Figure 4. Replication of polished enamel surface.

Untreated control ($\times$ 7,000)
Figure 5. Enamel surface replica showing the effect of acidified 25 sodium fluoride (HCl) pH 3.5 the deposit (Calcium fluoride) formed within 5 minutes on the damaged surface. (x 10,000)
Figure 6. Replica of enamel surface after prolonged exposure to 3% sodium fluoride, pH neutral. 2-4 weeks exposure are required for the crystals to become as large as those pictured but they are beginning to form after as little as a few minutes. This can be shown by diffraction. Deposit is identified as calcium fluoride. (x 20,000).
Figure 7. Replica of enamel surface of an untreated sample subjected to 5 minutes etching with II/10 lactic acid pH 5.0. Note the depth to which the prism ends have been affected. To overcome the protective effect afforded by stannous fluoride solution, the etching time must be increased to 20 minutes and pH reduced to 5. (x 7,000)
Figure 8. Replica of enamel surface treated with stannous fluoride solution (1,000 ppm F) for 5 minutes and then subjected to a 5 minute test etching with n/10 lactic acid at pH 6.0. The treated surface resists etching markedly and is similar to the untreated control. (x 7,000).
When the protective effect of ammonous fluoride solution is not quite as great, there is seldom more prism detail shown than in this illustration when the surface is treated with lactic acid solution. The protection seems to result from a protective layer and can be decreased by brushing lightly with an abrasive. (x 7,000).
Figure 10. Replica of enamel surface after long exposure to 1,000 ppm fluoride as stannous fluoride at pH 2.9. Treatment was continued for several hours changing the solution every 10 minutes. The deposit is hydrous hydrated stannous oxide \(2\text{SnO}_2\cdot\text{H}_2\text{O}\). The layer is best seen when it is damaged mechanically by brushing and illustrated is the layer on the right and underlying tooth surface on the left. (x 10,000).
ANTI-CARIES MECHANISM OF FLUORIDES IN DENTIFRICE

The evidence for the effectiveness of certain fluoride-containing dentifrice in preventing dental caries is quite convincing, but the mechanism by which it works is still controversial.

The two theories, that are most acceptable at present, are: the anti-enzymatic theory, and the solubility theory. However, these two theories are to some extent contradictory, as if the solubility was reduced virtually to nil, then no inhibitory ions could be released to leave the enamel surface to exert the anti-enzymatic action against the bacteria in the surrounding.

THE ANTI-ENZYMATIC THEORY

According to this theory the action of fluoride in preventing the initiation of the carious process is due to enzymatic inhibition of the activities of the bacteria causing the process. For inhibition to occur fluoride must be present in a suitable form in sufficient concentration in or around the bacteria of the dental plaque to reduce the rate of formation of some end products of glycolysis sufficiently to prevent decalcification of the underlying hard dental tissues.

The inhibitory action of fluoride was described as long ago as 1889 by Tappeiner. He and his associates
established the inhibiting action of fluoride on the fermentation of sugars by yeasts. Lohmann & Meyerhof later showed that the fluoride inhibited the conversion of phosphoglyceric acid to phosphopyruvic acid. Warburg & Christian in 1942 isolated the enzyme, enolase, that catalyzed this reaction. The inhibitory action of fluoride was shown by them to involve a displacement of magnesium ions from the active enolase complex by magnesium fluorophosphate, resulting in an inactive enzyme complex. They also showed that the inhibition of pure magnesium enolase varies as the magnesium concentration and the square of the fluoride concentration, and as the phosphate concentration and the square of the fluoride concentration.

Ellfolk notes that the degree of inhibition by fluoride depends upon the degree of dissociation of the magnesium from the enzyme Carboxypeptidase, a magnesium enzyme, is not inhibited by fluoride and alkaline phosphatase, likewise a magnesium protein, was inhibited by fluoride only under special experimental conditions.

The first studies on the effect of various concentrations of fluoride on bacterial acid production were made by Bibby & Van Kesteren. They found that one ppm has a detectable effect on acid production (as measured by titration acidity) but that much higher concentration (greater than 250 ppm) were needed to inhibit growth. McClure found similar salivary level in persons living in areas with only traces
and up to 3 ppm of fluoride in water supply. Wright & Jenkins have carried out similar experiments on mixed salivary organisms and have confirmed that one ppm is effective; they have found that even 0.5 ppm fluoride produces a small, but statistically significant, inhibition of acid formation.

Lilienthal & Hartin (1956) have found that, in general, 19 ppm is the minimum concentration of fluoride that inhibits salivary bacteria under their experimental conditions. The negative results with these concentrations found by Lilienthal may have arisen from his use of a bicarbonate buffer at pH 6.8 as his incubating medium and anaerobic environment also increase the sensitivity to fluoride. Calcium and phosphate ions (salivary constituents found by Warburg & Christian, 1942) to enhance fluoride inhibition greatly diluted by bicarbonate buffer. It was after the addition of phosphate that Lilienthal observed his only positive results with 1.0 and 0.5 ppm fluoride.

Jenkins has proposed that acid formed in the plaque could release fluoride from the enamel surface, thus providing the concentrations needed to inhibit additional production of acid. He observed that the same concentration of fluoride caused increasing inhibition with decrease in pH, such small concentrations as 6 ppm being effective at pH 5. However, there is no evidence that fluoride is dissolved from enamel at these pH's. On the contrary, fluoride is taken up
extremely fast at acid pH, and is fixed by the crystal as shown by Neumann & Neumann (1958), and Brudevold et al. (1957). The observations of Brudevold et al. (1956) show an increased depth of high fluoride concentration with age on to the surface of whole enamel.

The high concentration of fluoride at the surface of enamel must mean that the fluoride is either quite firmly bound to the enamel, or at least, if temporarily released from the surface must be taken up again, otherwise there would be a relative fluoride deficiency at the surface. The high fluoride concentration is present under conditions in which calcium fluoride formation was very unlikely to have occurred (low calcium and fluoride) and must be present as fluorocapatite.

When a fluoride-containing dentifrice is used, those parts of the plaque which remain after brushing the teeth would be expected to acquire quite high concentrations of fluoride by diffusion from the mixture of dentifrice and saliva with which the teeth are bathed. With some fluoride, such as a sodium salt at the concentrations probably present in the mouth during the use of the dentifrice, calcium fluoride would probably be formed on the tooth surface and fluoride would gradually dissolve in plaques as they formed in the intervals between toothbrushing. By this means the plaque concentration of fluoride might be built up to reach inhibitory level, although this is uncertain. The action of stannous
fluoride dentifrices is not precisely known. Evidence that stannous ions can leave the enamel surface (and presumably enter the plaque) is provided by the fading of the brown staining of the enamel surface.

In the initial attack of caries it is the activities of bacteria within the dental plaque itself which will be predominantly important, and it is the concentration of fluoride ions immediately around these bacteria which will determine whether an anti-enzymatic effect occurs. As a first step in determining whether a lower caries susceptibility may be produced due to enzyme inhibition by fluorides, it is, therefore, necessary to determine the fluoride content of the dental plaque. If the fluoride concentration is found to be within the range, which inhibits bacterial metabolism, it will also be necessary to determine whether the fluoride is present in a form which will inhibit the bacteria. This is a complex problem, as it is possible, especially if the calcium ion concentration is high, that the fluoride in the plaque may be present largely as insoluble amorphous or microcrystalline precipitates formed by the interaction of the fluoride with calcium and other ions in this region. Much of any calcium in the plaque is likely to be bound to the protein.

Kudahl (1963)\textsuperscript{173} using an isotope dilution method of analysis, showed that the fluoride content of about half his samples from individual sites on teeth, was more than 2 ppm.
Hardwick & Leach (1963) found that the mean fluoride concentration of the pooled plaque sample from people, using no fluoride-containing dentifrice, showed a wide range from 9.3 to 93.8 ppm.

Examination by electron and X-ray diffraction of samples of dental plaque, by Hardwick (1963), failed to reveal evidence of a crystalline lattice in the form of an apatite or of a calcium fluoride. This finding, although it does not absolutely preclude the presence of apatites or of calcium fluoride, does suggest that if they are present they will exist either in an amorphous or an extremely small micro-crystalline state; in either case it would be expected that they would dissolve rapidly under suitable conditions such as might occur with a lowering of pH. It also suggests that most of the fluoride in the dental plaque will not always remain in an insoluble and, therefore, enzymatically inactive form. The demonstration by chemical analysis of fluorides in the dental plaque in concentrations, which if in a reactive form would inhibit bacterial glycolysis would, therefore, be substantial, but not conclusive evidence that enzyme inhibition would occur.

Hardwick's finding on dental plaque can be summarized as follows:

1. In every sample collected the fluoride concentration of the plaque material from caries-free area appeared to be higher than 6.0 ppm.
2. Fluoride contents of the plaque showed a remarkable range from 6.4 to 179 ppm. The plaque material examined is, therefore, unlikely to be homogeneous in composition.

3. A significant higher fluoride content was found in the fluoridated area than in non-fluoridated area.

A high but very variable fluoride content in the plaque from caries-free areas has been noted, but the form in which the fluoride is present is still not known. To strengthen the enzymatic theory it is essential to establish whether sufficient fluoride is present in the plaque in a form which will inhibit, or can be released to inhibit its bacteria. In samples with high fluoride concentration it is unlikely that the fluoride remains permanently in the form of fluoride ions for two reasons:

1. Around neutrality and in the presence of appreciable quantities of ionised calcium, high concentrations of ionised fluoride cannot occur, as one of the factors influencing the free fluoride concentration is the free calcium concentration; unfortunately, there is little certain knowledge regarding the state of the calcium (which is present in high concentration) in the plaque. Another factor limiting the concentration of fluoride ions would be the nature of the calcium and fluoride (and
possibly phosphate) containing precipitates, which form when their solubility products are exceeded.

2. Ionised fluoride ions in the plaque would quickly diffuse to the saliva or be adsorbed on to the enamel surface, thus being lost to the plaque. It must, therefore, be assumed that when high fluoride concentrations are present much of the fluoride must usually be bound to the inorganic matter within the plaque. In either case the bound fluoride might act as a reservoir of fluoride available to be released under suitable conditions in a form which would affect bacterial metabolism.

Essentially, the fluoride content of the outer layer of the enamel is of significance, according to this theory. If it is high, less ionised fluoride from the plaque will tend to be adsorbed on to it, thus protecting the "fluoride reservoir" in the plaque against loss. In addition, the fluoride content of the plaque, itself, as an equilibrium will tend to be reached between the tooth surface and plaque fluoride.
SOLUBILITY THEORY

According to this theory, caries resistance of a high fluoride content of enamel is by the reduction of its solubility in acid and other decalcifying agents.

Volker (1939) showed that the presence of fluorides in large amounts in the diets of experimental animals decreased the solubility of their enamel and dentine. Correlation of fluoride content of enamel with susceptibility in dental caries have met with varying degrees of success. Volker found that mottled enamel is as soluble as normal enamel. Mottled teeth are caries resistant, and yet it was concluded that the fluoride content in the enamel of these teeth was insufficient to reduce the solubility. However, Issac, et al. (1955) found mottled enamel with the highest concentration was more resistant to acid than enamel from the other groups. Now we realize that fluoride content is not evenly distributed in the enamel, high fluoride concentration being in the outer layer, which is in sufficient concentrations to reduce the solubility. (Table 13.)

The finding that high concentrations of fluoride extended further into the subsurface enamel in mottled teeth is probably related to at least two factors:

1. Obviously, is the greater amount of fluoride which is present in water, food, and tissues fluids in areas of endemic fluorosis.
<table>
<thead>
<tr>
<th>Layer</th>
<th>Contemporary Unerupted</th>
<th>Contemporary Erupted</th>
<th>Ancient Unerupted</th>
<th>Ancient Erupted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>Over 50 yrs.</td>
</tr>
<tr>
<td>1.</td>
<td>331</td>
<td>528</td>
<td>347</td>
<td>1,247</td>
</tr>
<tr>
<td>2.</td>
<td>101</td>
<td>232</td>
<td>391</td>
<td>667</td>
</tr>
<tr>
<td>3.</td>
<td>57</td>
<td>150</td>
<td>201</td>
<td>404</td>
</tr>
<tr>
<td>4.</td>
<td>33</td>
<td>96</td>
<td>172</td>
<td>315</td>
</tr>
<tr>
<td>5.</td>
<td>88</td>
<td></td>
<td>176</td>
<td>180</td>
</tr>
<tr>
<td>6.</td>
<td>64</td>
<td></td>
<td>147</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 13.** Concentration of fluorine (ppm) in successive layers of enamel of different ages.202
2. Defects were conspicuous in the outer enamel of the mottled teeth. This allows penetration of fluoride to deeper layers.

Finn & Demarco (1958)\textsuperscript{179} showed that enamel exposed to fluoridated water after eruption shows a very slight reduction in acid solubility as compared to enamel from fluoride-free areas, and deciduous enamel from an area of artificial water fluoridation has a reduced solubility in acid as compared to enamel from fluoride-free areas.

Schmid (1948)\textsuperscript{180} found that more fluoride deposits in the outer than in the inner layer of enamel. Jenkins (1952) found no difference between the fluoride content of the surface enamel and the rest of the enamel in deciduous teeth, contrary to Brudevold's finding (1956)\textsuperscript{182}. However, in both erupted and unerupted permanent teeth, he found at least five times more fluoride in the superficial fractions. Jenkins, Armstrong & Speirs (1952)\textsuperscript{181} found that the solubility rate of surface enamel of teeth from areas with 2 ppm in the water supply was less than that from areas with 0.25 ppm, although there was no difference in the solubility rate of the bulk of the enamel.

Similarly in vitro studies, it has been repeatedly shown that solubility of enamel in acid reduced by fluoride solutions including certain anime fluorides by Muhlemann & Wolgensinger\textsuperscript{184}. 
There can be little doubt that fluoride-containing dentifrices will raise the fluoride concentration of the surface enamel by fluorapatite formation and in some cases (but apparently not with stannous fluoride) also by calcium fluoride formation. The latter substance will readily dissolve off, being more soluble at neutrality than hydroxyl apatite, but is less soluble than this apatite at acid pH values.

Continued increase in fluoride content of the enamel apparently takes place, not by a movement of fluoride ions in depth from highly saturated to less saturated crystallites. In this way, a slow but gradual thickening of the saturated outer enamel layer may occur with age.

One of the advantages of dentifrices, over topical application, as vehicles for solubility-reducing substances is that they can restore, by their frequent use, substances which tend to be dissolved off enamel by the oral fluids. This is true of calcium fluoride and of the stannous ion.

It has been shown repeatedly in vitro by Muhler\textsuperscript{201} that fresh solutions of stannous fluoride have a greater effect in reducing enamel solubility than other fluorides.

The nature of the effect of fluorides on the solubility of apatite has not been decided. It has been tacitly assumed that this difference in solubility arises
because the lattice structure of hydroxyl apatite is less stable than that of fluorapatite. Recently Gray et al. (1962) have put forward the idea that the effect of fluoride on enamel solubility is a diffusion phenomenon as follows: in the presence of the fluoride which is released when fluorid-containing enamel dissolves, insoluble calcium fluoride is formed which precipitates on the enamel surface thus reducing the diffusion of acid to it. The evidence which they quote for this view is that they find that the initial rate of dissolving of enamel is independent of its fluoride content. The implication is that only after some enamel has dissolved and its fluoride precipitated, is the rate of solution reduced. Jenkins questioned this statement, and finds this theory difficult to reconcile with the fact that fluorapatite, and not calcium fluoride, is formed at concentrations which would be expected in the vicinity of enamel crystals in the process of dissolving (i.e. below 75 to 100 ppm). The comparison of solubility rates after very short intervals of shaking is technically difficult and this theory seems to depend largely on such comparisons.

On this view, the effect of high concentrations of sodium and stannous fluoride is to form a diffusion barrier before the enamel is attacked by the acids of the plaque. With sodium fluoride, the barrier is of calcium fluoride and with stannous fluoride the mixture, previously mentioned, of stannous phosphates and stannous oxides, and perhaps calcium fluoride, forms an even more effective barrier.
PHOSPHATE DENTIFRICE

In recent years practical methods of controlling dental caries have been largely concentrated on fluorides. Next to fluorides, the phosphates are attracting attention.

Sobel & co-workers (1948 and 1958)\textsuperscript{186} have shown that variation in Ca:P ratios in the diet of white rats and cotton rats alter the composition, not only of the blood, but also of the mineral salts deposited in the bones and teeth during these dietary manipulations.

Wynn et al. (1956)\textsuperscript{187} studied the effect of phosphates after the teeth were fully formed. In the first study, a progressive decrease in the caries score of rats was noted as the calcium-phosphorous ratio of a purified diet was varied from a ration of 1:0.5 to a ration of 1:2 by variations in the phosphate content. In the second study, when the phosphorous content of a purified diet was kept constant and the calcium-phosphorus ratio increased from 0.5:1 to as high as 3:3:1, there was a 50% decrease in the dental caries incidence.

In the same year, Stralfors\textsuperscript{188} reported a series of studies with the hamster, reductions of over 90% in the incidence of dental caries were reported when dietary supplements of 5% tridosium phosphate, 5% tricalcium phosphate, 2% and 1% calcium dibasic phosphate were used, and when 2% tricalcium phosphate was used in the diet along with 600 mg.
of calcium chloride per litre in the drinking water. Reductions in the caries incidence between 50% and 90% were observed when dietary supplements of 2% tricalcium phosphate and 2% calcium monobasic phosphate were provided and when a supplement of 600 mg of calcium chloride per litre of drinking water was used. The feeding of pills of tricalcium phosphate directly and of 2% calcium phosphate baked in bread gave comparable reductions.

McClure (1958)189 found that if 1.6% of sodium phosphate is added to a diet of which 80% is heat processed whole wheat flour, caries is inhibited. However, the addition of 2% secondary calcium phosphate to the same diet is not effective. If the whole wheat flour is supplemented with calcium carbonate to provide adequate calcium, secondary sodium phosphate added to the diet was effective in preventing caries, but secondary calcium phosphate was not.

An interesting relationship of the cariogenicity of the diet has been reported by Barnard & Johansen (1958)190 with respect to the influence of supplementation with 2% dibasic calcium phosphate. When a severely cariogenic diet was supplemented, no result was observed, whereas the addition of the same supplement to a diet with moderate or low cariogenic properties resulted in statistically significant reductions in dental caries incidence in the rat.

Nizel & associates (1958)191 note caries reduction in the hamsters when metaphosphoric acid was supplemented in
the diet. Subsequently, Nizel and Harris (1960)\textsuperscript{192} showed that when 1.36\% of metaphosphoric acid was added to the hamster diet, a 70\% inhibition of caries was observed.

Similar cariostatic effect of phosphates on animal caries was observed by McClure & Muller (1959)\textsuperscript{193}. Another study was carried out by McClure on rats with lysine-deficient diets that were also borderline in calcium and phosphate. Under these conditions there was a high susceptibility to carious lesions on the smooth surfaces of the molars.

In general these studies whenever a relatively soluble phosphate supplement was given, there was a reduction in the incidence of carious lesions. When a relatively insoluble phosphate was given, either no reduction was observed or a very small one. However, when the insoluble salts were administered along with sodium chloride, an increase in caries reduction resulted.

McClure (1960)\textsuperscript{194} in a study of the addition of 2\% sodium phosphate or 2\% calcium phosphate to bread flour prior to baking found that this bread incorporated in the rats' diet inhibited caries. The fact that the calcium phosphate was effective was related to the possible combination of the sodium chloride in the bread with the calcium phosphate and an increase in solubility of the phosphate. If tertiary calcium phosphate is substituted for primary monohydrated calcium phosphate, no inhibition occurs.
In the subsequent studies, he found that \( \text{Na}_2\text{HPO}_4 \), \( \text{Ca}_3(\text{PO}_4)_2 \), sodium phytate, diammonium phosphate, b-glycerol phosphate, and 1,6-fructose diphosphate were effective as phosphate supplements and significantly inhibited caries in white rats. Osborn, Noriskin, and Staz postulated, in 1937, that crude cereals and sugars contain substances which inhibit dental caries but are removed during the refining process. Osborn reported a reduction in decalcification of teeth in vitro by cooked brown flour. The inhibitory effect of unrefined sugars, various hexose-phosphates, calcium phytate, and calcium glycerol phosphate was investigated. Jenkins et al. in their extensive experiments on white and brown flour, confirmed the evidence of Osborn et al. "that cooked brown flour contains a substance which reduced the solubility of teeth in vitro", and concluded "that certain organic phosphates, including phytate, reduce the solubility of calcium phosphate and teeth." These may be active substances in brown flour. The caries-inhibiting action of organic phosphates may coincide with a caries-protective factor presumed lost in the refining of sugar and in the processing of certain cereal foods, particularly the phytate that occurs naturally in unrefined carbohydrates and probably in some unprocessed cereal foods, could be related to the lessened cariogenicity of these foods. The phosphate becomes available from these foodstuffs by hydrolysis of the organic phytate by the enzyme phytase.
Thus, there is accumulated evidence on the caries-reducing effect of phosphate admixed in food. The phosphate may act locally by diffusing into caries susceptible areas where its presence would:

1. cause a decrease in the dissolution of phosphate by common ion effect;

2. decrease dissolution of calcium by increasing the activity product $\text{aCa}^+ \cdot \text{aHPO}_4^-$, where 'a' represents activity coefficient;

3. bring about an exchange with carbonate in the tooth mineral. This exchange which is known to operate under acid conditions, should decrease the solubility of enamel; or

4. increase buffer capacity and thus counteract a marked fall in pH.

The mechanism of the anticaries effect of organic phosphates as studied poses a problem no less complicated than that of the inorganic phosphates. Nonetheless, their anticaries activity is suspected of being localized within the oral cavity. Perhaps through salivary or bacterial hydrolysis, inorganic phosphorus could become available in the oral milieu, but it seems likely that these compounds could be active as intact molecular entities. As noted above, the results of Osborn et al. and particularly those of Jenkins et al., suggest that their effect may be due to a stabilization of the oral tooth surfaces, that is, the teeth become more resistant to acid.
These investigators note further that "this effect is observed in experiments with buffers (that is, in the absence of saliva) and is, therefore, evidence of a property of organic phosphates as such, and is quite independent of the capacity of some of these substances to act as substrates for phosphatases during incubation with saliva and thus be a source of inorganic phosphorus.

Relating to this problem also is the following, quoted from U.S. dentifrice patent of 1960: "The present invention is predicated upon the discovery that a dentifrice containing as an essential ingredient certain organic phosphates and their water soluble salts, will reduce the dissolving action of acids on dental enamel." Furthermore, according to Manly & Manly\textsuperscript{197} the solution rate of enamel in acid was reduced by a solution of cephalin, or one of its component phosphatides, when brushed onto human enamel. These investigators postulated that a cephalin film, formed on a tooth surface, becomes impermeable to other ions. Indeed, there is need to differentiate between the possible oral environmental action and effect of phosphate in contrast to its role as an essential systemic nutrient.

The clinical testing of the effectiveness of a high soluble phosphate (10\%) dentifrice as a source of readily available phosphate ion in the oral cavity is being currently planned by McClure.
SECTION III
DISCUSSION

It has been proved conclusively so far that a brand of toothpaste (Crest, which is not available in Australia) containing stannous fluoride is effective in the prevention of dental caries, when it is used with correct oral hygiene care.

Although virtually all authorities put strong emphasis on the fluoride approach to reducing dental caries, it is only one of the measures of preventive dentistry to which the public should give regular attention. To control dental caries, the "Multiple Principles of Preventive Dentistry" have to be instituted:

1. Fluoridation of the communal water supplies.
2. Careful brushing of the teeth after each meal.
3. Topical application of fluorides at appropriate ages.
4. A dental checkup at least twice a year, with prompt attention to any existent pathological conditions.
5. Minimize refined carbohydrate intake, especially between meals.
SUMMARY

1. Dentifrices have been used since time immemorial.

2. The chief function of a dentifrice is to aid in the removal of food debris and stains of the tooth.

3. A number of agents with therapeutic claims of dental caries prevention have been incorporated into dentifrices for the past two decades.

4. Crest (stannous fluoride toothpaste) is the only brand so far that has been proved conclusively in the prevention of dental caries.

5. Practice of "Multiple Principles of Preventive Dentistry" reduces dental caries remarkably.
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