get the product to the consumer as quickly as possible.

TOXICITY OF FLUORIDE-CONTAINING DENTIFRICES

The introduction of fluoride-containing dentifrices for prevention of caries necessitated the assessment of the safety of such dentifrices if they are to be used daily by children and adults over prolonged periods of time. Sodium fluoride, stannous fluoride or amine fluoride are incorporated into dentifrices at concentrations of between 1000-2000 ppm of fluoride. Thus rather high concentrations of fluoride preparations are recommended for daily use in oral hygiene.

ACUTE TOXICITY

Several studies have been conducted in order to evaluate the LD_{50} of fluoride-containing dentifrices in experimental animals. For fluoride if incorporated in a stannous fluoride dentifrice (fluoride of 100 ppm) the LD_{50} value for rats and mice was found to be about 100 mgm./kg and 70 mgm/kg of body weight, respectively.¹⁶²

In the human the possibility of ingestion of a lethal amount of fluoride toothpaste can safely be considered as a non-existent danger. Even if the entire contents of a large tube of fluoride dentifrice of approximately 140 gram, furnishing 140 mgm of fluoride, would be ingested by a child, the average lethal dose of 50 mgm/kg of body weight, as calculated for the human by Cox & Hodge,¹⁶³ would not be reached.

In their review on fluoride toxicity, Smith & Hodge calculated the lethal dose of between 2.5 gm and 5.0 gm of fluoride.¹⁶⁴ These figures are calculated for soluble fluoride salts as e.g. sodium fluoride or sodium fluosilicate. In the case of fluoride dentifrices the acute toxicity is markedly reduced by the presence of some compounds or ions which interfere with fluorine absorption.

CHRONIC TOXICITY

When fluoride-containing dentifrices were first introduced to the market, the possibility was discussed of cumulative effects of additional daily ingestion of fluoride, which might be especially harmful in areas where drinking water already contained one or more ppm of fluoride.

Eichler & co-workers (1955)¹⁶² determined in children the amount of fluoride swallowed by weighing the fluoride dentifrice on the brush and subsequently analyzing the fluoride recovered in the rinsing water 80%. Since on the average 0.5 gm of dentifrice was used for one brushing, about 0.2 mgm of fluoride would be ingested in 2 brushings with a dentifrice containing 1000 ppm of fluoride. Another report gives an average ingestion of 0.3 mgm of fluorine with 2 brushings using similar method.

Schweinberg & Muhler (1956,¹⁶⁵ 1957¹⁶⁶) determined in two studies the urinary fluoride levels of school-age

children using a stannous fluoride-containing dentifrice over prolonged periods of time. The total daily urinary fluoride excretion was found to be 0.22 mgm in dentifrice groups as compared to 0.84 mgm in the fluoride group. Thus, not the least increase in urinary fluorine excretion was observed if stannous fluoride-containing dentifrice was used.

Duckworth (1963)¹⁶⁷ using radioisotope-labelled fluoride found that about 75% of the fluoride was recovered after brushing the teeth for one minute and rinsing with a mouthful of water. Similar results were reported by Ericsson (1961)¹¹⁹ using three simplified fluoride dentifrices.

In radioisotope studies on adults (Duckworth, 1963)¹⁶⁷ less than 2% of the fluoride originally present on the brush was excreted during the 4 hours after toothbrushing.

Thus, it appears that very little fluoride is retained in the body when dentifrices containing stannous fluoride are used in the normal way.

Animal experiments upon the toxicity of sodium monofluorophosphate by Ericsson (1961)¹¹⁹ and amine fluorides by Marthalar (1960)⁸¹, and Buttner & others (1961)¹⁶², indicate that the use of these compounds in dentifrices is a safe procedure.

LOCAL TOXICITY

When a 10% solution of stannous fluoride is applied to the teeth, blanching of the gingival tissue occurs, but no lasting histological or clinical abnormality has been detected by Sweitherman, et al. (1961).¹⁶⁸ It seems unlikely that the continued use of a dentifrice containing a much lower concentration of stannous fluoride could exert a harmful effect upon the soft tissues. It has been argued that fluoride in a dentifrice may interfere with the lactate-peroxide metabolism of the oral flora, making the mouth and throat more liable to infection (Kraus, 1962).¹⁶⁹ but this is not supported by Goose & Melville.¹⁷⁰ In their trial of 68 students for a period of 6 weeks, there was no readily detectable increase in soft tissue inflammation in the tonsillar region and the upper anterior gingiva in those using a stannous fluoride toothpaste.

MECHANISM OF ACTION OF FLUORIDE

THE ENAMEL SURFACE

Enamel is the most highly mineralized tissue in the body. It contains on a weight basis, 96-97% of mineral, 2-3% of water and less than 1% of organic material.

The main mineral component of enamel is a hydroxy-apatite, whose "unit cell" or simplest repeating structure may be represented by the formula,



This formula does not indicate the ionic arrangement but only the number and kind of ions in the hypothetical unit cell.

The inorganic phase is not pure and is not of constant composition. The variations, however, are within narrow limits and are primarily in respect to fluorine, magnesium, carbonate, sodium, potassium, chloride, and other minor trace elements.

In intact enamel the apatite crystals are closely packed together, but exceedingly small spaces do exist between the crystals. These spaces which are greater in young than in old enamel are filled in part with organic structure and in part with water.

It has been found that the water adjacent to the crystal is attracted to the crystal surface by electrostatic forces which are so powerful that it may actually be considered

part of the crystal. This tightly bound water layer, or hydration shell, may be regarded as first part of the crystal, the surface of the crystal as another part, and the interior of the crystal as a third portion.

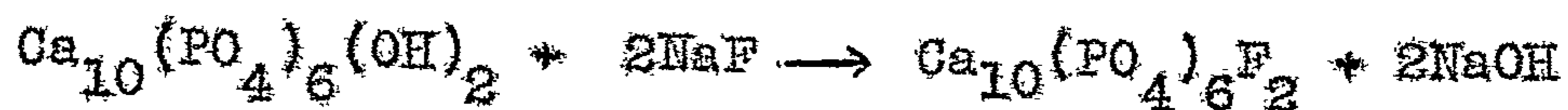
At the interface of the hydration layer numerous ions may adsorb. Much effort has been expended in studying the orientation of the ions in and around the crystal lattice. Although the positions that each ion may occupy are known, the positions that some of the ions do occupy are still a matter of discussion.

Thus there are three sites where the components of the enamel mineral can exist, within the crystal, on the surface of the crystal and in the hydration shell. Exchange reactions will be easiest in the hydration shell and most difficult deep within the crystal. Only those ions which are the correct size can substitute within the crystal lattice, e.g., F^- , Sr^{++} , H_3O^+ , others may be adsorbed on to the surface, e.g., Na^+ , F^- , Mg^{++} and possibly citrate. The hydration shell may contain many ions in addition to Ca^{++} and $HPO_4^{=}$.

REACTIONS OF FLUORIDE WITH ENAMEL

It is now well established that the fluoride ion can react with enamel in several ways. McCann and Bullock concluded that five different reactions could occur, the relative importance of which depended on the concentration

of fluoride. At low concentrations, as with fluoride in water, the reaction is mostly an ionic exchange leading to the formation of fluorapatite, which can be regarded as irreversible. The reaction is represented by the following equation:²⁰⁰



At the concentrations relevant to dentifrices or topical application, additional reactions with sodium fluoride occur including the precipitations of calcium and magnesium fluorides (especially at low pH values) exchange with carbonate and adsorption. Calcium fluoride formation occurs only at fluoride concentrations greater than 75 to 100 ppm.



The calcium fluoride will precipitate as a very fine powder on the tooth surface, and the other products, the Na_3PO_4 and NaOH , will dissolve and wash away. Part of the calcium fluoride will wash away too, but whatever is left will slowly dissolve and participate as in the first reaction as above, i.e. the remainder is slowly converted to the more stable fluorapatite.

Fluoride exchanges with hydroxyl ion. This is a completely different reaction in which crystal structure remains intact, but hydroxyl groups will be replaced by

fluoride. This second reaction will take place only at high concentration of fluoride and calcium fluoride which is slightly soluble, will provide such a low fluoride solution when it is precipitated on the tooth's surface. The fluorapatite formed by this second reaction is quite insoluble compared to the original hydroxyl apatite, and therefore represents a more resistant material.

This reaction of fluoride with tooth structure is essentially a surface reaction. Isotope studies have shown that this latter reaction takes place in three steps, involving the hydrated spaces between the apatite crystals, the crystal surfaces and the body of the crystals, respectively.

In the first of these phases, fluoride diffuses into the hydration shell. This process is extremely rapid, it is reversible, and the fluoride is not firmly bound. In the second phase, fluoride assumes the positions of hydroxyl ions on the crystal surfaces. The rate of this reaction is slower than that of the first phase and the attached fluoride is firmly bound. Finally, in the third phase, fluoride may penetrate into the crystal and exchange with hydroxyl groups located in the body of the crystal. This reaction is exceedingly slow and has no significance in topical applications or with the use of dentifrices.

Reaction of the enamel with stannous fluoride

Topical applications of stannous fluoride in the form either of solution or of dentifrice involve reactions of the stannous as well as the fluoride ions. The initial rate of reaction of fluoride is much faster than the steady rate established after some minutes of treatment. The steady state for the reaction of tin is one of equilibrium, in which the enamel receives no net increase of tin after the initial reaction. Fluoride penetrates into the enamel, whereas most of the tin is on or near the surface as a uniform, tough coating. Presence of the coating inhibits diffusion, slows reactions and protects the enamel from dissolution through acid attack. Both the fluoride and the tin reaction rates are dependent on concentration in dilute solutions. In stronger solutions, a change of concentration has little effect about 0.1M is reached. Thereafter, fluoride reactivity increases with concentration and tin reactivity is influenced by hydrolytic precipitation of tin onto the enamel.

Large amounts of tin containing precipitate gather on enamel whenever treatment is prolonged, concentration of pH is high, or readily hydrolyzing salts such as tin chloride are used.

Table 12 shows that appreciable concentrations of tin are acquired by intact enamel surfaces, and that there is some penetrations of tin into the enamel. Certain studies¹⁵⁶

TEST AGENT	pH	% IN TEST SOLUTION		ENAMEL			
		TIN	FLUORIDE	TIN PPM LAYER	FLUORIDE PPM LAYER		
Sodium fluoride	5.6	0.0	0.452	25	5.6	1440	561
Stannous fluoride	2.9	1.41	0.452	600	250	1220	580
Stannous chlorofluoride	1.6	2.82	0.452	640	300	1051	570
Control	-	0.0	0.0	15	10	924	400

TABLE 12. Fluoride and tin concentration in external enamel after 20 minute exposure to 1% sodium fluoride, 1.86% stannous fluoride and 4.12% stannous chlorofluoride.

have reported greater deposition of fluoride from stannous fluoride than from sodium fluoride, which is contrary to the figures given in the table. The reason for the discrepancy lies in the fact that stannous fluoride reacts with the enamel to form fluoride containing complexes which precipitate from the stannous fluoride solution. These soluble compounds are not firmly bound to the enamel, and, therefore, are of little, if any, significance in regard to caries reduction. Inclusion of these precipitates in the analyses will give the impression of increased fluoride deposition by stannous fluoride as compared with sodium fluoride. This is only an apparent effect. Although acid solutions of sodium fluoride do cause a greater fluoride deposition than neutral solutions, the naturally acid stannous fluoride does not follow this pattern. The pH will rise when stannous fluoride reacts with the tooth mineral, and insoluble tin fluoride complexes are formed which reduce the amount of reactive fluoride available.

Electronic-microscopy and X-ray diffraction studies show the protective surface layer is hydrous hydrated SnO (Figures 4-10).¹⁷² Further studies of such oxide layers, have demonstrated that they are very resistant to washing with water, etching with acid, and brushing with water alone but are quite readily damaged by brushing with an abrasive slurry. Among similar lines, when teeth have been immersed in dentifrices containing sodium or stannous fluoride, protection against acid etching was also noted, that provided

by the stannous fluoride dentifrice being considerably more pronounced. If the dentifrices were applied by brushing, however, the degree of protection was markedly reduced.