The Radiographic Assessment of Posterior Interproximal Dental Caries - a Longitudinal Analysis.

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DECLARATION

This thesis is the original work of the author.

Denise M. Strang.

SUMMARY

The aim of this study was to investigate the changes in radiographic scores of individual interproximal tooth surfaces over the three-year period of a double-blind anti-caries dentifrice clinical trial. Six dentifrices were employed in the trial. For each of three fluoride levels studied, pastes were formulated with and without the addition of zinc citrate.

In this trial, 3005 Lanarkshire schoolchildren enrolled, and bitewing radiographs were taken at baseline and 1, 2 and 3 years later. These were read cross-sectionally and the interproximal surfaces of all posterior teeth scored. The radiographic changes over the four examinations were classified into five groups: (a) surfaces which had a score of 'zero' at all four examinations; (b) surfaces which 'Progressed'; (c) surfaces which 'Reversed'; (d) surfaces which remained 'Stable' and (e) surfaces which were 'Borderline'. Only data which fulfilled certain selection criteria were included in the analysis. Surfaces which had an 'illogical' radiographic combination were re-read longitudinally. In addition, X-rays from surfaces which had a controversial classification were also re-read.

The effects on the radiographic changes of (1) dentifrice fluoride concentration (1000, 1500 and 2500 ppm F as MFP); (2) dentifrice zinc citrate content (0 or 0.5 % (w/w));

(3) sex of the volunteer, and (4) the initial radiographic score at baseline examination, were investigated using X^2 tests and Generalised Linear Interactive Modelling (GLIM).

A significant increase in the proportion of surfaces which remained radiographically sound with increasing dentifrice fluoride content was obtained. A similar decrease in the proportion of surfaces which 'Progressed' was also obtained. Analysis of the data in terms of the baseline radiographic score, showed that only those surfaces which had an initial radiographic score of 'zero' had significant fluoride dose-responses. The addition of zinc citrate to the dentifrices had no effect on the proportions in each category. Females were shown to have fewer surfaces which 'Progressed' than males.

Although the classification of radiographic combinations can never be entirely objective, the benefits of longitudinal consideration of these data has been demonstrated.

CHAPTER 1 INTRODUCTION

1.1 Introduction and Aims

Dental caries is a peculiarly local disease which involves the destruction of the hard tissues of teeth by metabolites produced by oral microrganisms. It is now recognised as a multifactorial disease and is considered to be the result of the interplay of three principal factors: the host (teeth and saliva), the microflora, and the diet (Fig. 1.1). The common dietary sugars (sucrose, fructose and lactose) can all act as a substrate for plaque bacterial metabolism. Fermentation of these carbohydrates causes an increase in plaque organic acid production, and the consequent drop in pH causes tooth demineralisation. However, the almost neutral pH of plaque which has not been subjected to the effects of carbohydrate consumption can encourage remineralisation of the early lesion. If these acid attacks are prolonged and / or frequent, the remineralisation / demineralisation balance will be upset and the outcome will be a carious lesion.

In the 19th century, caries experience in Britain, in common with most industralised countries, increased rapidly after 1850. This was related to a three-fold increase in sugar consumption between 1830 and 1880, and also a dietary change to more refined foods. Over this period, the mean percentage caries values rose from 18% to 26% in incisors, from 18% to 66% in first molars, and

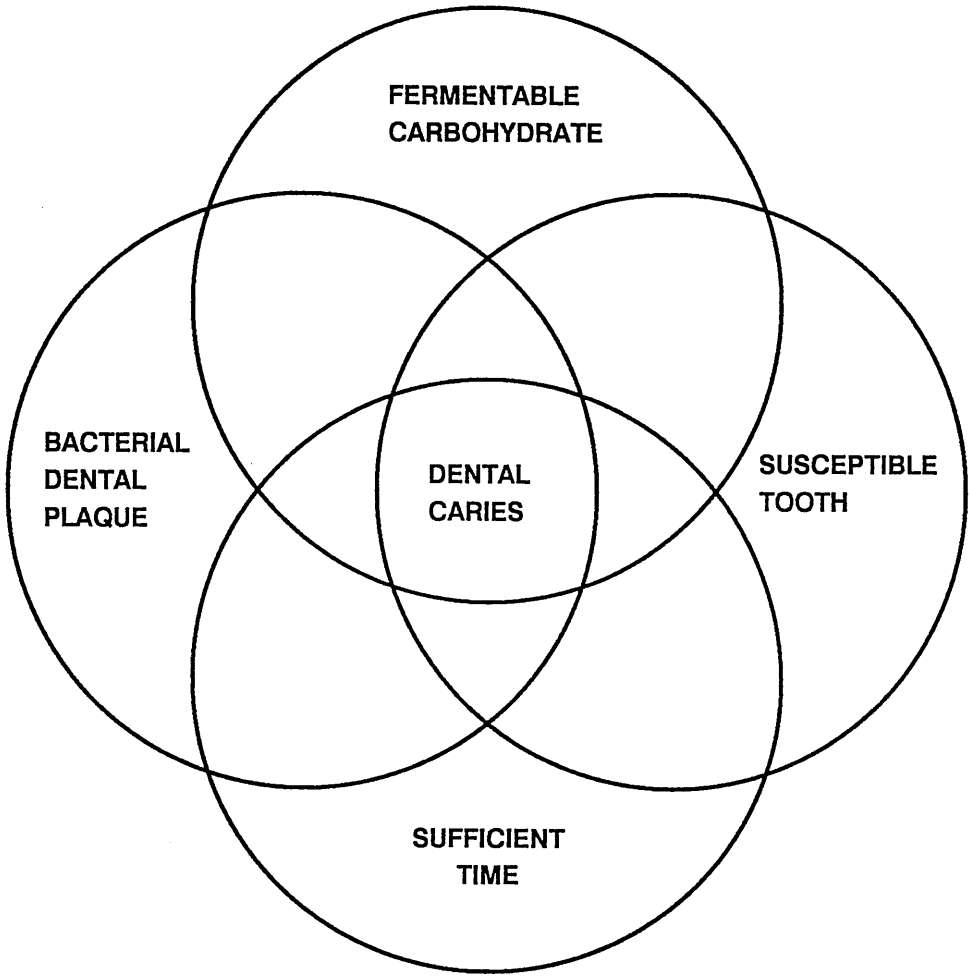


Figure 1.1 Principal aetiological factors in dental caries.

from 16% to 62% in second molars (Nikiforuk, 1985).

However, in developed countries, caries prevalence has declined from a peak in the 1950's (Sheiham, 1984). At the first Conference on the Declining Prevalence of Dental Caries (Naylor, 1982), caries reductions of 44% over the period 1970 - 1980, were reported in children aged 4 to 12 years in a water fluoridated area, while even in the unfluoridated north of Scotland, where caries prevalence had been high, there was a 14% drop. Similar declines have been reported for many countries (FDI / WHO, 1985). Many reasons have been reported for this decline (White Paper, 1987), including:

(a) greater public awareness of the need to care for teeth,

(b) greater use of fluoride dentifrices,

(c) fluoridation of water supplies in some areas,

(d) changes in the pattern of sugar consumption,

-and-

(e) wider access to dental care.

In addition, dental practitioners have become more aware of the need for prevention programmes which include the use of fissure sealants, other topical fluoride vehicles, oral hygiene instuction and professional tooth cleaning.

In the last decade, there has also been a general increase in public awareness of factors affecting health, and changing attitudes to dental health have followed. Furthermore, consumer pressure has led to the introduction

of more 'wholesome' foodstuffs, including the use of sugar substitutes such as saccharin and, more recently, aspartame.

It could be postulated that increased oral hygiene efforts following increased awareness would lead to a reduction in dental caries. However, while several studies have investigated the effectiveness of unsupervised oral hygiene procedures, some have observed a correlation between increased frequency of toothbrushing and decreased caries prevalence (Dale, 1969; Berenie, Ripa & Leske, 1973; Tucker, Andlaw & Burchell, 1976; Ainamo, 1980), whereas others have not (Savara & Suher, 1955; Ainamo & Parvianen, 1979). In a three year study, Koch and Lindhe (1970), investigated the effects of supervised brushing with a fluoridated and a non-fluoride dentifrice in 9 - 14 year old children. Daily brushing with the fluoridated dentifrice resulted in a caries increment (DS) of 4.4 over the three year period, compared to a value of 8.3 for the non-fluoride toothpaste, implying that conventional, and even supervised, toothbrushing has a limited effect on pronounced caries activity.

Greater access to dental care does not, in itself, imply better dental health. Nuttall (1984) has shown that the majority of frequent dental attenders received some restorative treatment during a five year period and that they had a total of almost twice the number of tooth surfaces filled, on average, in comparison with infrequent

attenders over the same time-scale. Elderton *et al.*, (1985) also found that frequent attenders, especially those who changed dentists, were particularly prone to have teeth filled and that two-thirds of restorative costs were spent on treating tooth surfaces that had previously been filled. They concluded that dentists had to acquire a more positive attitude towards prevention.

Many countries have introduced caries prevention programmes which may include the application of fissure sealants, the use of fluoride supplements, a health education component and professional tooth cleaning (eg Axelsson & Lindhe, 1974; Stephen & MacFadyen, 1977). Thus, it is often difficult to ascertain the benefits of the different components. Surveys carried out in the Netherlands, to test the hypothesis that dental health education programmes reduced caries, revealed that in the period 1965 - 1980, caries in six year olds decreased by the same amount with or without the health education contribution (Kalsbeek, 1982). There is no evidence to support the idea that mass dental health education, intended to change individual behaviour, is successful (Frazier, 1978). Nevertheless, it must be noted that the intensive marketing campaigns of dentifrice companies have undoubtably had the effect of making people more aware to the possibility of preventing dental disease.

As far as professional tooth-cleaning is concerned, it is again difficult, in many studies, to ascertain the

benefit of this component. Using a split mouth technique, two investigations have studied the effect of daily professional flossing and a 30 - 50 % caries reduction has been reported (Wright, Banting & Feasby, 1979; Wright, Feasby & Banting, 1980). However, in a supervised flossing study in 12 - 13 year children, no caries benefit was observed (Granath, *et al.*, 1979).

From the 11th to the 15th century sugar, although scarce and expensive, was consumed by the upper classes. One of its earliest uses was to disguise the bitter taste of medicines, but it soon became enjoyable in its own right. Demand, and therefore production, grew. With the discovery of sugar beet, sugar become abundant and cheap. The increase in dental caries in the 19th century mimicked this rise in sugar consumption. However, it was not until the famous Vipeholm study that the link between sugar consumption, in particular the frequency of intake, and caries was scientifically established (Gustafsson *et al.*, 1954). Sheiham *et al.*, (1985) reported that for the under-35 age group, sugar consumption was a significant influence on the number of missing teeth. In a recent report on the changing patterns of oral health (FDI / WHO, 1985), five industralised countries (Norway, Denmark, The Netherlands, U.S.A. and the U.K.) reported significant decreases in sugar consumption, but for four others (Australia, Finland, New Zealand and Sweden) no such reductions were detected. However, in all countries sugar consumption remained high and in most cases the *per*

capita figure was more than twice the world average. Kalsbeek (1982) speculated that children in the early 1980's had a less cariogenic diet than those a decade earlier. In a survey of 246 Glasgow children, Hackett & Stephen (1983) reported that 63 % had eaten potato crisps within a 24 hour period and that production had increased by 52 % between 1970 and 1980. In addition, Koch (1982) held the view that while sugar consumption remained constant, the frequency of intake had decreased. As stated above, recently there has been a trend towards less cariogenic sweeteners, so-called sugar (sucrose) substitutes, these being either non-caloric (aspartame, saccharin) or caloric (fructose, glucose and lactose).

There is general agreement that the use of fluoride supplements, and in particular fluoride dentifrices, have undoubtably played a major part in the caries decline. However, the optimum fluoride concentration, frequency of exposure, and exposure time for the different supplements has not yet been established. Thus further clinical and laboratory studies are required.

The work reported in this thesis utilises data from such a clinical trial i.e. a 3-year fluoride dentifrice caries and oral health study involving 3005 Lanarkshire schoolchildren (see Chapter 2). In particular, the changes in bitewing radiographic scores of individual interproximal surfaces over the four examinations were correlated with such factors as dentifrice formulation

(fluoride concentration, presence or absence of zinc citrate trihydrate), and some social parameters.

1.2 Flouride and Dental Caries

1.2.1 History of fluoride

As early as 1902, Eager, in Naples, reported brown and white stains on enamel which he surmised were due to a water-borne agent. Similar 'mottling' was noticed in Colorado by McKay (1916) who, following an analysis of water supplies by Churchill (1931), came to the conclusion that it was caused by high water fluoride levels (McKay, 1933). The U.S. communities of Oakley and Bauxite were the first to recognise the effect of high concentrations of fluoride and abandoned their water supplies after a campaign was launched by the Women's Civic League (McKay, 1933).

However, it was not until the wholly independent English observations of Ainsworth were published in 1931, that the association between decreasing caries prevalence and high water fluoridation was recognised. Consequently, the U.S. Public health department commissioned Dean (1933, 1934 & 1936) to discover the extent and geographical distribution of mottled enamel in the U.S. - the so-called 'Shoe Leather Epidemiology Survey'. He established that fluoride concentrations in the drinking water were correlated with the clinical severity of fluorosed enamel and hence a classification (Dean's Index) of fluorosis was devised (Dean, 1934). Thereafter, a

clinical study was initiated involving 7527 children (Dean, Arnold & Elvove, 1942) to establish the dose of fluoride suitable to inhibit caries, but eliminate fluorosis. Although complete caries inhibition did not occur, a 60% difference was observed between areas with >1.0 ppm fluoride in their water supplies and low fluoride towns (<0.3ppm). In addition, it was noted that those who moved into naturally fluoridated areas after their teeth had erupted, showed no signs of mottling. These workers concluded that a concentration of fluoride at 1.0 ppm would give the optimum benefit in caries reduction with little noticeable mottling effect (Dean *et al.*, 1942).

In the light of the above observations, the logical recommendation was to artificially fluoridate water supplies where the fluoride level was below the optimal 1 ppm F^- concentration, and the first study commenced, in 1945, at Grand Rapids, Michigan (Arnold *et al.*, 1962). By 1959, caries attack rates were lowered by 57% in children born after fluoridation, and by 46% in children less than two years old at the time of water F^- adjustment. Furthermore, no fluorosis was observed.

1.2.2 Cariostatic mechanisms of fluoride

Several mechanisms have been proposed as to how fluoride acts in reducing tooth decay. These include the following:

1. Action on the hydroxyapatite of enamel by:-
   (a) decreasing its solubility
   (b) remineralising early lesions
2. Action on dental plaque bacteria

- and -

3. Alteration of tooth morphology.

The fluoride ion is known to inhibit numerous enzymes, especially enolase, an important enzyme for acid formation by bacterial fermentation. Neither the fluoride in plaque, which is relatively high, nor that in saliva would be available at a sufficient concentration as free ions to inhibit the bacterial enzyme under normal circumstances, but if the pH drops, more plaque fluoride becomes ionized. Whether sufficient fluoride is released to inhibit enzymatic activity is not known, although MacFadyen *et al.*, 1977 have shown that the drop in plaque pH following a sucrose rinse is transiently inhibited by a 1500 ppm F^- rinse. No such effect was noted with a 250 ppm F^- rinse. It has also been shown that high concentrations of fluoride, typical of those used in topical gel applications, can significantly reduce the proportions of *S. Mutans* in interproximal plaque (Loesche, Murray & Mellberg, 1973; Loesche *et al.*, 1975). While it is not clear by what mechanism high fluoride concentrations specifically affect this cariogenic organism, as such high levels of fluoride are not attained with water fluoridation, this mechanism cannot explain fully the anti-caries benefit of fluoride. De Stoppelaar, Houte & Backer-Dirks, (1969) found slightly lower levels

of *S. Mutans* in a fluoridated area than in a non-fluoridated area and suggested that the absence of significantly lower proportions of *S. Mutans* indicated an increased resistance of tooth surface enamel, due to fluoride.

Molars formed in fluoridated communities tend to be smaller, with pit and fissures shallower than teeth formed in non-fluoridated communities (Lovius & Goose, 1969). Although the shallower pits and fissures may be of some benefit with respect to occlusal caries, fluoride reduces caries on smooth surfaces significantly more than in pits and fissures (Backer-Dirks, 1966, 1967; Groenveld & Backer-Dirks, 1988). Therefore, altered tooth morphology also cannot explain the caries decrease resulting from fluoride ingestion.

Enamel exposed to fluoride pre-eruptively has a high fluoride content. It was originally thought that replacement of some OH^- groups by fluoride in hydroxyapatite would reduce the solubility of enamel to acid attack. However, several studies have indicated that fluoride incorporated into enamel does not significantly influence the resistance of the tooth to caries development (Fejerskov, Thylstrup & Larsen, 1977; Weatherell *et al.*, 1986). In addition, Thylstrup & Fejerskov (1986), after re-analysing the data from post- and pre-eruptive exposures to water fluoridation, concluded the previously thought-of inferior

post-eruptive exposure results were due to the length of exposure time, and not to a significant systemic effect in the pre-eruptive group. They concluded that "the importance of the pre-eruptive ingestion of fluoride for caries inhibition is only of borderline significance relative to the much more important post-eruptive effect".

It is now generally accepted that low salivary fluoride levels can markedly decrease enamel demineralisation at low pH, and enhance subsequent remineralisation, such effects having been shown *in vitro, in vivo* and *in situ*. *In vivo* studies were pioneered by von der Fehr, Loe and Theilade, (1970) who asked subjects to refrain from oral hygiene and to rinse nine times daily with a 50 % sucrose solution. After 23 days, more white spot lesions developed in the sucrose group than with the six control subjects. Most of the lesions were reversed when oral hygiene and daily 0.2 % NaF mouthrinses were resumed.

Fluoride enhancement of this natural remineralisation process has been reported *in vitro* (Koulourides *et al.*, 1961; ten Cate & Arends, 1977; Silverstone *et al.*, 1981; Featherstone *et al.*, 1982; Damato, Strang & Stephen, 1988) and *in situ* (Featherstone *et al.*, 1982; Mellberg *et al.*, 1985; ten Cate & Rempt, 1986; Strang *et al.*, 1987). Featherstone *et al.*, (1982) and Mellberg *et al.*, (1985) showed significant differences between test and control toothpastes in *in situ* remineralisation. Creanor & Strang (1989), using a 'single-section' *in situ* technique

demonstrated that exposure to fluoridated dentifrices gave increased lesion remineralisation compared to a non-F control paste, although no fluoride dose-response was noted.

There is general agreement that the primary mode of action of topical fluoride is on the incipient enamel lesion, rather than on normal enamel (ten Cate & Arends, 1977). In addition, *in vitro* remineralisation experiments have suggested that the entire body of white spot lesions does not have to be remineralised for it to become protected. A lesion can become arrested if the surface zone alone is preferentially remineralised (Silverstone *et al.*, 1981).

1.2.3 Fluoride vehicles - other than dentifrices

In this section, the different fluoride administration vehicles which have been employed (apart from water *vide supra*: Section 1.2.1) will be discussed. These include: salt, milk, tablets (and drops), gels, mouthrinses and dentifrices. Dentifrices, gels and mouthrinses were applied solely for their topical action, whereas tablets, drops, and milk were originally utilised in an attempt to mimic the systemic role of water fluoridation, where this was not possible for political or socioeconomic reasons. However, it was later realised they could also be of topical benefit.

Since 1955, fluoride has been added to table salt (at 90 mg F^- / Kg) in some parts of Switzerland (Marthaler *et*

al., 1978) and was subsequently tested in Columbia, Spain and Hungary. In the latter country, 200 - 300 mg F^- / Kg salt was employed when, for the 7 - 11 year age group, after 8 years of salt fluoridation, there was a 58% decrease in the DMFT index (Toth, 1976). However, in the 12 - 14 year old group, a decrease was not observed until after five years' usage. This compared favourably with data from the Grand Rapids water fluoridation study. More recently, fluoridated salt has been introduced in Mexico and Costa Rica (FDI, 1990).

The use of fluoridated milk has been considered as a possible alternative to water fluoridation, despite the fact that childrens' consumption decreases after the age of 2 years. Also, it may be difficult to separate distribution between fluoridated and non-fluoridated areas. Rusoff *et al.*, (1962) and Stephen *et al.*, (1981) overcame some of these problems by issuing milk at school and the former authors even provided a sodium fluoride solution to allow continuation in the summer holiday period. In the 1981 Scottish study, milk was given 15 minutes before the morning class-interval, to allow some topical effect before possible ingestion of more food or drink. Here, it was not until the 4th year that a significant difference was obtained between the fluoridated and the non-fluoridated groups, when the DMF reduction was 35.8%.

Another practical method of systemic and topical fluoride administration is in the form of tablets. Drops, introduced to the U.K. in the 1970's are more feasible for use with children under two years of age, since the neuromuscular coordination necessary for coping with tablets will not have developed. However, they are of little topical benefit due (a) to the few teeth present at such an age, (b) the short intra-oral contact time and (c) the small volume dispensed. Bibby, Wilkins & Witol (1955) suggested that a post-eruptive effect could be obtained from the use of tablets which were dissolved in the mouth, but not from pills that were swallowed whole. That study involved daily use of 2.2 mg NaF lozenges which were sucked and dissolved, and fluoride-coated pills which were swallowed. The lozenge group had, on average, four new carious areas during the year of study compared to 6.6 such areas in the pill-swallowing group. It has been suggested that tablets should be large, chewable and slow-dissolving, to ensure topical benefits prior to swallowing (Nikiforuk, 1985), the greatest benefit (81.3 % caries reduction) having been shown when school-distributed tablets were allowed to slowly dissolve (Stephen & Campbell, 1978). In addition, Graf & Muhlemann (1969) suggested that tablets should be placed successively in different areas of the dental arch in order to provide high fluoride concentrations in various regions of the mouth. More recently, Weatherell *et al* (1984) have investigated F clearance at different sites in the mouth following dissolution of a fluoride tablet.

However, their results failed to show a predictable pattern in the transfer of fluoride from one area of the mouth to another. Tablets have also been used prenatally, but the benefits have yet to be proved fully as high parental motivation must obviously be a factor here. In addition the placental rate of fluoride transfer to the foetus is disputed. Carlos, Gittelsohn & Haddon (1962) found no prenatal benefit in caries reduction between prenatal and postnatal ingestion when compared with postnatal only, but Kailis *et al* (1968) found there was a significant difference between these groups for def scores. Ericsson & Wei (1979) suggested that placental blood levels did not exceed 25% of the maternal blood fluoride level, whereas Gardner *et al.*, (1952) found high fluoride levels in placental blood.

Neutral sodium fluoride solutions were the first form of topical fluoride studied for effectiveness in preventing dental caries. Initially, treatments were applied at weekly intervals, for four weeks, at ages 3, 7, 11, and 13 years. This was recommended to minimise the time teeth were at risk to caries after eruption (Knutson, 1948), and many studies using fluoride solutions and rinses have been reported since. In one such investigation, Harris (1959) employed five annual applications of a 2 % NaF solution and found test group children had a 33% caries reduction compared to control group subjects. Ripa & Leske (1979) showed that 19 rinses during the first "school-year" with a 0.2 % neutral NaF solution did not

affect caries prevalence of participants, but, two years of 49 weekly rinses resulted in a 23.8 % caries reduction of primary teeth. According to Ericsson & Forsman (1969), mouthrinses should not be used by children below 4 years of age as they are unable to control their swallowing reflexes and thus could ingest significant amounts of fluoride.

Stannous fluoride solutions have been used as a professionally-applied topical agent. A 39 % DMFS reduction was noted after one year, but tooth discolouration was also apparent (Ripa, 1981). In the same study, it was shown that an APF solution gave a smaller caries reduction but without the discolouration. Aasenden, DePaola & Brudevold (1972) showed that APF was superior to NaF in depositing fluoride in intact enamel.

Gels are normally used with a high fluoride concentration, typically 12000 ppm F^-, and were developed in the belief that their viscosity would make them both easy to work with, and that they would adhere closely to the tooth surface. Horowitz & Doyle (1971) compared three annual applications of a 1.23% NaF acidulated gel (APF), with a similar solution, and with a control group. They found a 24 % reduction in DMFS between the fluoride groups and the control group, but with no obvious difference between the gel and solution. Because of the possibility of significant fluoride ingestion, it has since been recommended that home gel treatments should not be used;

that caution be exercised in applications to children, and that custom-made trays should be employed (McCall *et al.*, 1983).

Waterproofed fluoride-containing varnishes have been developed to provide a more long-lasting fluoride source. Mellberg, Nicholson & Laakso (1967) found that a barrier-coating applied to enamel, after fluoride treatment, increased the amount of fluoride acquired. In addition, the amount of fluoride depended on the time the coating remained on the enamel.

1.2.4 Fluoridated Dentifrices

Dentifrices were initially introduced as a cosmetic product for the purpose of cleansing and polishing the teeth, and as a breath freshener. Since the middle 1950's, when it was first reported that the use of a fluoride-containing dentifrice (stannous fluoride) reduced the incidence of dental caries, research has concentrated on formulations which could provide both therapeutic and cosmetic effects.

If a fluoride toothpaste is to be effective, the fluoride must be present, both in a chemically reactive (ionic) and stable form. In particular, laboratory and clinical data have shown that the fluoride must not be made insoluble by the toothpaste's abrasive, if anti-caries activity is to result (Forward, 1980). Loss of fluoride activity, due to reaction with the dentifrice constituents, was the primary

reason why early clinical formulations, containing dicalcium phosphate as an abrasive, produced a negative result (von der Fehr & Moller, 1978). As a result, in recent years, abrasive systems have been changed and the fluoride source has come mainly from either sodium fluoride, or sodium monofluorophosphate.

(a) Sodium Fluoride Dentifrices

Sodium fluoride was the first fluoride compound to be added as an active ingredient to a dentifrice. After a disappointing beginning due to interaction with the abrasive (von der Fehr & Moller, 1978), many successful trials, utilising different abrasives, have been undertaken. The results from some such studies are shown in Table 1.1 from where it is evident that considerable variations have been reported in clinical NaF studies, reductions varying from nil with a calcium carbonate, or heat-treated calcium orthophosphate abrasive, to 50% with a silica abrasive.

(b) Sodium Monofluorophosphate Dentifrices

Sodium monofluorophosphate (MFP) is one of the most widely used dentifrice constituents today, but even so, the mechanism of MFP in caries prevention is not fully understood. Ingram (1977) suggested that the MFP anion ($PO_3F_2^-$) has anticariogenic properties of its own and may exchange with phosphate groups in the apatite crystals, and that this reaction is not competitive with fluoride. Another study (Gron, Brudevold & Aasenden, 1971)

Table 1.1. Results of clinical trials of sodium fluoride dentifrices with different abrasives. (von der Fehr & Moller, 1978)

Principal abrasive	n studies	Age of subjects	Caries Reduction
Calcium carbonate	3	4-23	nil
Calcium orthophosphate (heat treated)	1	4-15	nil
Insoluble metaphosphate	4	9-24	0-20%, 1-2 surf/2yrs
Dicalcium phosphate	1	11-12	1-2 surf/2yrs
Calcium pyrophosphate	5	5-15	0-38%
Sodium bicarbonate	1	10	1-2 surf/2yrs
Plastic particles	5	8-15	38-48%
Silicon dioxide	2	9-11	50%

suggested that the caries-inhibiting action of MFP is linked to its slow hydrolysis, whereby small concentrations of fluoride ions are released as follows:

$$PO_3F_2^- + H_2O \rightarrow (H_2PO_4)^- + F^-$$

A review by DePaola (1983) summarised the effectiveness of MFP dentifrices when compared to an inactive control dentifrice (Table 1.2). Decreases in DFS or DMFS ranged from 0% to 27% with a $NaPO_3$ abrasive (Glass, Peterson & Bixler, 1983), to 40% (Glass, 1981). Andlaw & Tucker (1975) reported there was virtually no difference in the DMFS percentage reductions in a study where an aluminium oxide trihydrate base was used instead of the usual orthophosphate.

(c) **Stannous Fluoride Dentifrices**

Muhler (1956) found a greater reduction in enamel solubility in teeth treated with stannous fluoride, than with any other fluoride salt. Subsequently, several fluoride-containing formulae were tested, and stannous fluoride was shown to give superior results. This led, firstly, to solutions being used, and then to a 0.4% stannous fluoride dentifrice in a calcium pyrophosphate abrasive system being developed in 1955 (Muhler, 1956). Duckworth (1963) reviewed ten stannous fluoride dentifrice trials, and seven showed a reduction in caries rate. However, in these studies, the control and test groups were not balanced at the outset and Duckworth concluded that "unqualified acceptance of a stannous fluoride

Table 1.2 Clinical studies of 24 months or longer in which a MFP formulation was contrasted to an inactive control dentifrice (DePaola, 1983).

Investigators	% Reduction DFS or DMFS	
Torell & Ericsson (1965)	15	(in 11 yr olds)
	6	(in 10 yr olds)
Naylor & Emslie (1967)	18	
Fanning et al., (1968)	20	
Kinkel & Stolte (1968)	25	
Mergele (1968a)	21	
Mergele (1968b)	17	
Moller et al., (1968)	19	
Torell (1969)	29	
Thomas & Jamison (1970)	34	
Zacherl (1972)	20	
Hargreaves & Chester (1973)	26	(over 3 age groups)
Forsman (1974)	no meaningful effects	
Kinkel & Raich (1974)	32	
Kinkel et al., (1974)	33	(average)
Lind et al., (1974)	32	
Andlaw & Tucker (1975)	19	
Peterson & Williamson (1975)	23	
Ashley et al., (1977)	21	
James et al., (1977)	30	
Glass & Shiere (1978)	23	
Howat et al., (1978)	26	
Mainwaring & Naylor (1978)	15	
Naylor & Glass (1979)	22	
Peterson (1979)	23	($CaCO_3$ abrasive)
	0	($NaPO_3$ abrasive)
Barlage et al., (1981)	19	(0.8 % MFP)
	26	(1.2 % MFP)
Hodge et al., (1980)	7	NS
Mainwaring & Naylor (1980)	17	
Murray & Shaw (1980)	30	
Glass (1981)	40	
Cahen et al., (1982)	5	NS
Glass et al., (1983)	22	($CaCO_3$ abrasive)
	27	($NaPO_3$ abrasive)

dentifrice would still seem to be premature". Like Naylor & Emslie (1967), Duckworth found that SnF_2 was specifically responsible for a brown-black staining on teeth. As of October 1984, the stannous fluoride / calcium pyrophosphate dentifrice formulation was removed from the list of ADA-accepted Dentifrices (Newbrun, 1986).

(d) **Amine Fluoride Dentifrices**

Muhlemann, Schmid & Konig (1957) showed that organic fluorides were superior to inorganic fluorides. Cahen *et al.*, (1982) reported that an amine fluoride dentifrice resulted in a greater caries reduction compared to a monofluorophosphate paste. However, concern has been expressed about the taste characteristics and the long-range toxic effects of amine dentifrices (Nikiforuk, 1985). For these reasons, they are not available in North America (Nikiforuk, 1985) nor in the United Kingdom (Duckworth, 1963).

(e) **Comparison between single and combined fluoride formulation dentifrices**

Cahen *et al.*, (1982) compared the effect of monofluorophosphate and amine fluoride dentifrices and, although both showed a significant reduction in DMFS increments, after three years the reduction from amine fluoride was significantly higher (20.94 % as compared with 5.17 %). According to DePaola (1983) none of the four ADA-accepted dentifrices (MFP / $(Na_2PO_3)_x.CaHPO_4$; MFP / $CaCO_3$; MFP / $CaCO_3.SiO_2$; MFP / SiO_2) have ever been

tested directly against the one accepted NaF dentifrice (NaF / SiO_2).

Ripa *et al.* (1988), using equimolar amounts of NaF and Na_2PO_3F in dentifrices of 1000 ppm F and 2500 ppm F, found no superior caries inhibition, with unsupervised brushing, compared to a conventional sodium monofluorophosphate dentifrice containing 1000 ppm F. However, dentifrice compliance was under 25 per cent. Juliano *et al.*, (1985) compared a mixed dentifrice with 500 ppm sodium monofluorophosphate and 500 ppm sodium fluoride, with one containing 1000 ppm F as sodium monofluorophosphate. Even with supervised toothbrushing there was no significant difference with regard to the anti-caries effect. On the other hand, Hodge *et al.*, (1980) indicated that a dentifrice containing 0.76 % sodium monofluorophosphate plus 0.1 % sodium fluoride may be more effective in controlling caries than one containing only 0.76 % monofluorophosphate, especially in girls who "are more sensitive to treatment effects when taking part in dentifrice trials". A greater caries reduction with a sodium monofluorophosphate dentifrice was also found by Naylor & Emslie (1967), when they compared it to stannous fluoride.

(f) Fluoride Concentration in Dentifrices

Once compatible abrasive systems were established, attempts to improve the efficacy of dentifrices were made by increasing the concentration of fluoride. Reed (1973)

compared NaF dentifrices containing 250, 500 and 1000 ppm F with a 0 ppm F control dentifrice. After two years, DMFS reductions with the three fluoride dentifrices were 8 %, 8 % and 20 % respectively. Barlage, Buhe & Buttner (1981) studied the effect of increased concentrations in monofluorophosphate dentifrices. These workers found that, when the concentration of fluoride was increased from 1000 to 1500 ppm F, DMFS increments were reduced by 19 % (1000 ppm F) and 26 % (1500 ppm F) as compared to the placebo. In another MFP study, a 7% (1500 ppm F) and a 16 % (2500 ppm F) reduction in three-year caries increments was noted compared to a 1000 ppm F control (Stephen *et al*, 1988). The bitewing X-ray information from this study has been used as the data source for the investigations reported in this thesis.

Koch *et al.*, (1982) used a 250 ppm F as NaF dentifrice, a 1000 ppm F as NaF dentifrice and a 1000 ppm F as MFP dentifrice. Here it was found that the low fluoride dentifrice (250 ppm F) was as effective in controlling caries development as the 1000 ppm F formulations. On the other hand, Mitropoulous *et al.* (1984), using 250 and 1000 ppm F (as MFP) dentifrices found a significant difference between these two preparations with the higher concentration being more effective. The results of further studies comparing dentifrices with different fluoride levels are shown in Table 1.3 (Mellberg, 1990).

Table 1.3 Percentage caries inhibition of dentifrices with different fluoride levels (Mellberg, 1990).

Study	F type	0	Dentifrice F concentration (ppm) 250	500	1000 1100	1500	2000	2500
Reed (1973)	N	C	7.5	8.5	20			
Forsman (1974)	M	C	4		25			
	M	C	15		28			
	N	C	32					
Barlage et al., (1981)	M	C			19.0	26.0		
Buhe et al., (1984)	M	C			17.5	26.3		
Koch et al., (1982)	N		0		C			
Mitropoulous et al., (1984)	M		-19		C			
Stephen et al., (1988)	M				C	10.0		17.0
Triol et al., (1987)	M				C	8.9	11.9	
Conti et al., (1988)	M				C	21.8		
Fischman et al.,(1987)	M				C	21.5		
Fogels et al., (1988)	M				C	14.4		
Leverett & Curzon (1988)	M				C		16.0	
Lu et al., (1987)	N				C			11.8*
	M							0.7*
Ripa et al., (1987)	M/N				C+			1.9+
Diodati et al., (1986)	M/N					C	11.7+	13.4+
Hodge et al., (1980)	M/N					C	17.8+	

N - NaF
M - MFP
* 2800 ppm F in the dentifrice
+ mixed F dentifrice : 1000 ppm F (MFP), 450 ppm F (NaF)
C = control i.e. basis of comparison

(g) Ingestion of Dentifrices

The amount of toothpaste ingested has been shown to be greater among younger children (Barnhart *et al.*, 1974), from 34.9 % at ages 2 - 4 years, to 2.9 % at ages 20 - 35 years. Ericsson & Forsman (1969) reported that children aged 4 - 5 years, who used 0.5 g of dentifrice per brushing, retained 26 - 33%. Ekstrand, Koch and Petersson (1983) also found that blood plasma levels showed a significant increase from 1000 ppm F dentifrice but an insignificant increase with a 250 ppm F dentifrice. To combat the problem of possible fluorosis through dentifrice ingestion, parents should regularly assist pre-school children in brushing their teeth and ensure only a pea-size portion of fluoride toothpaste is placed on the child's toothbrush (Newbrun, 1986). Also, fluorosis would be increased by 150% if toothpastes with 2500 ppm fluoride became widely available without prescription (Newbrun, 1986).

1.3 Methods of Caries Detection

Coronal caries occurs on three distinct regions of both deciduous and permanent teeth, i.e. on smooth surfaces (buccal and lingual), on interproximal surfaces, and on occlusal surfaces (pits and fissures). Pits and fissures are also found on buccal surfaces of lower first and second molars, the palatal surfaces of the upper first and second molars, and on the palatal surfaces of the upper centrals and laterals. Different methods of caries detection and diagnoses are used in these different areas.

Visual examination depends on the fact that demineralised enamel scatters light differently from sound enamel. On smooth surfaces, provided the tooth is clean, dry and well lit, sharp eyes can detect early white spot lesions (Kidd, 1984). Brinkman, ten Bosch & Borsboom (1988) described an optical instrument which measures the intensity of light scattered from enamel surface lesions. The instrument uses a bundle of small fibres in an 'optical needle' with a flat end that is placed on the lesion. Half the fibres are used to illuminate the lesion and the other half to collect the light backscattered by the lesion interior. The authors reported that the intensity of backscattered light can be used to give a quantitative measurement of mineral loss in the lesion. However, the major disadvantage of this instrument is that it can only be used on smooth surfaces.

The fact that there is a difference in luminescence between intact and carious enamel has been utilised by Bjelkhagen *et al.* (1982). These workers illuminated smooth tooth surfaces by an argon laser emitting light in the blue-green region and observed (photographed) the reflected light using a filter which only transmitted light at wavelengths longer than 540 nm. Here it was stated that lesions, not visible to the naked eye under normal illumination, could be observed. However, this method could only be used on smooth and occlusal surfaces. Pitts & Longbottom (1987a), and Longbottom & Pitts (1988), adapted this fluorescence technique for use with an

endoscope, enabling it to be employed with interproximal surfaces. Preliminary results indicated that a greater number of small carious lesions were detected than by visual, fibre-optic transillumination (FOTI), or radiographic methods (*vide infra*). The technique is being further investigated.

In pits and fissures, visual diagnosis at the early stages of lesion progression is difficult because the white spot defects form bilaterally on the walls of the fissure (Kidd, 1984). The use of a sharp dental probe as an adjunct to visual examination is now not recommended as the probe may break down the intact surface layer of a white spot lesion and thus initiate a cavity, making remineralisation impossible (Bergman & Linden, 1969). In occlusal caries, the stickiness of the probe may be more indicative of the fissure shape or the pressure exerted, rather than caries. Hence Downer & O'Mullane (1975) suggested the probe should only be used to remove plaque and debris from a fissure, so that trained eyes could then pick-up any discolouration.

Occlusal caries can also be detected by radiographs, although King & Shaw (1979) reported these were considerably less sensitive than clinical examination, with radiographs detecting only 33.2 % of carious lesions discovered by dental probing. However, in view of the above difficulties relating to fissure probing, the number of lesions determined by the probe may have been

overestimated. In addition, Sawle & Andlaw (1988) when analysing data from a 1974 study involving 1949 first and second molars, found that 10.3 % of the radiographically diagnosed lesions (360) were not noted clinically. Similarly, for data from a 1982 study involving 3766 first and second molars, they found that 32.2 % of X-ray detected caries were not diagnosed clinically. The reason given for the significant difference in clinical diagnosis was the greater exposure of teeth to fluoride dentifrices in 1982. This finding supported the impression gained by practitioners that occlusal caries has recently become more difficult to diagnose clinically (Millman, 1984). Furthermore, Creanor *et al.*, (1989, 1990) found there was a greater tendency to underdiagnose clinically mandibular occlusal caries; 3.5 % of clinically sound upper first molars showed radiographic evidence of occlusal caries, whilst for the lower first molars the comparable figure was 13.5 % ($p < 0.001$).

Measurement of the electrical resistance between the occlusal surface and the pulp, has also been used to detect occlusal caries (Pincus, 1951; Nomura, Onoue & Nemoto, 1971). This technique has been shown to be more sensitive and consistent than examination with a dental probe when verified by histological examination (White, Tsamtsouris & Williams, 1978). In a study utilising 37 teeth, Rock & Kidd (1988) reported that four methods of clinical examination (visual examination alone, mirror and blunt probe, mirror and sharp probe, and

transillumination) all failed to detect histologically-verified caries. However, the Vanguard electronic detector correctly identified demineralisation in 26 of the 37 teeth; a sensitivity of 70 %. This method of caries detection is, however, not widely used since each tooth has to be isolated. In addition, suitable equipment is not readily available.

Because of access problems, early approximal lesions are difficult to diagnose visually, or with a probe. Hence radiographs and FOTI have been employed to assist detection at these sites.

The X-ray was introduced by Roentgen in 1895, but it was not until the early 1900's that their potential for caries diagnosis was recognised (Bodecker & Bodecker, 1912). The first dental X-ray unit did not appear until 1917 with the bitewing film following in 1926. However, the use of X-rays to diagnose caries did not become common until the 1930's, and Anderson *et al.*, (1934) were the first to employ radiographs for caries diagnosis in a clinical trial. Since then, the bitewing has become an important and widely used means of caries assessment.

Caries diagnosis by X-rays is based on the fact that demineralised enamel/dentine absorbs fewer X-rays than sound tissue. Thus a carious lesion will appear as a dark area on an X-ray film. Normally, the film is assessed visually by a clinician, and a score which is related to

lesion extent is allocated (see Chapter 2). This is a semi-quantitive measure of caries and although it has been shown that the visual acuity of the examiner, the viewing illumination (Mileman *et al.*, 1984), and choice of film (Svenson *et al.*, 1985; Waggoner & Ashton, 1989) are not important, it is open to systematic and random errors (*vide infra*). Recently, Pitts (1986a, 1987a), and Pitts & Renson (1986a,b) have investigated the use of image analysis techniques to provide a semi-automatic quantitative measurement. They concluded that the diagnostic accuracy of the image analysis method was comparable to that of an oral radiologist, although it tended to be more sensitive, but less specific.

Fibre optic transillumination (FOTI) has been suggested as a non-invasive (Elderton, 1985a) alternative to bitewing radiography (Mitropoulos, 1985a). It is based on the assumption that demineralised enamel / dentine will modify the transmission of light through the tooth. Here a fibre optic probe is placed in the embrasure immediately under the contact point of approximal surfaces to be examined and, as a carious lesion has a lowered index of refraction, an area of caries appears as a darkened shadow that follows the spread of decay through the dentine. Mitropolous (1985a,b) reported that for 98 % of surfaces examined, FOTI and radiographic diagnosis were in agreement. However, this data was based on only 50 patients and Stephen *et al.* (1987b), in a study of 2247 subjects, came to the conclusion that FOTI is no

substitute for bitewing radiography. Nonetheless, should radiographs not be available, FOTI could enhance the clinical diagnosis of posterior approximal caries by approximately 48 %. In a follow-up study of 2010 subjects available one year later, Stephen *et al* (1989) still found that FOTI detected only 20 % of X-ray diagnosable lesions. These workers also reported that four factors could influence FOTI false-positive results, viz:- (a) presence of an adjacent occlusal amalgam, (b) presence of an adjacent interproximal amalgam, (c) presence of adjacent occlusal caries, and (d) the lack of interproximal contact which revealed "healed" white spot lesions only on the mesial surface of permanent molars. However, via FOTI, these "scars" were recorded as caries-like shadows.

At the individual patient level (as distinct from the clinical trial situation), X-ray, FOTI, and electronic examinations can also be augmented by the use of elastomeric separating modules (Seddon, 1986, 1989; Pitts & Longbottom, 1987b). Here, temporary tooth separation allows the distinction between cavitated and non-cavitated lesions to be made. In addition, even in the case of radiographic examinations, this technique provides a clear pathway for the central ray through the interdental space. Unfortunately, as yet, a universally acceptable separating device has not been produced.

1.4 Errors and reversals

1.4.1 Introduction

In all forms of measurement, errors are to be expected. Since this thesis is concerned with the comparison of anti-caries agents using caries increments and, in particular, following the caries score of individual surfaces rather than with the estimation of caries prevalence, random sampling errors and others e.g. partial recording (Welander, 1960), will not be discussed here. However, even in well-designed clinical trials with proper stratification for age, sex, dental age and caries experience, errors will still occur in the calculation of DMFT / DMFS values. The errors encountered can be categorised into two types: systematic and random.

1.4.2 Systematic errors

Systematic errors are those inherent in the measurement protocol and beyond the control of the examiner. In clinical trials involving bitewing radiographs, possible sources of systematic errors are:

(a) beam angulation,

(b) method of X-ray reading

- and -

(c) errors in identification.

Beam Angulation

The correct scoring of the extent of an interproximal carious lesion will depend on the horizontal angulation of the central X-ray beam. Sewerin (1981b) showed, by varying

the angulation in steps of 2.5°, that only 21 out of 43 surfaces had identical scores in all of 16 possible views. However, the fact that three different observers read the radiographs may have affected this result. Furthermore, eight of the ten lesions extending into dentine had identical scores, suggesting that beam angulation is more important for smaller lesions with lower radiographic scores. Leijon (1969) demonstrated that when the direction of the beam was changed, different carious lesions could be made more visible. Nysether & Hanson (1983) found that 10.6 % of overlaps were due to the wrong horizontal angulation of the central beam. They also found that 2.2% under/overaxial exposures were due to incorrect angulation of the vertical beam. On the other hand, Espelid & Tveit (1984) showed that large changes in horizontal beam angulation of up to $\pm$12.5° did not affect artificial lesion detection. When Backer-Dirks, Amerongen & Winkler (1951) took duplicate X-rays (within a fortnight), 746 out of a theoretical possible total of 8512 surfaces were not equally present on both radiographs. As a result, it was stated that if there was a slight difference in the angle of projection, lesions previously invisible could become visible, and the reverse could also occur.

Incorrect beam angulation can also lead to surfaces which either overlap or "are not present on the radiograph". Many studies have either ignored or excluded such situations (Naylor & Emslie, 1967; Wright, Banting &

Feasby, 1976; Grondahl *et al.*, 1977a,b; Mainwaring & Naylor, 1978; Naylor & Glass, 1979). Haugejorden (1974) rated 38.6% of the surfaces in his data as unreadable, whereas Berman & Slack (1973) excluded unreadable surfaces but reported their presence. Murray & Shaw (1975) included "category 9" surfaces ("not completely readable, but presumed sound, - less than half of the enamel overlapped") in their final analysis, but not "category 7" surfaces ("overlap, - unreadable"). Pitts (1986a) concluded that partially overlapped surfaces were inevitable, but stated they should not be ignored because the significance of results would be affected. He suggested that an image analysis method (*vide supra*) may enable additional data to be obtained from such partially overlapped images (Pitts, 1984).

The use of film-holding devices that allowed duplication of the angular relationship between the X-ray beam and the film at subsequent examinations, and also reduced the number of overlaps and missing surfaces, was recommended by Williams (1968). Backer-Dirks, Amerongen, & Winkler, (1951) investigated the use of a rigid apparatus consisting of a solid metal ring to fit on the X-ray tube cone and a perforated metal plate to which the film could be fastened. This prevented bending of the film. Film holders were also used by Updegrave (1967) to define the correct beam-object-film alignment, thus eliminating the necessity for a specific head position and predetermined tube angulation.

Methods of Film Reading

There are two methods of reading X-rays in clinical trials, longitudinally or cross-sectionally. In Haugejorden's (1974) study of 283 female subjects, the annual bitewing radiographs were read by both means and compared. He found that, after 2 years, the percentage of subjects with zero DFS increment was consistently greater when radiographs were assessed longitudinally, but this difference disappeared when the whole three year trial period was considered. However, Haugejorden (1974) also found the reversal rate was significantly higher when radiographs were assessed by the cross-sectional method. Marthaler (1973) reported that the misreading of radiographs was kept to a minimum by reading simultaneously, all radiographs of a child.

Errors in Identification

Errors in identification may be the result of several factors outwith the control of the examiner. For example, a tooth may be fractured and initially scored as sound. However, between examinations, the fracture may be treated by restoring the tooth and up to five new filled surfaces added to the caries increment. Similarly, teeth restored as the direct result of trauma, or extracted for orthodontic reasons, can also artificially increase the caries increment (Glass, 1968). An audit of subjects' clinical records should enable the extent of such errors to be estimated and thus corrected. However, in a clinical trial, such records are not normally available. In

addition, such artificial caries increments are likely to be minimal in interproximal sites.

A major source of identification errors is undoubtably attributable to the experience and training of examiners. Systematic errors can occur if an examiner consistently assigns wrong scores to a particular size of lesion. Numerous attempts to overcome this problem have been undertaken by studying inter-examiner variability where different examiners score the same subjects and / or X-rays. Any disagreement between examiners will highlight such systematic faults. Quensel, Gustafsson & Grahnen (1954), and Poulsen (1980) found that training programmes were unsuccessful at reducing the number of such errors, but that there was a decrease in the number of decayed surfaces recorded. Grondahl (1979) stated that even with additional training, there was wide variation amongst observers and that inter-examiner variations still prevailed even when only taking into account diagnoses which were made with absolute certainty i.e. after eliminating possible random errors (*vide infra*). Horowitz (1968) recommended that when data are pooled, and more than one examiner participates, an intensive training period should be undertaken and the number of disagreements should be reduced to an acceptable, defined minimum, such remaining errors being possibly due to a random component.

1.4.3 Random errors

Random errors include such factors as incorrect scribing of the stated score which, obviously, will be random in nature. However, even though careful checks can be instigated to minimise such errors, the examiner will always be faced with the decision to place an ambiguous score into one of two possible categories. Such an allocation will be random. The study of intra-examiner variability, where the examiner re-examines a subset of the subjects, has been used to determine the extent of such errors.

Karjalainen & Hannula (1988) stated the best reproducibility ratios were obtained from recordings made twice by the same examiner, but the differences in intra-examiner variability could be as much as 30-fold. They, as well as Alanen & Tiekso (1986), found that examiners who had weak intra-examiner correlations, had weak inter-examiner agreements, whereas Russell (1987), observed that two examiners who had high inter-values also had, individually, high intra-coefficients. Karjalainen & Hannula (1988) suggested that Markens' (1962) method of a group decision by two or four examiners might be the answer. However, this could be very wasteful of clinician's time and would appear less desirable than having good examiners in the first place.

1.4.4 Methods of error assessment

Various methods exist for the assessment of errors in clinical trials. Rugg-Gunn & Holloway (1974) reviewed five types of reliability coefficients, three of which are applicable to incremental data, viz: (a) Marthaler's immediate re-examination method, (b) sum of prevalence error variances, and (c) internal consistency. These methods were developed from the concept that total variance is the sum of true, and error variances, and that the coefficient of reliability, r_t, is the ratio of true to total variances, viz:

$$r_t = S_x^2 / S_e^2$$

$$= 1 - S_e^2 / S_t^2$$

where S_x^2 = true variance

S_t^2 = total variance

and S_e^2 = error variance

Thus, if the error variance is zero, the reliability coefficient will equal 1, and similarly if the total variance is due solely to error ($S_e^2 = S_t^2$), then the coefficient will equal zero.

Marthaler's (1964) method is based on the assumption that the variance of a six month increment is an estimate of incremental error variance and this could be compared to the total variances for longer periods. However, the disadvantage of this method is that it involves the re-examination of subjects, and there is the possibility that some true change in subject status may have occurred in the interim. Thus a shorter re-examination time would

appear appropriate.

In the sum of prevalence variances method, the incremental error variance is the sum of the error variances associated with the two prevalence scores which are evaluated using one of the methods available for determining error variances in prevalence data e.g. Dahlberg's (1940) method. This method assumes that the error variances of the two prevalence scores are independent.

In the internal consistency method, comparison of the caries score is made between the two halves of a mouth and a modified Pearson's correlation coefficient calculated. Although this method has the advantage that subjects do not have to be re-examined, caries scores, and in particular incremental scores, tend not to be homogeneous between the two sides. Thus the basis for this method can be false.

Hunt (1986) reviewed three other reliability coefficients: (a) percent agreement, (b) Pearson's correlation coefficient, and (c) Kappa. He discouraged the use of percent agreement as it does not take into account any possible agreement occurring by chance. He also cautioned against the use of Pearson's correlation coefficient as it ignores any systematic bias which might be present. However, it accurately represents the reliability of mean caries scores assigned by the examiners.

Kappa is defined as:-

$$(P_o - P_e) / (1 - P_e)$$

where P_o is the percent agreement observed and P_e is the percent agreement expected. It can be interpreted as the proportion of possible agreement beyond chance that was actually observed (Cohen, 1960). Unlike, Pearson's correlation coefficient, Kappa detects non-random (systematic) bias and accurately represents the reliability of caries diagnosis on individual teeth (Hunt, 1986). Hunt suggested the use of both Pearson's correlation coefficient and Kappa. Fleiss *et al.* (1979b) discussed two versions of Kappa for inter / intra reliability and came to the conclusion that Kappa "is subject to the same kind of anomalies as other statistics when the phenomena studied varies little or not at all, but it may be safely used even when the rates of decay are as low as two or three percent".

When whole mouth scores, such as means, are being used, the interclass correlation coefficient (Fleiss *et al.*, 1979a) has been recommended (Hunt, 1986). This coefficient is calculated using analysis of variance to partition the variance into components such as: subjects, examiners, repeat examinations, and interactions amongst these terms.

The values of the coefficient of reliability, calculated using the test-retest method, for the trial data analysed in this thesis were all found to be of the order of 0.92

and above (Russell, 1987), thus showing the errors were acceptable.

1.4.5 Reversals and remineralisation

Carlos & Senning (1968) utilised a mathematical model to investigate the effect of diagnostic errors on the calculation of caries increments. They concluded that errors were likely to bias the outcome of a clinical trial in favour of not rejecting the null hypothesis. It is interesting to note, however, that the authors stated reversals in diagnosis (i.e. carious to sound) could be used as an indicator of the extent of the errors, and suggested that reversals be subtracted from the true caries rate. The possibility of remineralisation, and consequently the concept of a true reversal, was not envisaged at that time. Radike (1968) supported this idea and stated that reversals were wholly due to examiner misdiagnosis, or inconsistency, or clerical error. In addition, Ship, Jones and Laster (1966) using combined radiographic and clinical data from a longitudinal study, investigated three categories:- reversals, errors and questionable dental caries diagnosis. Errors they attributed to surfaces which, for example went from filled to sound. Reversals they classified as unexplainable changes from carious to sound, and were to be "recognised as a natural occurrence ..... due to different examiner criteria, population characteristics, and the materials and methods of the studies". No mention was made of remineralisation. Based on data from a two year study,

Torell & Ericsson (1965) stated that the majority of reversals (their name for all charting indescretions) emanated from observation and recording errors, and that only a fraction of reversals could have been the result of remineralisation. On the other hand, Goaz *et al.* (1963) reported a high number of reversals, due in part to diagnostic criteria, and to remineralisation caused by fluoride and low caries activity.

With the increased interest in remineralisation (see Section 1.2.2) and Von der Fehr, Loe & Theilade's (1970) experiment on dental students, reversals are now regarded as true reversals and not charting errors (Pitts, 1984, 1986b, 1987a). Pitts (1984) showed, by computer-aided image analysis, that radioluciences monitored by serial standardised bitewing radiographs, actually decreased in size and became more radiopaque with time. In addition, Etty *et al.* (1988) stated that 46.2% of approximal, and 57.3% of smooth surface lesions regressed over a one year period. They also found their regressions decreased in time, in favour of stabilisation.

CHAPTER 2 THE CLINICAL TRIAL

2.1 Introduction

In this chapter, the double-blind clinical dentifrice trial which provided the bitewing radiograph data source for the studies reported in this thesis, will be described.

2.2 The aims of the clinical trial

There were two principal aims of the trial:

(i) to study the effect of dentifrice fluoride concentration on caries increments. The three fluoride levels used were 1000, 1500 and 2500 ppm F^- as sodium monofluorophosphate.

(ii) to determine whether zinc had an effect on plaque, calculus and caries increments. (Only the caries aspect is of relevance to this thesis).

In addition to the clinical and radiological caries data gathered to satisfy the above aims, information was also obtained on various behavioural and sociological aspects of the subjects as well as other clinical indices such as those relating to gingival health and plaque.

2.3 Trial Subjects

The subjects for this three year anti-caries clinical trial were schoolchildren selected from twelve schools in the Lanarkshire area of Scotland. At the start of the trial in August 1983, the subjects were entering their first year of secondary education and had a mean age of

12.55 years, ranging from 11.25 - 14.0 years. Parental consent and Ethics Committee approval were obtained for all aspects of the trial.

After their first clinical examination, children were allocated to six toothpaste groups by a process of stratified randomisation. Each child was allocated to one of 36 groups depending on (a) examining clinician, (b) sex of the child, and (c) baseline dental status. Initially, 3005 subjects were examined at baseline. Fewer subjects were allocated to groups 5 and 6, the highest dentifrice fluoride groups, as it was anticipated that, at this fluoride concentration (2500 ppm), the lower numbers would be adequate to identify any significant fluoride effect. The number of subjects allocated to each agent is shown in Table 2.1. No significant differences were found to exist between the mean DMFT, DMFS, DFS and DS values of the six groups (Russell, 1987).

By the final examination, 2315 subjects remained. The fall-off in numbers was due either to (a) the subject being absent during the examination, (b) the subject having left the area, (c) the subject being deceased, (d) the child or parent making a request to leave the trial or (e) the subject being excluded for non-adherence to the trial protocol.

Table 2.1 Number of subjects initially allocated to each dentifrice group.

Agent	No of subjects
1	599
2	597
3	600
4	604
5	299
6	306

2.4 Caries data

2.4.1 Clinical data

Each child was examined clinically by one of two calibrated clinicians, and remained that clinician's responsibility for the rest of the trial. Furthermore, approximately 5% of the subjects were re-examined by the same clinician to permit intra-examiner comparisons, and another 5% were re-examined by the other examiner in order to calculate inter-examiner reliability coefficients according to the test-retest method advocated in 1974 by Rugg-Gunn & Holloway, (see Section 1.4.4). The inter-examiner reliability coefficients ranged from 0.92 to 0.99 at the different examinations, whereas the intra-examiner coefficients ranged from 0.97 to 0.99 for Clinician 1, and were 0.99 at all examinations for Clinician 2.

2.4.2 Radiographic data

At baseline and subsequent examinations, bilateral bitewing X-rays were taken of the approximal surfaces of permanent posterior teeth from the mesial surface of the second molar to the mesial surface of the first premolar. X-rays were taken by an experienced dental radiographer using a transportable Philips Oralix 65 kV, 7.5 ma machine, with a 20 cm cone (Philips Medical Systems, Hammersmith, London), mounted on a specially adapted Atomscope mobile stand (Hikassa X-ray Co. Ltd., Japan). Kodak Ultra Speed dental film DF-56 (Eastman Kodak Co., New York, U.S.A.) was employed and the films held in preformed cardboard bitewing holders to allow for correct

beam alignment. The radiographs were read cross-sectionally at yearly intervals without reference to the clinical findings, by one of the two examining clinicians, although it was not necessarily the same clinician who had examined the subject clinically. Subsequent radiographs were read by the same clinician. Queries in radiographic scores between two consecutive years were re-read by the clinician. However, only the current radiograph and that immediately preceding were involved. Again, 5% of the radiographs were re-read for inter-, and 5% for intra-examiner reliability. The former coefficients were 0.99 at all examinations, whereas the latter were 0.99 at all examinations for Clinician 1, and varied between 0.98 and 0.99 for Clinician 2.

The radiographic scoring of each surface was adapted from the criteria of Rugg-Gunn (1972), viz:-

0 - sound surface

2 - radiolucency in enamel, up to the amelodentinal junction

3 - radiolucency in enamel and dentine not involving pulp

4 - radiolucency involving dentine and pulp

5 - restored surface

7 - surface unreadable and no diagnosis possible due to overlapping surfaces on X-ray

8 - surface not present on X-ray

9 - some overlap of surfaces involving not greater than half the enamel width, with no caries visible

and thus deemed apparently sound.

In addition, a code of 6 on the occlusal surface was used to indicate that a tooth was missing, the reason why being coded in the next data column, viz:-

61 - unerupted

62 - extracted for caries

63 - impacted, or congenitally missing

65 - extracted for orthodontic reasons

66 - extracted due to trauma.

2.5 Trial dentifrices

Six different toothpastes were used, with three levels of sodium monofluorophosphate (1000, 1500 and 2500 ppm) tested. At each fluoride level pastes were formulatd with and without 0.5% zinc citrate. A more detailed list of the paste formulations is shown in Table 2.2.

Sufficient toothpaste to supply the whole family was delivered to each subject's home by a team of specially recruited home visitors. The dentifrices were packaged in colour-coded tubes, the composition of which was unknown to the subjects, the home visitors and the examining clinicians. Details of the frequency of use, and the amount used were obtained, both at the clinical re-examinations, and by the home visitors.

Table 2.2 Percentage weight per weight composition of the six toothpastes (Agents 1 - 6) used in the Lanarkshire clinical trial.

	Toothpaste					
	1 1000 ppm F No Zn	2 1000 ppm F + Zn	3 1500 ppm F No Zn	4 1500 ppm F + Zn	5 2500 ppm F No Zn	6 2500 ppm F + Zn
Polishing agent	50.0	50.0	50.0	50.0	50.0	50.0
Humectant	30.0	30.0	30.0	30.0	30.0	30.0
Binder	1.0	1.0	1.0	1.0	1.0	1.0
Detergent	1.5	1.5	1.5	1.5	1.5	1.5
Stabiliser	0.3	-	0.3	-	0.3	-
Flavour/ colouring	1.5	1.5	1.5	1.5	1.5	1.5
Sodium monofluoro-phosphate	0.76	0.76	1.14	1.14	1.90	1.90
Zinc citrate	-	0.50	-	0.50	-	0.50
Demineralised water	<---------- to 100% ---------->					

CHAPTER 3 MATERIALS AND METHODS

3.1 Introductions

In Chapter 1, it was stated that the aim of this thesis was to investigate the changes in the radiographic scores of individual interproximal tooth surfaces over the three year period of a dentifrice clinical trial. In this chapter, the methods used to obtain the individual scores, the classification of these scores, and the methods employed to study the effects of dentifrice fluoride and zinc citrate concentrations, sex and handedness of the subject, on the radiographic scores are described. The results of these studies are presented in the next chapter.

3.2 General Methods

3.2.1 Data storage and SPSS×

Data from the clinical coding forms was encoded at Unilever Research Port Sunlight. For each examination, a file was created containing the data of all subjects present. In each file, every subject could have up to six records, depending on whether or not they had a radiographic examination. The first record included subject details, the agent / toothpaste used, sex, handedness (first examination only), protocol (Exams 2, 3 and 4), oral debris and calculus indices, time since last brushing, and frequency of brushing. The second and third records contained the clinical examinations results. The fourth record held a repeat of some personal details,

while the fifth and sixth records contained the X-ray data.

The data were transferred to the University of Glasgow's ICL 3980 mainframe computer and were stored as four 1 Mbyte files, containing 17790, 15786, 15438 and 13899 records respectively.

The Statistical Package for Social Sciences (SPSS) was created in 1966. It is a comprehensive software programming language for managing, statistically analysing, and displaying data with facilities for sorting, splitting and matching / merging data from different files. In 1983, an updated version, SPSS* was released to provide greater facilities.

3.2.2 Radiographic combinations

The X-ray scores from the dentifrice clinical trial described in the previous chapter were used in this study. As stated, the scores of the mesial and distal interproximal surfaces of upper and lower posterior teeth, from the mesial of the first premolar to the mesial of the second molar, were studied. An SPSS* program was written, which matched the four data files described above in terms of subject number. The program then selected-out those surfaces which satisfied certain criteria (see Section 3.2.5), and produced a list of the four radiographic scores for each surface, noting where appropriate, the paste used, the sex, and left- or

right-handedness of the subject. The baseline radiographic score and those from the three subsequent annual examinations, for each selected surface, were referred to as the radiographic 'combination'.

3.2.3 Classification of combinations

Combinations from '0002' to '3555' were classified into surfaces which 'Progressed' (P), surfaces which 'Reversed' (R), or surfaces which remained 'Stable' (S). It was decided that a few combinations, did not fit into any of the above classifications. A new category called 'Borderline' (B) was created to categorise such situations. Surfaces which had a radiographic score of 'zero' at all four examinations, i.e. combination '0000', were treated separately.

The classifications and numbers in each combination, for each paste, are shown in Appendix 1. Surfaces with a radiographic score of '9', i.e. slight overlap but apparently sound, in any of the four examinations, were also classified as 'zero'.

In general, where a score of 'zero' increased to a '2', '3', '4', or '5', or a score of '2' increased to a '3', '4', or '5', or a score of '3' increased to a '4' or '5', the combination was classified as a surface which 'Progressed'. Combinations with three or four years of the same score, unless preceded with a score of 'zero', were classified as 'Stable', although it may have been equally as valid to have classified these latter combinations also as 'Stable'.

For some combinations, assumptions were made that mistakes had been made in the radiographic scoring in intervening years. For example, the score of 'zero' in the combination '3022' was assumed to be an error and this combination was assumed to be either '3222' or '2222' both of which were classified as 'Stable'. Similarly, the combination '3033' was assumed to be '3333'. However, these assumptions must be treated with caution. For example, in the combination '3033', the '3' may have been a '2' and the '0' may also have been a '2' due to beam angulation problems. This would give the combination '2233' which would then have been classified as 'Progressive', (see Section 1.4.2).

A radiographic score of '2' going to a 'zero' at the next examination was, in general, classified as a 'Reversal' unless the '2' was assumed to be a mistake (see above). In addition, a score of '3' going to a '2', in some cases, was also taken as a 'Reversal' (*vide supra*, & Section 3.2.4).

The radiographic combinations, '0202', '2002', '2020', '3020' (and the associated combinations with a score of '9') were classified as 'Borderline'. Originally the combination '0220', was classified as 'Borderline'. However, it was decided that X-rays of these cases should be re-read (see Section 3.2.4).

3.2.4 Re-reading of X-rays

Inspection of the different radiographic combinations obtained as a result of the cross-sectional reading of the X-rays, showed there were some 'illogical' combinations e.g. a radiographic score of '3', '4' or '5' going to a 'zero' at the next examination. An SPSS* program was written to produce a list of the subject numbers for all

the 460 surfaces belonging to the starred (*) combinations in Appendix 1, including the corresponding combinations containing a '9'. All bitewing radiographs of these surfaces were re-read longitudinally by Professor K W Stephen, the X-rays being read blind. During this exercise a radiographic score of '1' was introduced, which corresponded to an unsound surface where the lesion extended less than half-way through enamel and a score of '2' could not be justified. The classification of these combinations is shown in Table 3.1.

The results of re-reading surfaces with these 'illogical' combinations are shown in Table 3.2. Of the 460 surfaces, 12 could not be re-read as the films were either no longer available or had been misfiled; 238 surfaces were awarded a radiographic score of 'zero' at all four examinations, and 210 emerged with a new radiographic combination. None of the longitudinally re-read combinations exhibited any of the previous 'illogical' classifications.

In addition to the combinations discussed above, it was decided that certain other controversial combinations (highlighted with ** in Appendix 1) should be confirmed, e.g. the combination '0220' (and the corresponding ones containing a '9') was originally classified as 'Borderline', but it was decided to re-read the 211 such classifications and, if judged genuine, to reclassify them as 'Reversals'. The results of this re-reading are shown

Table 3.1 Classification of re-read surfaces containing a score of '1'.

Re-read Combination	New Classification
0012	P
0101	P
0112	P
0122	P
0210	R
1000	R
1100	R
1122	P
1211	R
1220	R
2111	R

P = 'Progressive'
R = 'Reversal'

Table 3.2 Result of re-reading X-rays having 'illogical' original scoring combnations.

Original Combination	Combinations (and number) after re-reading
0030	0000 (60), 0002, 0020 (7), 0022 (3), 0023, 0025, 0033 (6), 0220 (6), 0222 (3), 0225, 0233 (3), 0101, 2225, 2233, 2020, 2332, 3355
0040	0000 (2)
0050	0000 (41), 0055, 0555, 2220, 2355
0052	0000 (3), 0023
0053	0055
0203	0000 (10), 0002 (2), 0003, 0022, 0023 (2), 0033, 0112, 0200, 0202, 0222, 0223 (3), 0233 (2), 2203, 2233 (2), 2333
0230	0000 (8), 0012, 0022, 0210, 0220, 0222 (5), 0223 (2), 0233 (2), 0235 (2), 2111, 2200, 2222
0250	0000 (3), (1 N/A)
0252	0222, (1 N/A)
0300	0000 (38), 0200, 0255, 2222, 2332
0303	0000 (4), 0203, 0233, 0333 (2), 1100, 2223
0304	(1 N/A)
0305	0005 (2), 0205, 0235, 0335 (2), 0355 (3), 2335 (2)
0320	0000 (2), 0200, 0323
0330	0000 (9), 0020, 0222 (3), 0233, 0235, 0333 (2), 1211, 2222, 2233, 3335
0350	0000 (2)
0404	0000, (2 N/A)
0500	0000 (5), 0200, 0220, 0222
0502	0000
0505	0000 (11), 0002, 0005, 0333 (2), 0555 (7)
0522	0002, 0022, 0220, 2222
0550	0000 (5), 0555
0552	(2 N/A)
2003	0000 (2), 0222 (2), 0223, 2000, 2222 (2), 2233
2005	0225 (2), 2000, 2005, 2225
2030	0000 (2), 0022, 1220, 2200, 3333, (1 N/A)
2050	0000
2052	(1 N/A)
2230	0000 (4), 0022, 0122, 0220, 1000, 1122, 2023, 2220, 2222 (2), 2233 (7)

Table 3.2 (Continued)

Original Combination	Combinations (and number) after re-reading
2250	2255
2302	2202
2303	2203, 2222, 2333
2305	0000, 2355
2350	2222
2352	2355
2505	2555
2522	2222 (2)
2550	2555
2552	3333
3002	0000 (2), 0002, 2202
3003	0000 (3), 0333, 3333, (1 N/A)
3005	0005
3025	2225
3030	0000 (6), 0235, 3333
3053	0000
3203	1211 2233
3230	2220
3303	0000 (2), 0003, 2333, 3333
3330	0000 (4), 2222, 2233, 3333, 3335, (1 N/A)
3350	2255, (1 N/A)
3420	3333
3430	0000
3505	0000 (3), 0005, 0555, 2555 (2), 3555 (3)
3530	0000
3550	2555

(N/A - X-ray no longer available or surface unreadable)

in Table 3.3. Of the 211 surfaces, 92 retained their '0220' scores after re-reading.

A radiographic score of '3' going to a '2' at the next examination was, unless preceded by a '0', originally classified as a 'Reversal'. However, because the enamel surface of such dentine-involving lesions is generally considered to be broken down, and hence impossible to remineralise, it was decided to re-read films of surfaces which had been accorded such changes. However, the six combinations, 2320, 3000, 3200, 3220, 3300 and 3320, were not re-read and were left classified as 'Reversals' on the assumption that if the score of '3' was incorrect, then it was probably a '2' and therefore should still be classified as a 'Reversal'. Also, the 11 surfaces with the combination '0332' were not re-read on the argument that the score of '2' should have been a '3' and that these surfaces should remain classified as 'Progressive'.

The results of re-reading the 102 such surfaces are shown in Table 3.4. Here, four single surfaces still had a score of '3' which became a '2' at the following examination. These were cautiously classified as 'Reversals' on the assumption they were non-cavitated lesions and therefore could have remineralised. The four combinations consisted of the scores 3322, 2232, and 2332 (x2).

Once the radiographs had been re-read and the

Table 3.3 Results of re-reading X-ray combination '0220'.

New Combination	n
0000	35
0002	2
0020	7
0022	8
0200	3
0202	1
0220	92
0222	38
0223	1
2000	1
2200	1
2220	6
2222	6
N/A	10

N/A X-ray not available or unreadable

Table 3.4 Result of re-reading controversial reversal combinations.

Original Combination	Combinations (and number) after re-reading
2232	0000 (2), 0020 (2), 0023, 0222 (4), 0233, 2200 (3), 2202 (6), 2220 (2), 2232, 2222 (21), 2223, 2233 (4), 2333, 3333, (6 N/A)
2322	0000 (2), 0222 (2), 2023, 2200 (2), 2220, 2222 (10), 2233, 2323
2332	0000 (3), 0202, 0222 (2), 2022, 2222 (5), 2223 (2), 2332 (2), 2333 (2), (1 N/A)
3322	0000, 3322
3332	0000, 0022, 0222, 2222, 2223

(N/A - X-ray no longer available or surface unreadable)

classification of the combinations finalised, it was decided it would be simpler to enter a summary of the data regarding sex, surface classification, etc into a BBC Computer (Acorn Computers, Cambridge) for further analysis, rather than set up another file in the ICL 3980 containing the classification of each individual surface.

3.2.5 Exclusions

Data were excluded from the analyses either because of the baseline radiographic score, or because the individual subject did not conform to selected conditions.

Surfaces were excluded which had a baseline radiographic score of either:

(a) 4 - lesion into pulp. This would almost certainly involve breakdown of the enamel surface, and hence no preventive measure could hope to be effective,

(b) 5 - surface restored

(c) 7 - surface unreadable

(d) 8 - surface not present on radiograph.

In addition, surfaces were excluded if the occlusal surface had a radiographic score of '6' at the final examination, signifying that the tooth had been extracted or was missing (see also Section 3.2.6).

All the surfaces from an individual subject were excluded if that subject had not conformed to either of two

criteria, viz:-

(a) the subject had not had an X-ray taken at all four examinations,

- or -

(b) the subject had not conformed to the protocol. Subjects who had used an alternative dentifrice more than 50 % of the time, or who brushed their teeth less than once per week, were coded as not conforming to the test protocol.

3.2.6 Extracted teeth / unerupted teeth

As stated in the above section, teeth which were missing at Examination 4 were excluded from the analysis. This selection excluded all teeth which were extracted at any time during the three years, including those extracted for caries, as well as trauma or orthodontic reasons. The exclusion of teeth extracted for interproximal caries obviously affects the numbers of surfaces which progressed. However, as it would be impossible to determine whether or not a tooth was extracted because of occlusal caries or interproximal caries, it was decided to exclude all subsequently extracted teeth from the analysis.

The exclusion of missing teeth at Examination 4 also excluded teeth which had not erupted during the three years of the clinical trial. However, because of restraints in the number of 'temporary selections' which SPSS^{x} could handle, i.e. the number of exclusions which

could be performed in the creation of the main list of surfaces / combinations, and because unerupted teeth had a value of 'zero' for the interproximal radiographic scores, it was impossible to eliminate initially surfaces which had erupted during the trial. A separate program was written to produce lists of subject number, tooth surface and radiographic combination for those surfaces erupting at different stages in the trial. Results of this investigation are presented in Section 4.1 and discussed in Chapter 5.

3.3 Methods - individual studies

3.3.1 Adjacent surfaces

One possible criticism of this study is that the tooth surfaces are assumed to be independent. It could be argued that surfaces in an individual subject's mouth are influenced by the oral environment and hence should not be treated independently. An extension of this argument, and more likely to be valid, is that adjacent interproximal surfaces, sharing a common plaque / environment, would behave similarly. In order to investigate this further, the number of adjacent surfaces which had identical radiographic combinations over the four examinations was determined.

3.3.2 Site variation and handedness

In order to determine whether there were any site variations in the radiographic data, the percentage of 'Progressive' (P), 'Reversal' (R), 'Stable' (S) and

'Borderline' (B) combinations was calculated for each surface. This data was determined (a) for all pastes together and (b) for Agents 1 & 2, 3 & 4 and 5 & 6 combined. As it has been reported that right-handed people brush the left-side of their mouth more effectively than the right (Schei *et al.*, 1959), it was decided to investigate the possible effect of right- / left-handedness on site variations.

3.3.3 Effect of sex

A comparison was made on the distribution of the four classifications (P, R, S and B) between male and female subjects. In this analysis, the data from all surfaces and agents were combined. A similar analysis was performed on the proportion of surfaces which had a radiographic score of 'zero' at all four examinations.

The effect of sex on fluoride dose-response was also investigated (see Section 3.3.5 and 4.6.2).

3.3.4 Effect of zinc citrate

The effect of 0.5 % (w/w) zinc citrate in the dentifrices on the radiographic combinations, was investigated by comparing the percentage of lesions which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) and were 'Borderline' (B) between appropriate dentifrices i.e. Agent 1 vs Agent 2, Agent 3 vs Agent 4, and Agent 5 vs Agent 6. In addition, a similar analysis was performed on the proportion of surfaces which had a radiographic score

of 'zero' at all examinations. In these analyses the data from all tooth surfaces and both sexes were combined.

The effect of zinc citrate on fluoride dose-response was also investigated (see Sections 3.3.5 and 4.6.1).

3.3.5 Effect of fluoride concentration

The effect of increasing dentifrice fluoride concentration (1000, 1500 and 2500 ppm as MFP) was investigated using Generalised Linear Interactive Modelling, GLIM, (see Section 3.4.2). Separate models were studied for (a) the proportion of lesions which 'Progressed', (b) the proportion of lesions which 'Reversed', and (c) the proportion of surfaces which had a radiographic score of 'zero' at all four examinations.

For each of these three dependent variables, several factors were investigated, viz:-

(a) two parameter models, with fluoride concentration as the independent variate for:

  (i) non-zinc Agents (1, 3 & 5),

  (ii) zinc citrate-containing Agents (2, 4 & 6),

  - and -

  (iii) non- zinc and zinc pastes combined.

(b) a three parameter model, i.e. fluoride and zinc citrate concentrations as the variates,

(c) two parameter models with fluoride concentration as the variate for:

(i) male subjects,

- and -

(ii) female subjects.

(d) a three parameter model with fluoride concentration and sex as the variates.

(e) two parameter models with fluoride as the variate for initial baseline radiographic scores of 'zero', '2' and '3', this model only being run for the first two dependent variables.

In all models, the data from all surfaces were combined.

3.4 Methods - statistical

3.4.1 Chi square tests

The X^2 test is a non-parametric (or distribution-free) test used when the data can be classified into discrete categories either at the nominal, or ordinal level. It tests the null hypothesis, either that there is no difference in the observed frequencies in the different categories (1 x k test) or, that there is no difference between different sets of the same categories (k x n test).

The X^2 statistic is calculated as the sum of the squared deviances for each cell (category) divided by the expected value, E, for that cell, i.e.

$$X^2 = \Sigma (O - E)^2 / E$$

where O is the observed frequency and the summation is over all categories. Probability values are obtained from

the X^2 statistic by consulting a table of X^2 values at the appropriate degrees of freedom. The degrees of freedom are equal to (r-1).(c-1), where r is the number of rows (sets of data), and c is the number of columns (different categories).

Although the X^2 test avoids errors due to assumptions that the data has a particular distribution, two errors are recognised. It is known that at one degree of freedom the calculation of the X^2 statistic is an overestimation. This is usually corrected by applying Yates' correction, viz:-

$$X^2 = \Sigma \left(|O - E| - 0.5 \right)^2 / E$$

although it has been suggested that Yates' correction overcorrects (Cohen & Holliday, 1982). The second error arises if an expected frequency in any cell is unusually small. In this case, the use of the X^2 test can lead to erroneous conclusions. Two general rules have been stated (Owen & Jones, 1982):-

(1) if there are only two cells, then the expected frequencies in each cell should be five or more,

- and -

(2) if there are more than two cells, X^2 should not be used if more than 20 % of the expected frequencies are less than five.

The X^2 test was used in this thesis to test if there were differences in the distribution of 'Progressive', 'Reversal', 'Stable' and 'Borderline' surfaces for

different selection criteria. The X^2 statistic was calculated using a software package written for the BBC-B computer.

3.4.2 Generalised Linear Interactive Modelling (GLIM)

Introduction

Linear modelling is one of the most basic of statistical operations. It involves the fitting to experimental data an equation such as:

$$y = a + b.f(x_1) + c.f(x_2)$$

where a,b and c are constants to be estimated. y is the dependent (or predicted) variate (proportion of lesions which 'Progressed' or 'Reversed' in the present data), and the f(x)'s are mathematical functions of the independent (or co-) variates which are believed to affect the dependent variate. The covariates in the present study include fluoride concentration, sex and presence or absence of zinc citrate.

It should be noted that the term 'linear', does not necessarily mean a straight line ($y = a + b.x$), but refers to the fact that the terms in the above equation are added [rather than multiplied, i.e. not $f(x_1).f(x_2)$].

A special-purpose package called GLIM (Generalised Linear Interactive Modelling) was constructed by a Royal Statistical Society group headed by J.A. Nelder (Nelder & Wedderburn, 1972). It is a specialised interactive computer language which has been developed to enable

investigators to fit a large range of possible models to their data, one of its possible uses being to investigate possible interactions between parameters (e.g. fluoride and zinc).

Materials and Methods

The data in this study is referred to as a 'counted proportion' (e.g. the proportion of lesion which 'Progressed'). The values must therefore lie between 0 and 1, and can be thought of as a probability, 'p'. Consequently, a straight line relationship between the probability, 'p', and another variable will not make sense since it may predict probabilities that are greater than 1 or less than 0.

Modelling of such binomial data is usually achieved by transforming the data by a link such as the logit, (or log odds) viz:-

$$\log_e(p/(1-p))$$

This allows the probability to be mapped on to the real line i.e. from - ∞ to + ∞, thus enabling standard curve fitting techniques to be applied (McCullagh & Nelder, 1983).

In this study, the proportions of lesions which (a) 'Progressed', (b) 'Reversed' and (c) remained with a radiographic score of 'zero' at all four examinations, (the dependent variables) were independently studied and the effect of fluoride concentration, zinc concentration,

and sex (the covariates) modelled. The sex of a subject is obviously either male or female. In order to include its effect in the GLIM models, a value of '1' was arbitrarily assigned to males and '2' to females. Similarly, non-zinc data were assigned a value of '1' and zinc data a value of '2' for the 'zinc' variable.

GLIM allows an equation to be fitted of the form (for two covariates in this example):

$$\log_e(p/(1-p)) = a + b.x_1 + c.x_2$$

where a, b and c are parameters estimated by the least squares fit to the data, p is the dependent variable and x_1 and x_2 are covariates.

Taking exponentials of both sides gives:

$$p/(1-p) = e^{(a + b.x_1 + c.x_2)}$$

and rearranging allows the best fit to the proportion (either 'Progressives', 'Reversals' or '0000's) to be calculated:

$$p = \frac{e^{(a + b.x_1 + c.x_2)}}{1 + e^{(a + b.x_1 + c.x_2)}}$$

The 95 % Confidence Limits are found from the equation:

$$C.L. = \frac{e^{(a + b.x_1 + c.x_2 \pm 1.96.\sqrt{v})}}{1 + e^{(a + b.x_1 + c.x_2 \pm 1.96.\sqrt{v})}}$$

where $v = SE_a^2 + SE_b^2.x_1^2 + SE_c^2.x_2^2 + 2.C_{ab}.x_1 + 2.C_{ac}.x_2 + 2.C_{bc}.x_1.x_2$

and the SE's are the standard errors of the estimate of the parameters and the C's are the appropriate covariances. Confidence Limits give a range of values consistent with the data. Generally, 95 % Confidence Limits are used, although in theory any value could be employed. If many repeat samples were taken, then for the 95 % Confidence Limits, it would be expected that 95 % of the samples would lie within these limits. It does not mean that a single sample has a 95 % chance of lying within the limits.

The discrepancy of a fit is proportional to twice the difference between the maximum log likelihood achievable and that achieved by the model under investigation. This is known as the scaled deviance. It is analogous to the residual sum of squares calculated for Normal data. The first stage in the modelling process is to find the grand mean. This is achieved by fitting the logit to a scalar (i.e. $\log_e(p/(1-p)) = a$). The deviance obtained is the total deviance. The appropriate model is then fitted using the covariate(s). The deviance obtained in this case is the residual deviance. The smaller the value, the better the fit. Subtraction of the residual deviance from

the total deviance, gives the deviance due to the regression fit. For large numbers, this value can be equated with X^2 and the goodness of fit (i.e probability value) obtained from tables.

CHAPTER 4 RESULTS

4.1 Unerupted surfaces

The fate of the mesial and distal surfaces which erupted between Examinations 1 & 2, 2 & 3, and 3 & 4 is shown in Tables 4.1, 4.2 and 4.3 respectively. A total of 3836 surfaces which met the inclusion criteria erupted between Examinations 1 & 2 with 3614 (94.2 %) surfaces having a radiographic score of 'zero' at subsequent examinations. The number of surfaces which 'Progressed' was 186 (4.8 %), with 36 (0.9 %) 'Reversing'. Of the 1872 surfaces which erupted between Examinations 2 and 3, 1854 (99.0 %) had a radiographic score of 'zero' at the last two examinations, 10 (0.5 %) 'Progressed' and 8 (0.4 %) 'Reversed' whereas, for the 652 surfaces erupting between Examinations 3 and 4, 647 (99.2 %) had a score of 'zero' at the final examination whereas 5 (0.8 %) 'Progressed'. Obviously, in this last group, there were no 'Reversals'.

In order to investigate if inclusion of erupting surfaces affected the results, the data in Table 4.4 were generated. Here the distribution of the radiographic combinations for each set of erupting surfaces was compared with the 29468 surfaces in the main data (minus erupting surfaces) which remained sound (78.7 %), the 5020 surfaces which 'Progressed' (13.4 %), and the 2947 surfaces which 'Reversed', remained 'Stable' or were 'Borderline' (7.9%). No 'Stable' or 'Borderline' combinations were obtained with the erupting surfaces.

Table 4.1 Fate of posterior mesial (m) and distal (d) surfaces erupting between Exams 1 and 2.

Tooth	No of surfaces with classification '-000'	P	R	S	B	Total
UR7m	349	8	1	0	0	358
UR6m+d	0	0	0	0	0	0
UR5m+d	348	23	6	0	0	377
UR4m+d	137	3	0	0	0	140
UL4m+d	144	7	0	0	0	151
UL5m+d	346	23	3	0	0	372
UL6m+d	0	0	0	0	0	0
UL7m	331	11	3	0	0	345
Total	1655	75	13	0	0	1743
LR7m	220	16	0	0	0	236
LR6m+d	0	0	0	0	0	0
LR5m+d	498	42	5	0	0	545
LR4m+d	246	3	2	0	0	251
LL4m+d	255	6	5	0	0	266
LL5m+d	500	31	10	0	0	541
LL6m+d	0	0	0	0	0	0
LL7m+d	240	13	1	0	0	254
Total	1959	111	23	0	0	2093
Grand n	3614	186	36	0	0	3836
Total %	94.2	4.8	0.9	0	0	100

P = Progressive, R = Reversal,
S = Stable, B = Borderline.

Table 4.2 Fate of posterior mesial (m) and distal (d) surfaces erupting between Exams 2 and 3.

Tooth	No of surfaces with classification '--00'	P	R	S	B	Total
UR7m	147	2	2	0	0	151
UR6m+d	0	0	0	0	0	0
UR5m+d	169	0	1	0	0	170
UR4m+d	36	0	0	0	0	36
UL4m+d	43	0	0	0	0	43
UL5m+d	160	1	1	0	0	162
UL6m+d	0	0	0	0	0	0
UL7m	131	2	0	0	0	133
Total	686	5	4	0	0	695
LR7m	138	0	1	0	0	139
LR6m+d	0	0	0	0	0	0
LR5m+d	317	0	0	0	0	317
LR4m+d	131	1	0	0	0	132
LL4m+d	135	1	0	0	0	136
LL5m+d	327	3	2	0	0	332
LL6m+d	0	0	0	0	0	0
LL7m	120	0	1	0	0	121
Total	1168	5	4	0	0	1177
Grand n	1854	10	8	0	0	1872
Total %	99.0	0.5	0.4	0	0	100

P = Progressive, R = Reversal,
S = Stable, B = Borderline.

Table 4.3 Fate of posterior mesial (m) and distal (d) surfaces erupting between Exams 3 and 4.

	No of surfaces with classification					
	'---0'	P	R	S	B	Total
UR7m	41	0	0	0	0	41
UR6m+d	0	0	0	0	0	0
UR5m+d	55	1	0	0	0	56
UR4m+d	14	0	0	0	0	14
UL4m+d	16	0	0	0	0	16
UL5m+d	59	0	0	0	0	59
UL6m+d	0	0	0	0	0	0
UL7m	38	1	0	0	0	39
Total	223	2	0	0	0	225
LR7m	34	0	0	0	0	34
LR6m+d	0	0	0	0	0	0
LR5m+d	145	1	0	0	0	146
LR4m+d	41	2	0	0	0	43
LL4m+d	28	0	0	0	0	28
LL5m+d	146	0	0	0	0	146
LL6m+d	0	0	0	0	0	0
LL7m	30	0	0	0	0	30
Total	424	3	0	0	0	427
Grand n	647	5	0	0	0	652
Total %	99.2	0.8	0	0	0	100

P = Progressive, R = Reversal,
S = Stable, B = Borderline.

Table 4.4 Number and percentage of surfaces in each radiographic combination for (a) all surfaces erupting during the trial, (b) all surfaces excluding those which erupted during the trial, and (c) all surfaces [(a) + (b)].

Group		No. of surfaces with classification '0000'	P	R	S	B	Total
(a)	n	6115	201	44	0	0	6360
	%	96.1	3.2	0.7	0	0	100
(b)	n	29468	5020	1735	963	249	37435
	%	78.7	13.4	4.6	2.6	0.7	100
(c)	n	35583	5221	1779	963	249	43795
	%	81.2	11.9	4.1	2.2	0.6	100

P = Progressive, R = Reversal,
S = Stable, B = Borderline.

Significant X^2 values of 542.7 and 457.5 (d.f. = 2, $p < 0.001$) were obtained for surfaces erupting between Examinations 1 & 2, and 2 & 3 respectively. However, a X^2 test was inappropriate in the third case since one cell ('Reversals') was zero, and combining 'Progressives' and 'Reversals' for the main data would obviously be erroneous. Nevertheless, inspection of the data in Table 4.5 would also lead to the conclusion that the distribution of the radiographic categories is also different for these erupting surfaces as compared to the main data, e.g. there were 78.7% sound surfaces in the main data compared to 99.2 % in this group.

The number of surfaces erupting within each classification ('0000', 'P' or 'R') is shown in Table 4.5 for the different fluoride concentrations, i.e. Agents 1 & 2, 3 & 4 and 5 & 6. Although the change in the proportion of surfaces erupting between Examinations 1 and 2, which remained radiographically sound ('0000') with fluoride concentration was just not significant [X^2(GLIM) = 3.5, d.f. = 1, $p = 0.07$], a significant fluoride dose-response was obtained for those surfaces erupting between Examinations 2 and 3 [X^2(GLIM) = 6.7, d.f. = 1, $p < 0.01$]. Not unexpectedly, no fluoride dose-response was apparent for those surfaces which erupted during the last year of the trial.

Table 4.5 Fate of posterior interproximal (mesial & distal) surfaces erupting during the trial, listed by agent.

	No. of surfaces with classification '0000'	P	R	Total
Surfaces erupting between Exams 1 & 2				
Agents 1 & 2	1374	73	16	1463
Agents 3 & 4	1526	88	14	1628
Agents 5 & 6	714	25	6	745
Surfaces erupting between Exams 2 & 3				
Agents 1 & 2	742	3	3	748
Agents 3 & 4	777	5	5	787
Agents 5 & 6	335	2	0	337
Surfaces erupting between Exams 3 & 4				
Agents 1 & 2	271	4	0	275
Agents 3 & 4	243	0	0	243
Agents 5 & 6	133	1	0	134

P = Progressive, R = Reversal
Agents 1 & 2 = 1000 ppm F as NaMFP
Agents 3 & 4 = 1500 ppm F as NaMFP
Agents 5 & 6 = 2500 ppm F as NaMFP

4.2 Adjacent surfaces

In Table 4.6, the number of adjacent mesial and distal surfaces which had identical radiographic combinations (P, R, S or B) are tabulated according to F^- paste. As indicated, the totals 'n_1' and 'n_2' are the numbers of surfaces included in the main study, excluding surfaces which had a 'zero' at all four examinations.

There was a total of 422 pairs of adjacent surfaces with identical combinations, giving 844 individual surfaces. This corresponds to only 10.3 % of the total of 8212 surfaces which had a 'P', 'R', 'S' or 'B' classification.

4.3 Site variation and handedness

The number of combinations in each category is shown in Appendix 2 for each Agent (1 - 6) and each surface. As both individual and total numbers were often low for each paste, it was decided to combine the data from all agents in order to look at variations in the proportions of 'Progressives' and 'Reversals' at different surfaces, in different jaws. The percentage of lesions which were then deemed to have 'Progressed' for each surface is shown in Figure 4.1 with the corresponding values for 'Reversals' in Figure 4.2. In all four cases (upper and lower jaws - 'Progressives', upper and lower jaws - 'Reversals'), significant X^2 values ($p < 0.001$) were obtained, indicating that there were differences in the percentage of 'Progressives', and 'Reversals', at the different sites in each jaw.

Table 4.6 Number of adjacent mesial and distal surfaces which had identical radiographic combinations, subdivided into pairs of surfaces which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) or were 'Borderline' (B), excluding '0000'.

	n_1	n_2	P	R	S	B
	UR7M	UR6D				
Agent 1	38	54	1	1	0	0
Agent 2	32	70	3	1	0	0
Agent 3	32	64	3	2	0	0
Agent 4	33	55	5	0	0	0
Agent 5	11	21	1	0	0	0
Agent 6	15	31	0	0	0	0
All agents	161	295	13	4	0	0
	UR6M	UR5D				
Agent 1	116	113	2	2	0	0
Agent 2	100	86	4	1	1	0
Agent 3	112	99	2	2	0	0
Agent 4	100	86	3	1	0	0
Agent 5	46	29	2	0	0	0
Agent 6	47	36	3	1	0	0
All agents	521	449	16	7	1	0
	UR5M	UR4D				
Agent 1	81	74	9	3	1	0
Agent 2	65	69	7	1	1	0
Agent 3	68	71	6	0	1	0
Agent 4	59	52	4	1	3	0
Agent 5	21	21	3	0	1	0
Agent 6	27	29	6	0	0	0
All agents	321	316	35	5	7	0
	UL4D	UL5M				
Agent 1	69	69	13	2	1	0
Agent 2	73	71	17	2	0	0
Agent 3	58	57	6	1	3	0
Agent 4	60	54	9	2	0	0
Agent 5	29	33	5	1	1	0
Agent 6	44	36	8	2	0	1
All agents	333	320	58	10	5	1

Table 4.6 (continued)

	n_1	n_2	P	R	S	B
	UL5D	UL6M				
Agent 1	104	116	4	1	1	0
Agent 2	98	114	3	0	0	0
Agent 3	98	116	5	0	0	0
Agent 4	88	108	2	3	0	0
Agent 5	39	42	1	0	0	0
Agent 6	46	51	1	1	1	0
All agents	473	547	16	5	2	0
	UL6D	UL7M				
Agent 1	69	37	2	2	0	0
Agent 2	71	40	3	0	0	0
Agent 3	67	31	2	0	0	0
Agent 4	62	32	2	1	0	0
Agent 5	28	13	0	0	0	0
Agent 6	29	20	0	0	0	1
All agents	326	173	9	3	0	1
	LR7M	LR6D				
Agent 1	72	81	9	0	0	0
Agent 2	63	86	9	2	1	0
Agent 3	87	82	14	2	2	1
Agent 4	61	69	6	2	1	0
Agent 5	28	31	2	1	0	0
Agent 6	27	31	4	1	0	0
All agents	338	380	44	8	4	1
	LR6M	LR5D				
Agent 1	74	83	1	0	0	0
Agent 2	78	90	3	1	0	0
Agent 3	79	86	4	1	0	0
Agent 4	62	74	3	1	0	1
Agent 5	28	35	2	1	0	0
Agent 6	40	33	2	1	0	0
All agents	361	401	15	5	0	1

Table 4.6 (continued)

	n_1	n_2	P	R	S	B
	LR5M	LR4D				
Agent 1	32	30	2	2	0	0
Agent 2	52	40	8	4	3	0
Agent 3	44	29	2	2	3	0
Agent 4	32	31	6	2	1	0
Agent 5	16	17	3	0	1	0
Agent 6	20	12	2	1	0	0
All agents	196	159	23	11	8	0
	LL4D	LL5M				
Agent 1	35	41	3	2	0	0
Agent 2	27	40	5	1	1	0
Agent 3	32	40	2	1	0	0
Agent 4	35	39	5	3	1	0
Agent 5	10	18	3	1	0	0
Agent 6	17	18	2	0	0	0
All agents	156	196	20	8	2	0
	LL5D	LL6M				
Agent 1	85	56	3	0	0	0
Agent 2	88	84	4	0	2	0
Agent 3	91	78	1	2	1	0
Agent 4	77	67	6	1	0	0
Agent 5	37	28	1	1	0	0
Agent 6	38	28	2	2	1	0
All agents	416	341	17	6	4	0
	LL6D	LL7M				
Agent 1	19	66	7	1	1	0
Agent 2	80	57	5	1	0	0
Agent 3	87	62	9	4	0	0
Agent 4	79	69	13	2	0	0
Agent 5	36	23	3	0	0	0
Agent 6	33	29	1	0	0	0
All agents	334	306	38	8	1	0
all surfaces / all agents	-	-	304	80	34	4

n_1 & n_2 = number of surfaces included in the main study, excluding those which scored 'zero' at all four examinations.

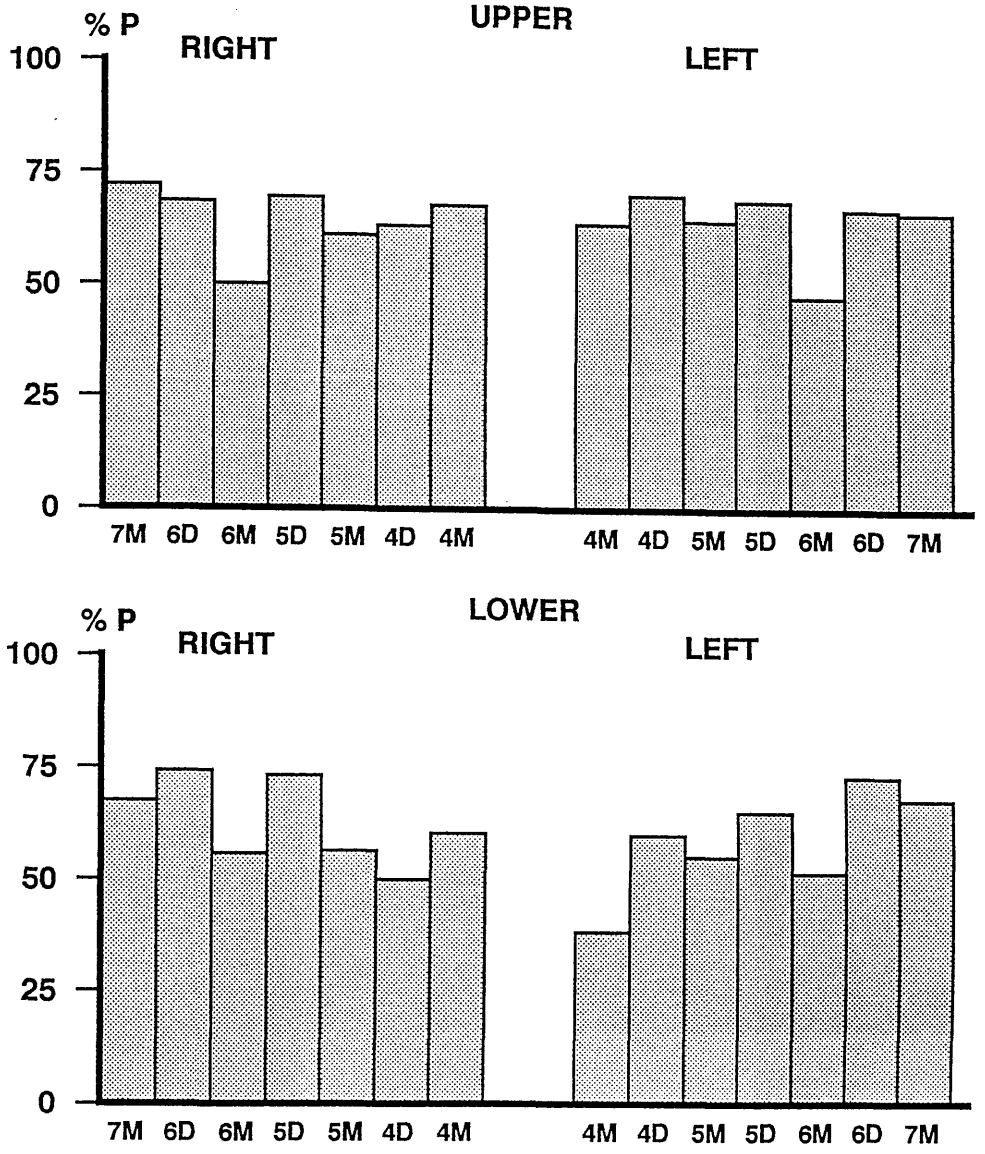


Figure 4.1 The percentage of surfaces which 'Progressed' (P) for each surface; in the upper or lower jaw, or right- or left-hand sides. Data from all agents combined. (M = mesial, D = distal).

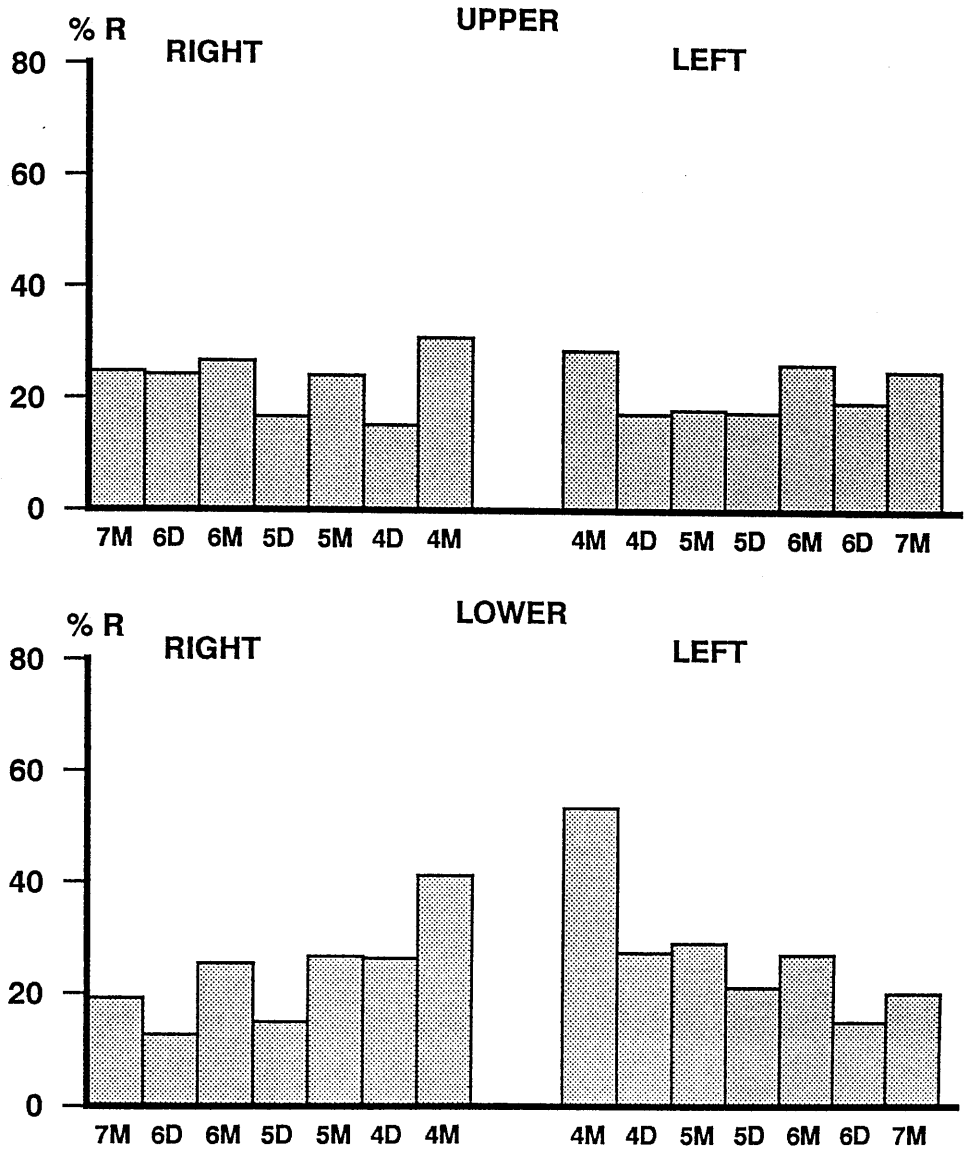


Figure 4.2 The percentage of surfaces which 'Reversed' (R) for each surface; in the upper or lower jaw, or right- or left-hand sides. Data from all agents combined. (M = mesial, D = distal).

As there were only 142 (7.1 %) left-handed subjects, it was decided to study the effect of handedness on a whole quadrant basis (Table 4.7). The percentage of surfaces in each category ('P', 'R', 'S' & 'B') are shown in Figure 4.3 for right- and left-handed subjects. For right-handed subjects there were no differences in the distribution of surfaces within each category between any of the quadrants ($p > 0.05$). However, for left-handed subjects, a significant difference in the category distributions was found between the upper right quadrant and the lower left ($X^2 = 9.53$, d.f. = 3, $p < 0.05$).

When comparing corresponding quadrants between the right- and left-handed subjects (Table 4.7), a significant difference was found only for the lower left quadrant ($X^2 = 7.92$, d.f = 3, $p < 0.05$).

4.4 The effect of sex

The percentages of lesions which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) and were 'Borderline' (B) are shown for each fluoride level in Table 4.8 for males and females separately. Data represented in Figure 4.4 show the percentages in each category for all pastes combined. At the 1000 ppm fluoride level, there were no differences in the distributions of the radiographic categories between males and females ($X^2 = 6.09$, d.f. = 3). However, at both the 1500 and 2500 ppm fluoride levels, there were significant differences (1500 ppm : $X^2 = 21.15$, d.f. = 3, $p<0.001$;

Table 4.7 Number and percentage of surfaces which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) and were 'Borderline' (B) by quadrant for left- and right-handed subjects. All agents.

Quadrant		Right handed P	R	S	B	Left handed P	R	S	B
UL	n	1340	451	258	67	104	34	25	5
	%	63.3	21.3	12.2	3.2	61.9	20.2	14.9	3.0
UR	n	1256	451	246	52	119	33	14	7
	%	62.6	22.5	12.3	2.6	68.8	19.1	8.1	4.0
LL	n	1083	404	186	52	85	31	26	2
	%	62.8	23.4	10.8	3.0	59.0	21.5	18.1	1.4
LR	n	1135	343	192	59	99	32	16	5
	%	65.6	19.8	11.1	3.4	65.1	21.1	10.5	3.3
all	n	4814	1649	882	230	407	130	81	19
	%	63.4	21.8	11.6	3.0	63.9	20.4	12.7	3.0

UL = upper left, UR = upper right,
LL = lower left, LR = lower right.

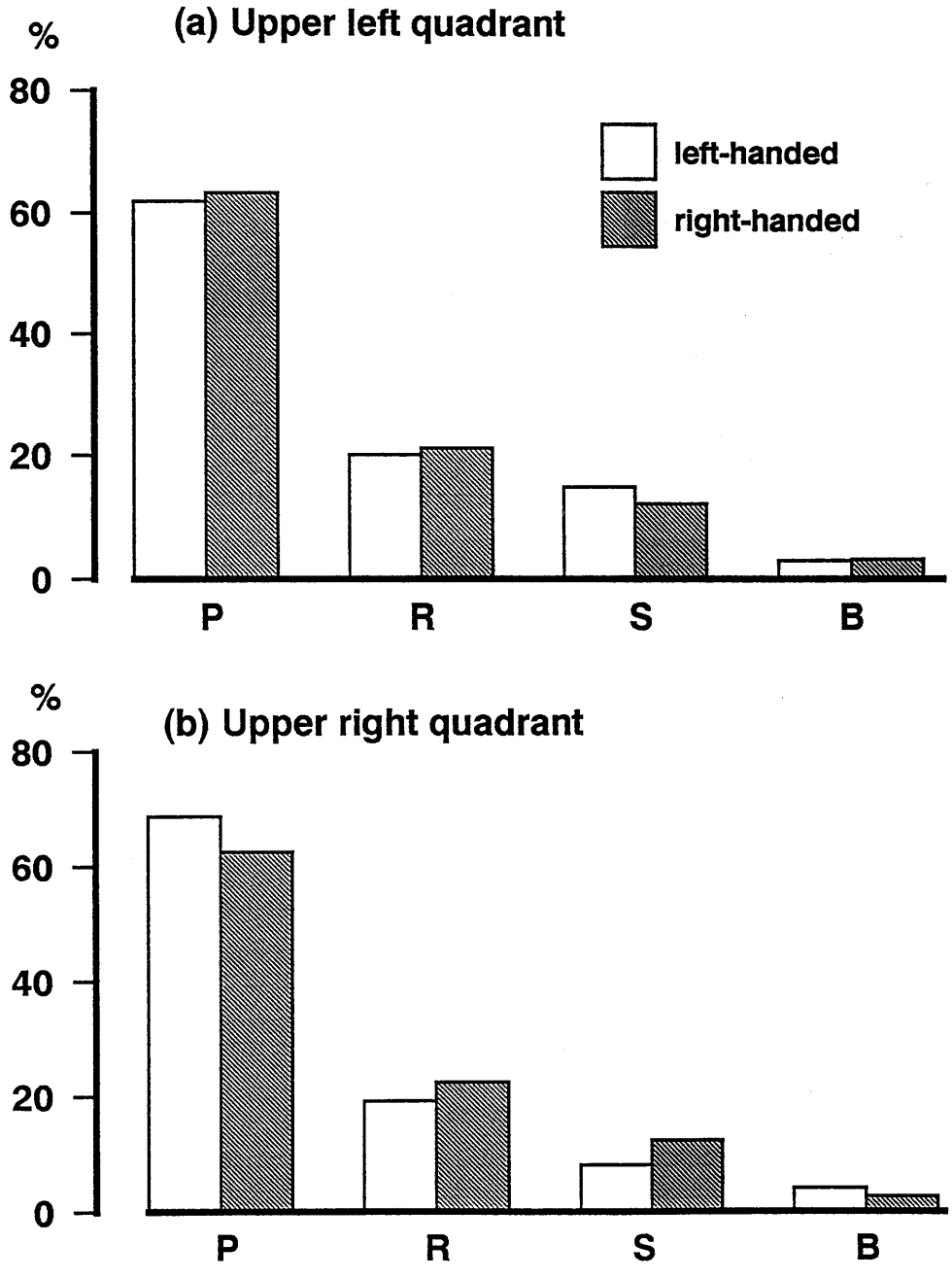
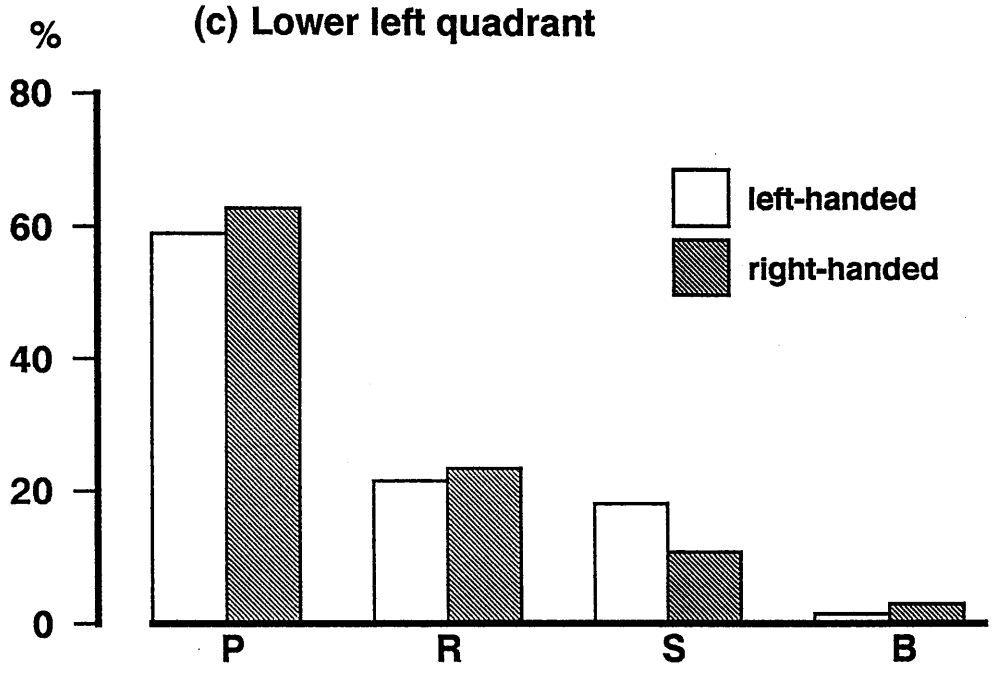


Figure 4.3 The percentage of surfaces in each category ('Progressives' - P, 'Reversals' - R, 'Stables' - S & 'Borderline' - B) in each quadrant for right- and left-handed subjects. Data from all agents combined. (a) upper left quadrant, (b) upper right quadrant.



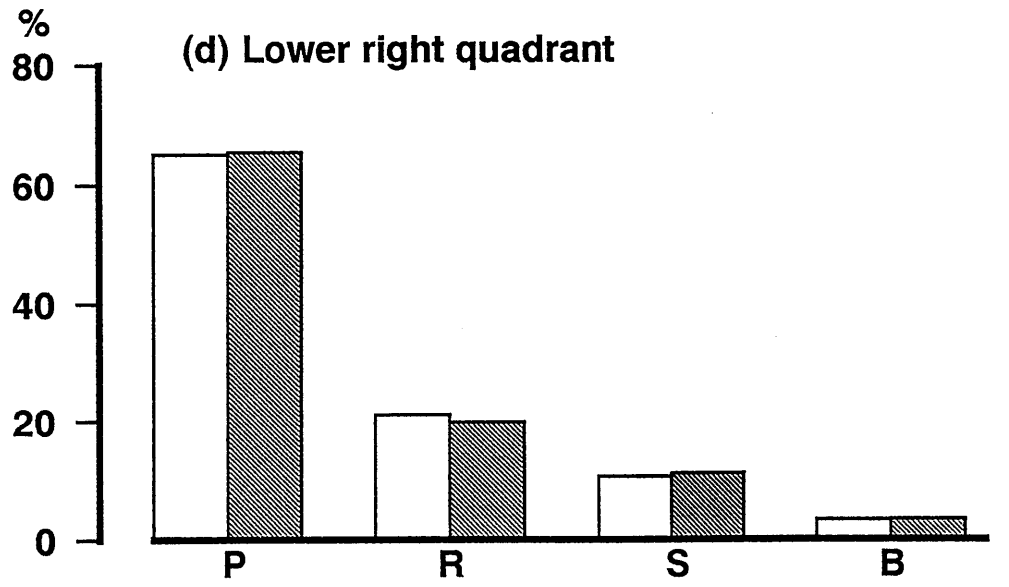


Figure 4.3 The percentage of surfaces in each category ('Progressives' - P, 'Reversals' - R, 'Stables' - S & 'Borderline' - B) in each quadrant for right- and left-handed subjects. Data from all agents combined. (c) lower left quadrant, (d) lower right quadrant.

Table 4.8 Number and percentage of surfaces which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) and were 'Borderline' (B) for males and females. All surfaces by different agent combinations.

Agent		MALES P	MALES R	MALES S	MALES B	FEMALES P	FEMALES R	FEMALES S	FEMALES B
1 & 2	n	1142	346	171	51	1146	375	217	42
	%	66.8	20.2	10.0	3.0	64.4	21.1	12.2	2.4
3 & 4	n	1010	296	157	48	1049	429	235	54
	%	66.8	19.6	10.4	3.2	59.4	24.2	13.3	3.1
5 & 6	n	489	180	60	20	385	153	123	34
	%	65.3	24.0	8.0	2.7	55.4	22.0	17.7	4.9
All	n	2641	822	388	119	2580	957	575	130
	%	66.5	20.7	9.8	3.0	60.8	22.6	13.5	3.1

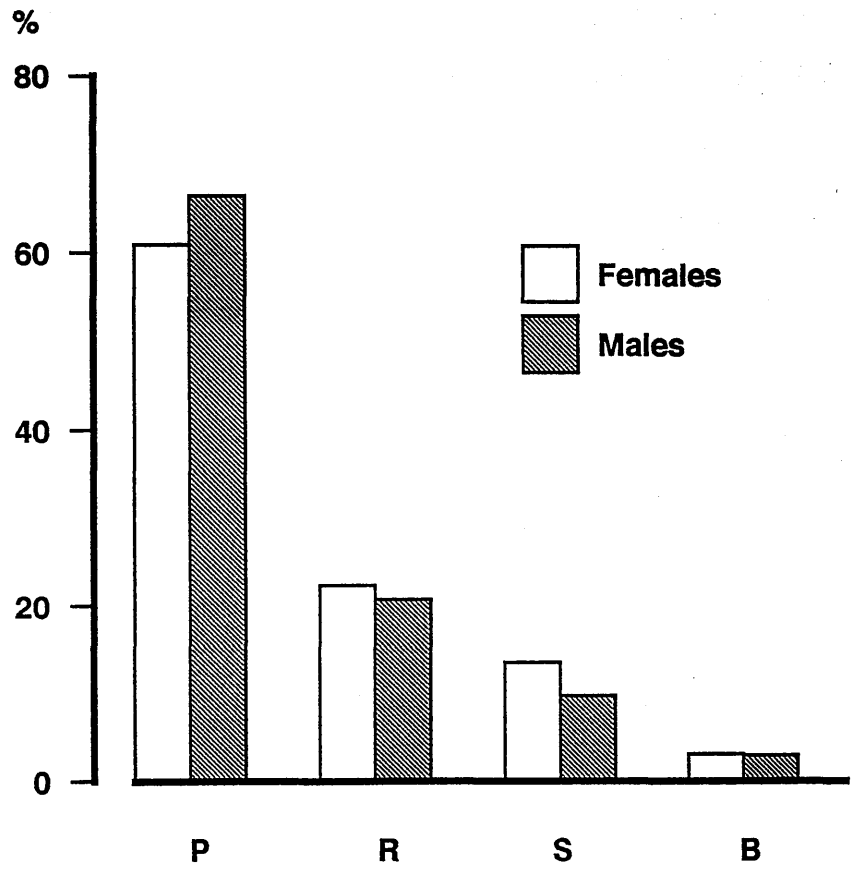


Figure 4.4 The percentage of surfaces in each category ('Progressives' - P, 'Reversals' - R, 'Stables' - S & 'Borderline' - B) for males and females. Data from all agents and all surfaces combined.

2500 ppm : X^2 = 37.92, d.f.= 3, $p<0.001$). At these levels, males had a higher percentage of 'Progressive' lesions than did females (66.8 % cf 59.4 % at 1500 ppm and 65.3 % cf 55.4 % at 2500 ppm respectively).

When data from all pastes were combined, the distributions were also significantly different (X^2 = 38.8, d.f. = 3, $p < 0.001$), the percentage of 'Progressive' lesions being 66.5 % for males, compared to 60.8 % for females, while the percentage of lesions which reversed was 20.7 % for males, and 22.6 % for females. There was no significant difference, between males and females with regard to the number of surfaces which had a radiographic score of 'zero' at all four examinations (X^2 = 0.45, d.f. = 1; Table 4.9).

Interestingly, a significant difference was observed in the distributions when comparing right- and left-handed males (X^2 = 8.12, d.f. = 3, $p < 0.05$) but not between the corresponding groups of females [X^2 = 2.36, d.f. = 3; Table 4.10; Figure 4.5). Inspection of the data for the left- and right-handed males revealed that the only difference was in the percentages of 'Stable' (S) lesions (13.8 % for left-handed males c.f. 9.3 % for right-handed males). This was confirmed by 2 x 2 X^2 tests, where the X^2 value for the 'Stable' data was 7.2, which, with one degree of freedom, gives $p < 0.01$.

The effect of sex on fluoride dose-response is described

Table 4.9 Number and percentage of surfaces which had a radiographic combination of '0000'. for males and females. All surfaces and all agents.

	No of '0000's	Total no. of surfaces	%
Males	17054	21024	81.1
Females	18529	22771	81.4

Table 4.10 Number and percentage of surfaces which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) and were 'Borderline' (B) for left- and right-handed males and females. All surfaces, all agents.

Handedness		MALES P	MALES R	MALES S	MALES B	FEMALES P	FEMALES R	FEMALES S	FEMALES B
Left	n	247	76	53	9	160	54	28	10
	%	64.2	19.7	13.8	2.3	63.5	21.4	11.1	4.0
Right	n	2394	746	335	110	2420	903	547	120
	%	66.8	20.8	9.3	3.1	60.7	22.6	13.7	3.0

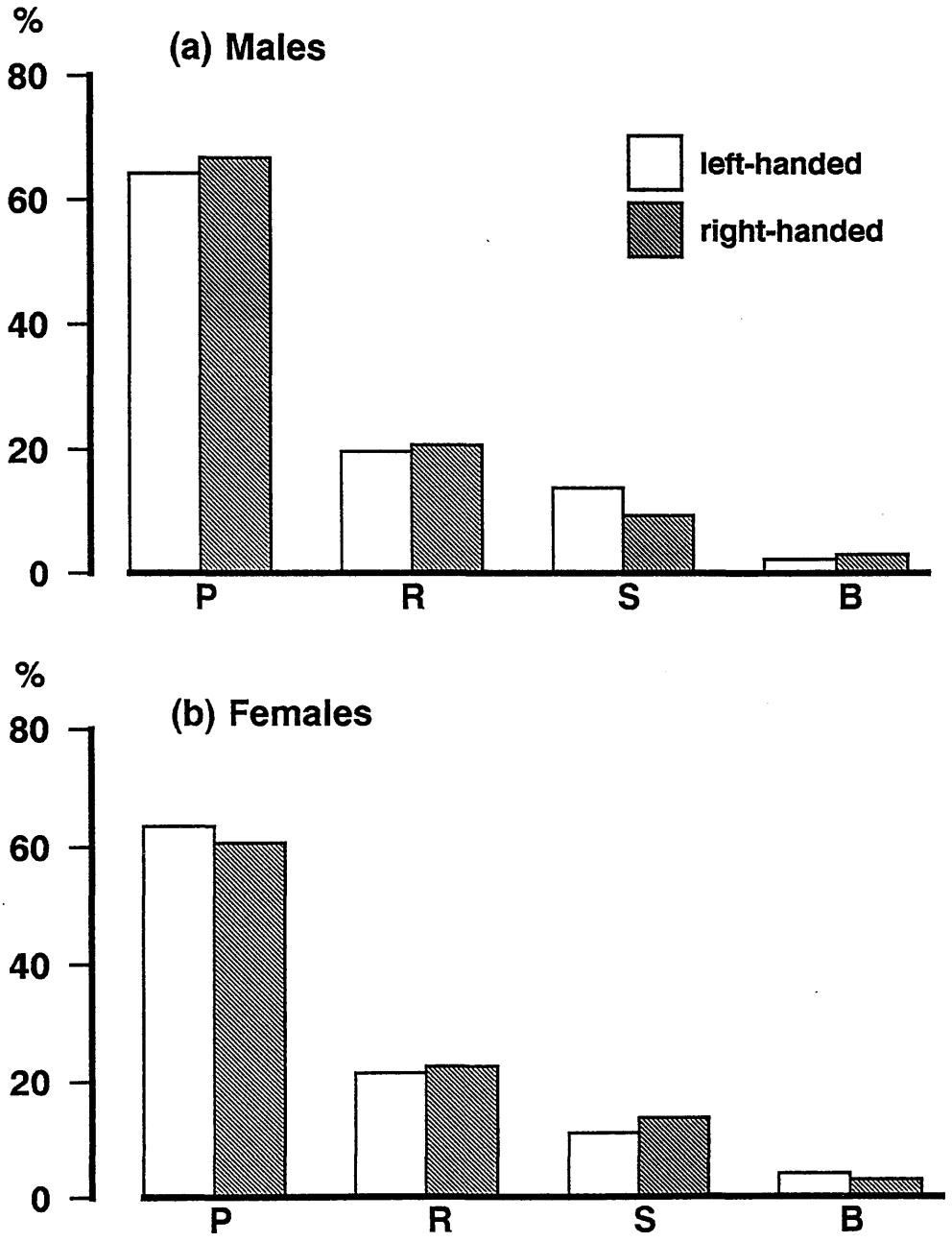


Figure 4.5 Comparison of the percentages of surfaces in each category ('Progressives' - P, 'Reversals' - R, 'Stables' - S & 'Borderline' - B) between (a) right- and left-handed males, and (b) right- and left-handed females.

later in Section 4.6.2.

4.5 The effect of 0.5 % (w/w) zinc citrate

The effect of the addition of 0.5 % (w/w) zinc citrate to the dentifrices (Agents 2, 4 & 6) on the percentage of surfaces which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) and were 'Borderline' (B) is shown in Figure 4.6 for the 1000 ppm dentifrices (Agents 1 & 2), in Figure 4.7 for the 1500 ppm dentifrices (Agents 3 & 4), and in Figure 4.8 for the 2500 ppm pastes (Agents 5 & 6). The values are also tabulated in Table 4.11. There were no significant differences between the distributions for Agents 1 & 2 (X^2 = 4.96, d.f. = 3) and for Agents 5 & 6 (X^2 = 2.39, d.f. = 3). For the 1500 ppm pastes (Agents 2 & 3), the distributions were significantly different (X^2 = 9.91, d.f. = 3, $p < 0.02$). The percentages of surfaces which 'Progressed' were similar [62.5 % for Agent 3 (no zinc), 63.2 % for Agent 4]. However, there were fewer lesions which 'Reversed' with Agent 3 (21.3 %) compared to Agent 4 (23.0 %). The results for surfaces which remained 'Stable' showed the opposite effect with 13.5 % for Agent 3 compared to 10.2 % for Agent 4.

The effect of zinc citrate on the proportion of surfaces which had a 'zero' score at all four exams is shown in Figure 4.9 and Table 4.12. For the 1000 ppm pastes, the addition of zinc citrate had no effect, the percentage of surfaces having a 'zero' radiographic score at all exams was 80.3 % (no zinc) compared with 79.5 % (zinc). At the

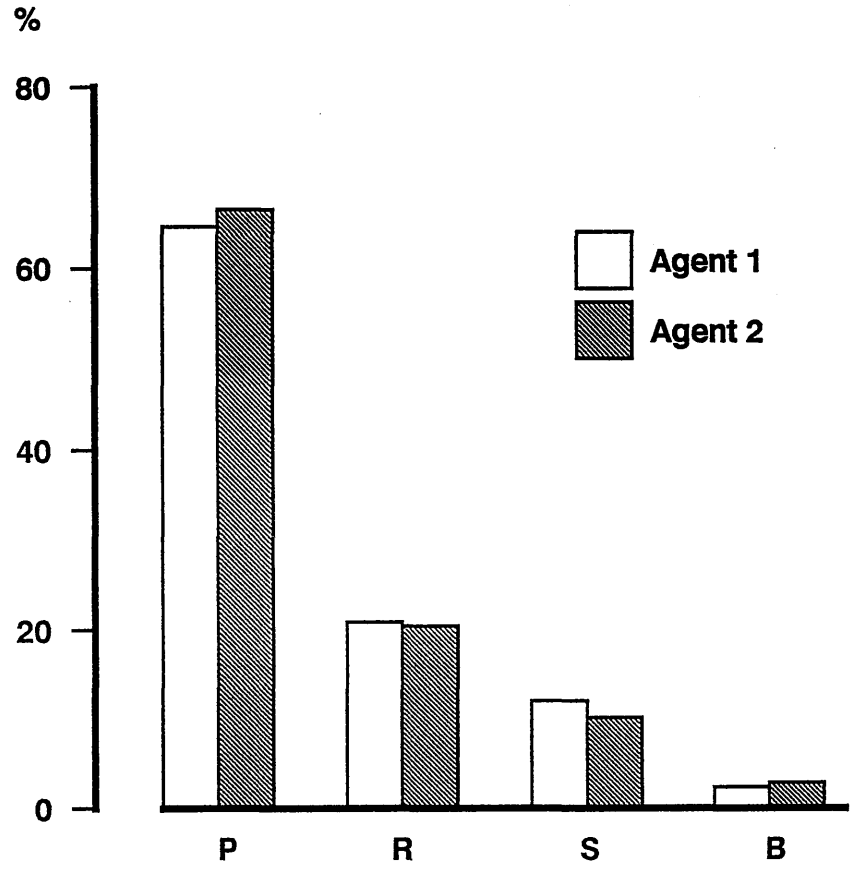


Figure 4.6 Comparison of the percentages of surfaces in each category ('Progressives' - P, 'Reversals' - R, 'Stables' - S & 'Borderline' - B) between the non-zinc (Agent 1) and the zinc (Agent 2) 1000 ppm F pastes. Data from all surfaces combined.

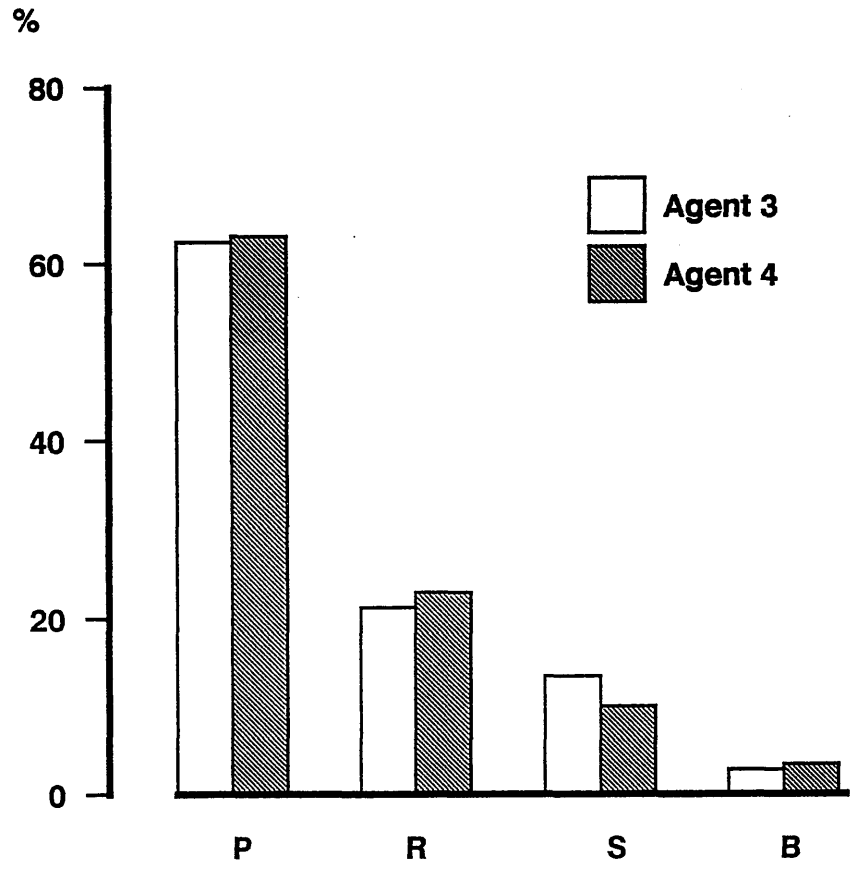


Figure 4.7 Comparison of the percentages of surfaces in each category ('Progressives' - P, 'Reversals' - R, 'Stables' - S & 'Borderline' - B) between the non-zinc (Agent 3) and the zinc (Agent 4) 1500 ppm F pastes. Data from all surfaces combined.

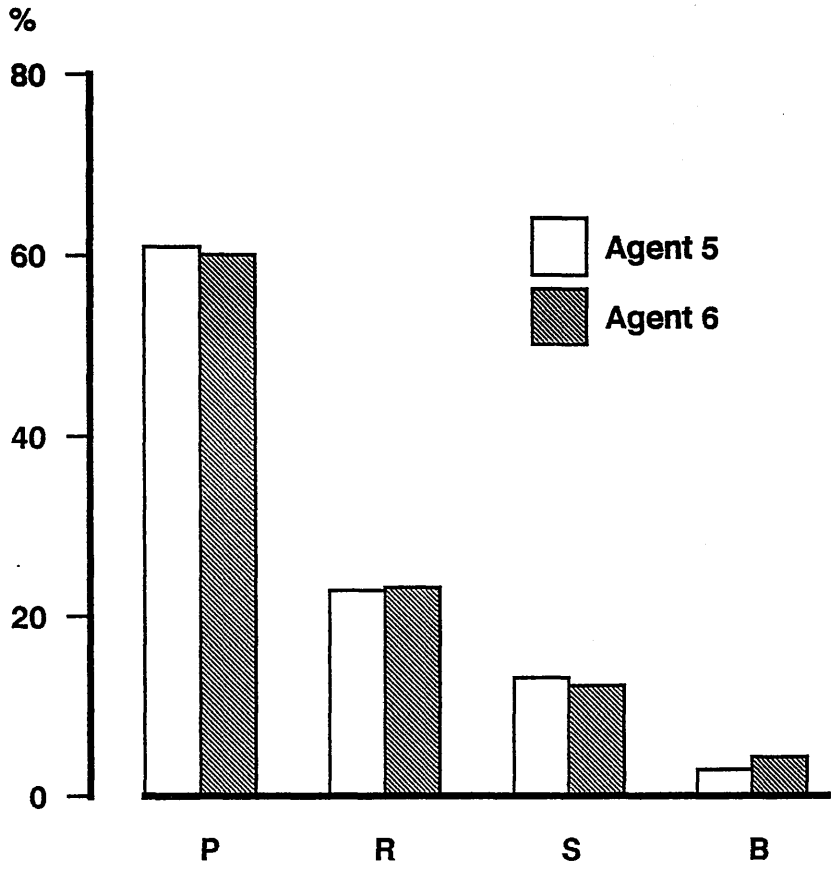


Figure 4.8 Comparison of the percentages of surfaces in each category ('Progressives' - P, 'Reversals' - R, 'Stables' - S & 'Borderline' - B) between the non-zinc (Agent 5) and the zinc (Agent 6) 2500 ppm F pastes. Data from all surfaces combined.

Table 4.11 Number and percentage of surfaces which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) and were 'Borderline' (B). Effect of agents with (Agents 2, 4, & 6) and without (Agents 1, 3, & 5) zinc citrate. All surfaces.

Agent	P		R		S		B	
	n	%	n	%	n	%	n	%
1	1137	64.6	367	20.9	212	12.1	43	2.4
2	1151	66.5	354	20.5	176	10.2	50	2.9
1 & 2	2288	65.6	721	20.7	388	11.1	93	2.7
3	1083	62.5	369	21.3	234	13.5	48	2.8
4	976	63.2	356	23.0	158	10.2	54	3.5
3 & 4	2059	62.8	725	22.1	392	12.0	102	3.1
5	413	61.0	155	22.9	89	13.2	20	3.0
6	461	60.1	178	23.2	94	12.3	34	4.4
5 & 6	874	60.5	333	23.1	183	12.7	54	3.7

Agents 1 & 2: 1000 ppm F
Agents 3 & 4: 1500 ppm F
Agents 5 & 6: 2500 ppm F

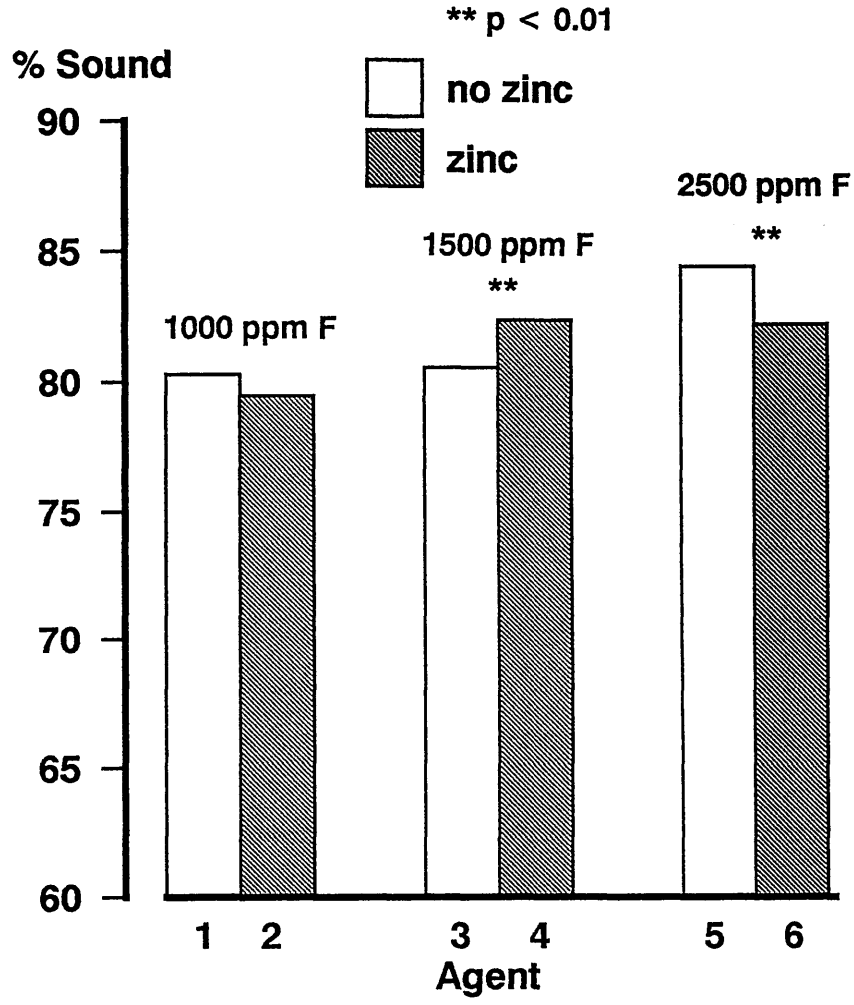


Figure 4.9 The effect of adding zinc citrate to the three different toothpastes, on the percentage of surfaces which were radiographically sound at all four examinations.

Table 4.12 Number and percentage of surfaces which had a radiographic combination of '0000'. Effect of agents with (Agents 2, 4, & 6) and without (Agents 1, 3, & 5) zinc citrate. All surfaces.

Agent	No of '0000's	Total no. of surfaces	%
1	7184	8943	80.3
2	6700	8431	79.5
1 & 2	13884	17374	79.9
3	7194	8928	80.6
4	7245	8789	82.4
3 & 4	14439	17717	81.5
5	3704	4381	84.5
6	3556	4323	82.3
5 & 6	7260	8704	83.4

Agents 1 & 2: 1000 ppm F
Agents 3 & 4: 1500 ppm F
Agents 5 & 6: 2500 ppm F

higher F^- levels, significant differences were observed. At the intermediate fluoride level (1500 ppm), the addition of zinc citrate to the paste (Agent 4) resulted in a higher percentage of '0000' combinations, 82.4 % compared to 80.6 for the non-zinc paste ($X^2 = 9.98$, d.f.= 1, $p<0.01$). However, at the 2500 ppm F level, the higher percentage was observed in the non-zinc group (84.5% - Agent 5 cf 82.3 % - Agent 6; $X^2 = 8.1$, d.f. = 1, $p<0.01$).

When the number of surfaces which remained 'zero' at all four exams was included with the numbers in the categories (P, R, S, & B), significant differences between the zinc and non-zinc pastes were also obtained for the 1500 ppm pastes ($X^2 = 20.0$, d.f. = 4, $p<0.001$) and for the 2500 ppm pastes ($X^2 = 10.6$, d.f. = 4, $p<0.05$).

The effect of the addition of zinc citrate to the paste on fluoride dose-response is discussed in the next section.

4.6 Fluoride dose-response

4.6.1 Effect of zinc citrate

The percentages of surfaces in the four classifications (P, R, S & B) for each fluoride concentration are tabulated in Table 4.11 for the zinc citrate and non-zinc pastes, both separately and together.

The variations in the percentage of surfaces which 'Progressed' (P) and 'Reversed' (R) with dentifrice fluoride concentration are shown in Figures 4.10 and 4.11

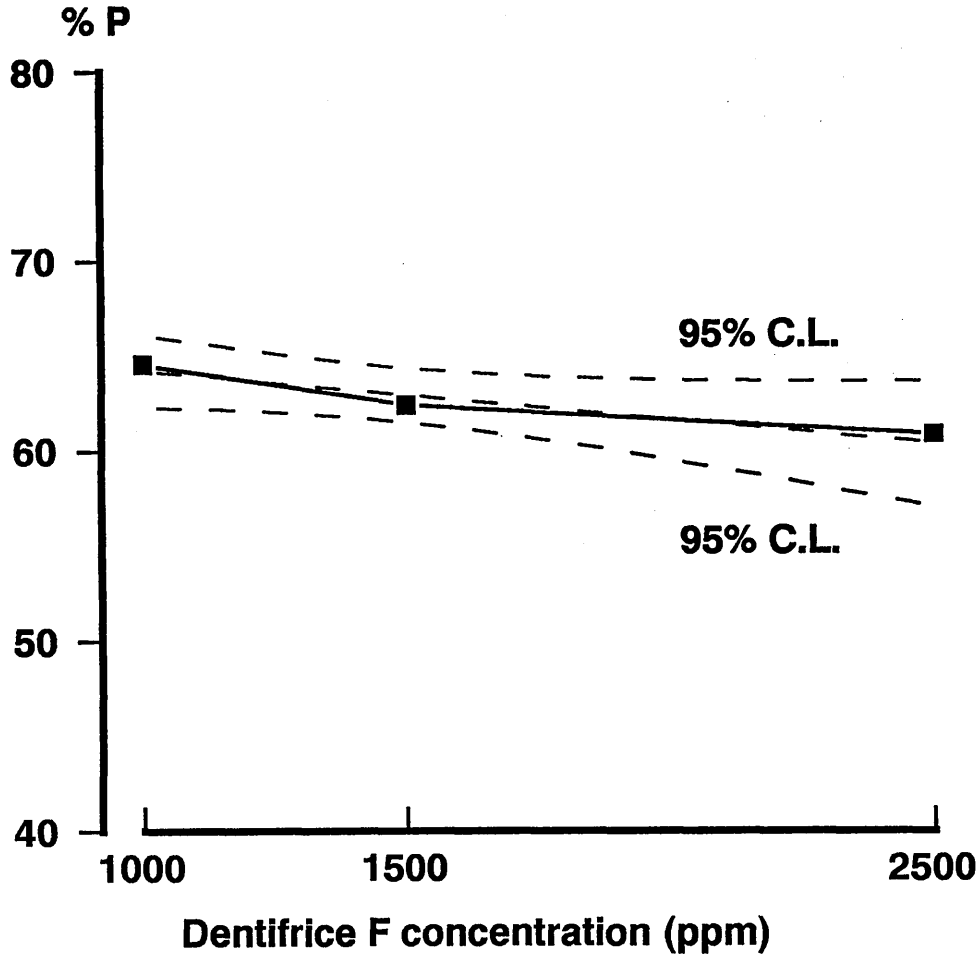


Figure 4.10 The percentage of surfaces which 'Progressed' (P), versus dentifrice fluoride concentration for non-zinc Agents (1, 3 & 5). The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

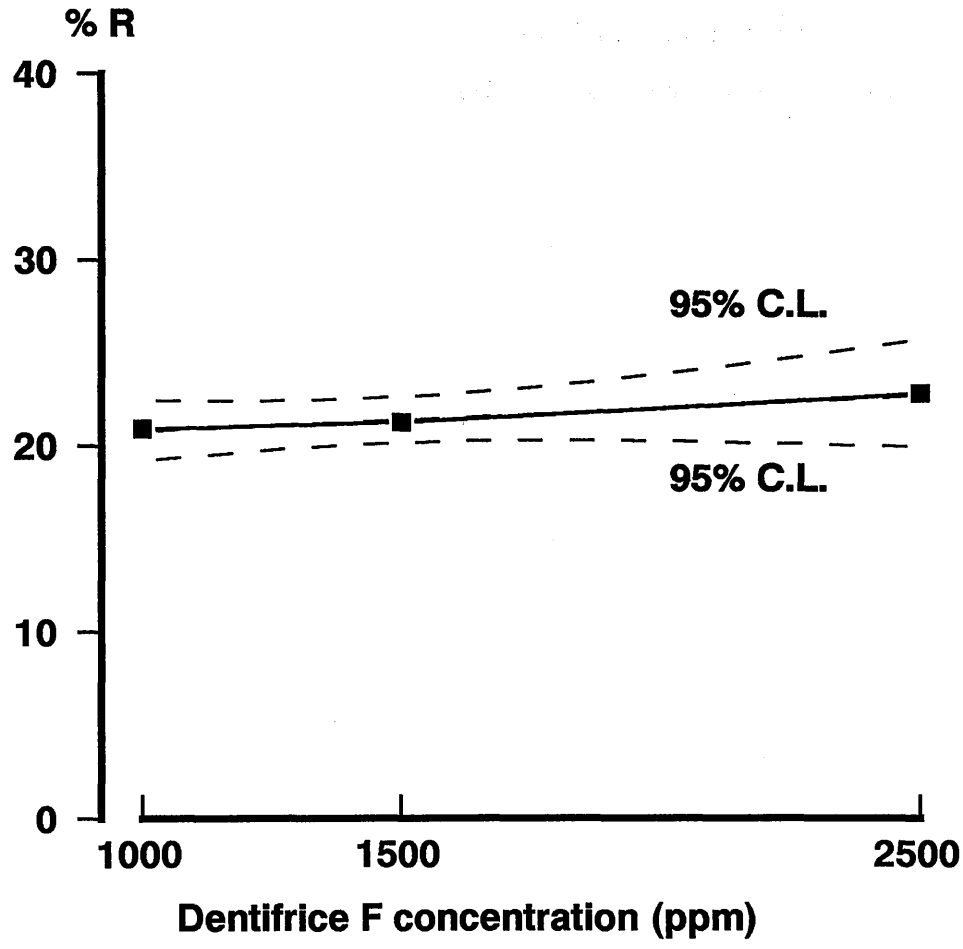


Figure 4.11 The percentage of surfaces which 'Reversed' (R), versus dentifrice fluoride concentration for non-zinc Agents (1, 3 & 5).
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

respectively for the non-zinc pastes (Agents 1, 3 & 5). The percentage of surfaces which 'Progressed' decreased from 64.6 % for the 1000 ppm paste, to 62.5 % and 61.0 % for the 1500 and 2500 ppm pastes respectively. This variation with fluoride dose was, however, not significant [X^2 (GLIM) = 2.95, d.f. = 1]. The percentage of surfaces which 'Reversed' increased with increasing dentifrice fluoride concentration from 20.9 % for the 1000 ppm paste to 21.3 % and 22.9 % for the 1500 and 2500 ppm pastes. This increase was also not significant [X^2 (GLIM) = 1.16, d.f.= 1].

For the zinc citrate-containing pastes (Agents 2, 4, & 6), the percentage of surfaces which 'Progressed' (P) (Figure 4.12) decreased from 66.5 % for the 1000 ppm paste, to 63.2 % and to 60.1 % for the 1500 and 2500 ppm pastes. This decrease with increasing fluoride level was significant [X^2 (GLIM) = 9.51, d.f.= 1, $p<0.01$]. The increase in the percentage of surfaces which 'Reversed'(R) from 20.5% to 23.0% to 23.2 % (Figure 4.13) was not significant [X^2 (GLIM) = 2.47, d.f. = 1]. The changes in the percentage of surfaces which remained 'zero' at all four examinations is shown in Figure 4.14 for the non-zinc agents, and in Figure 4.15 for the zinc-containing pastes. In both cases, a significant ($p < 0.001$) increase in the percentage remaining radiographically sound with increasing fluoride concentration was obtained [X^2 = 34.9 (non-zinc) and X^2 = 14.6 (zinc), d.f. = 1]. The calculated constants of the model are shown in Table 4.13 for the

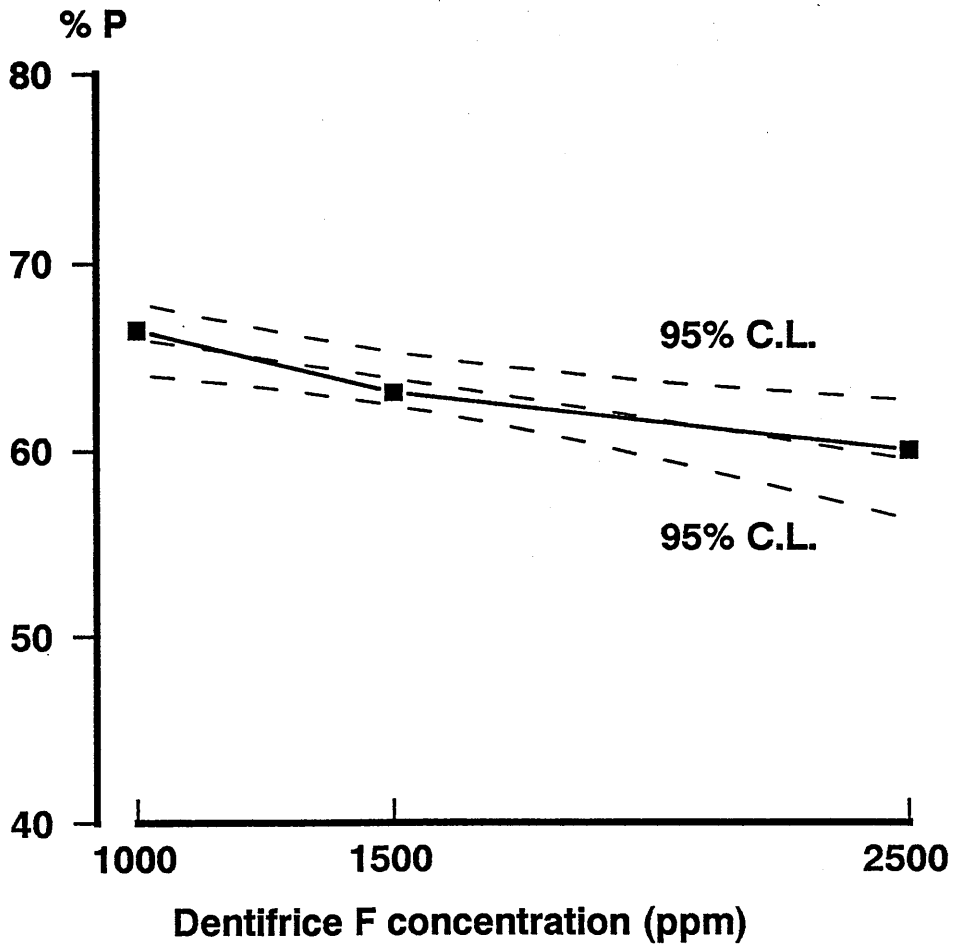


Figure 4.12 The percentage of surfaces which 'Progressed' (P), versus dentifrice fluoride concentration for zinc containing Agents (2, 4 & 6). The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

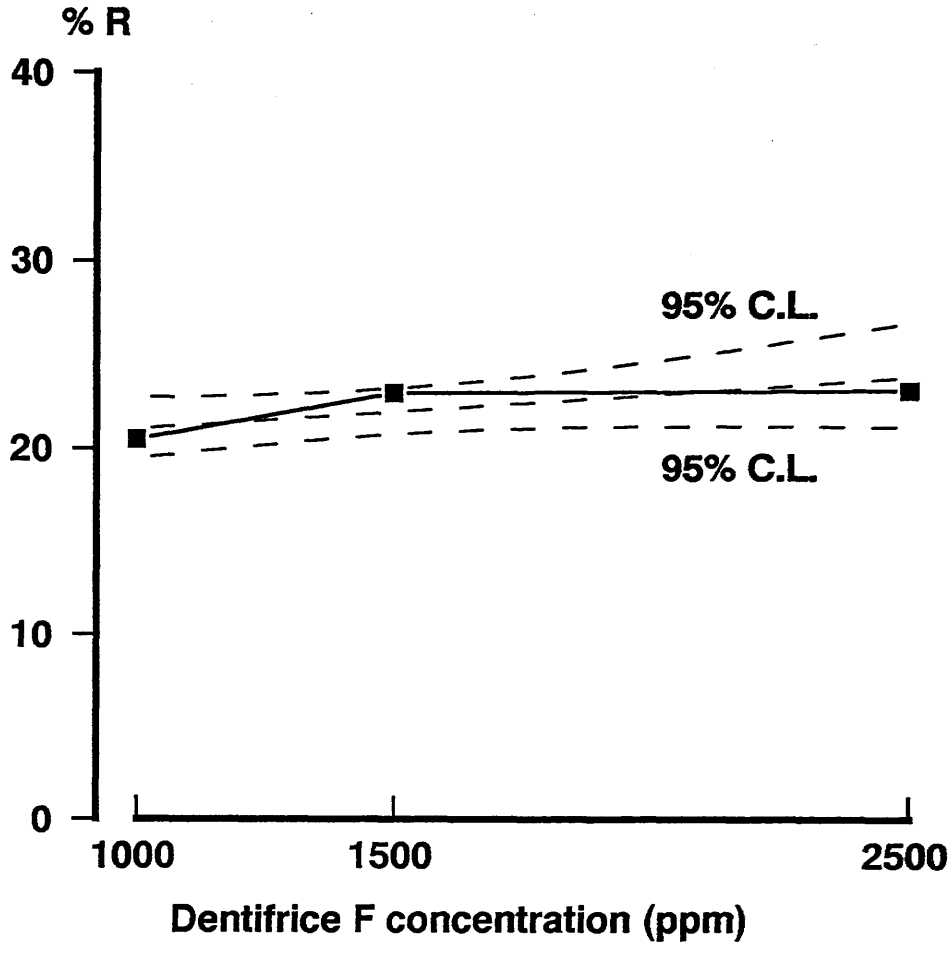


Figure 4.13 The percentage of surfaces which 'Reversed' (R), versus dentifrice fluoride concentration for zinc containing Agents (2, 4 & 6). The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

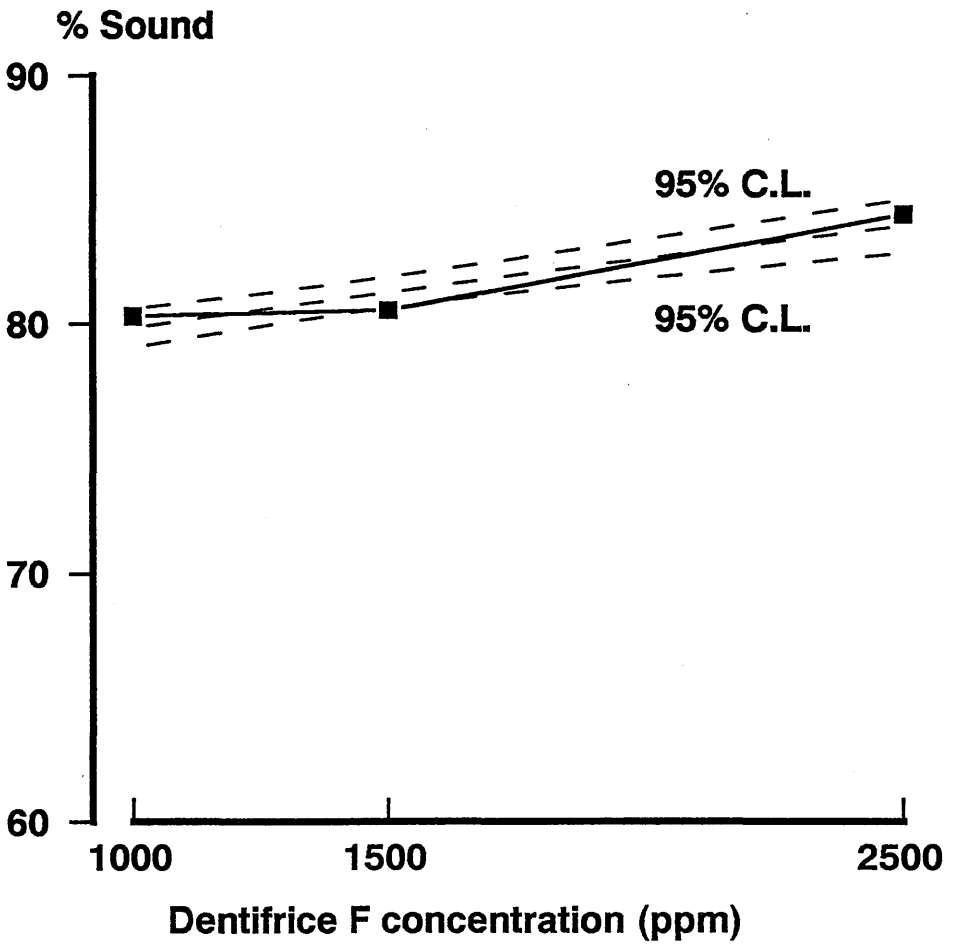


Figure 4.14 The percentage of surfaces which remained radiographically sound versus dentifrice fluoride concentration for non-zinc Agents (1, 3 & 5).
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

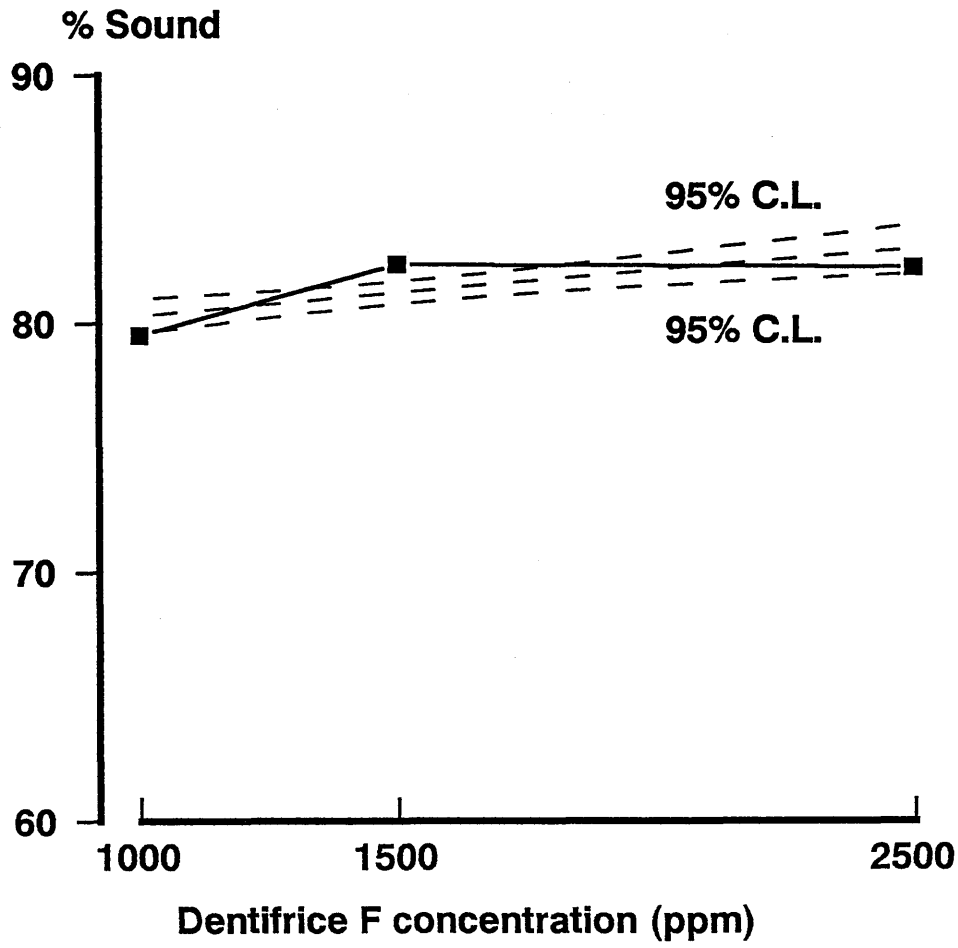


Figure 4.15 The percentage of surfaces which remained radiographically sound versus dentifrice fluoride concentration for zinc containing Agents (2, 4 & 6).
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

Table 4.13 Estimated constants (and standard errors) for significant GLIM models.

Model,p	Constant		S.E.	Log(p/(1-p))=
0000's	a	-0.452	0.02	a +
	b	0.048*	0.01*	b.F
0000's	a	-0.310	0.01	a +
	b	-0.140	0.01	b.S
0000's	a	-0.383	0.02	a +
	b	0.048*	0.01*	b.F +
	c	-0.140	0.01	c.S
Progressives	a	0.771	0.07	a +
	b	-0.146*	0.04*	b.F
Progressives	a	0.687	0.03	a +
	b	-0.247	0.05	b.S
Progressives	a	0.910	0.07	a +
	b	-0.250*	0.05*	b.F +
	c	-0.151	0.04	c.S
Progressives	a	0.751	0.10	a +
	b	-0.044*	0.06*	b.F +
	c	0.060	0.13	c.S +
	d	-0.211*	0.09*	d.(F.S)
Reversals	a	-1.343	0.04	a +
	b	0.110	0.05	b.S
0000's	a	1.233	0.04	a +
	b	0.157*	0.02*	b.F
0000's	a	1.234	0.04	a +
	b	0.157*	0.02*	b.F +
	c	-0.003	0.02	c.Z
Progressives	a	0.771	0.07	a +
	b	-0.146*	0.04*	b.F
Progressives	a	0.752	0.07	a +
	b	-0.147*	0.04*	b.F +
	c	0.042	0.05	c.Z
0000's (males)	a	-0.545	0.03	a +
	b	0.064*	0.02*	b.F

* values x 10^{-3}, F - fluoride, S - Sex, (F.S) - interaction between F & S, Z - zinc.

significant cases.

The results of combining the zinc citrate and non-zinc pastes, at each fluoride level, are shown in Figures 4.16 and 4.17 for the percentage of surfaces which 'Progressed' (P) and 'Reversed' (R) respectively. The percentage of surfaces which 'Progressed' (P) decreased from 65.6 % to 62.8 % to 60.5 % as the fluoride level increased. This decrease was significant [X^2 (GLIM) = 11.5, d.f. = 1, $p<0.001$]. The corresponding values for the surfaces which 'Reversed' (R) were 20.7 %, 22.1 % and 23.1 %. This increase in the numbers of surfaces which 'Reversed' with increasing fluoride concentration was just not significant (X^2 (GLIM) = 3.6, d.f.= 1, (critical value for $p<0.05$ is 3.84). In the case of the surfaces which remained sound (Figure 4.18), a significant increase with increasing fluoride was obtained (X^2 = 47.3, d.f = 1, $p < 0.001$).

The results of the three parameter model of fluoride and zinc are shown in Figure 4.19 for surfaces which 'Progressed' (P). The lines (a), (b), (c), (d) and (e) trace the effect of the addition of various covariates, e.g. (a) shows that the addition of fluoride as a covariate to the model reduced the scaled deviance from 14.18 to 2.68, giving a X^2 of 11.5. Lines (c) and (d) trace the effects on the scaled deviances of adding the effect of zinc to that of fluoride, and that of adding the effect of fluoride to zinc, respectively. The latter was significant [X^2 (GLIM) = 11.65, d.f. = 1, $p < 0.001$],

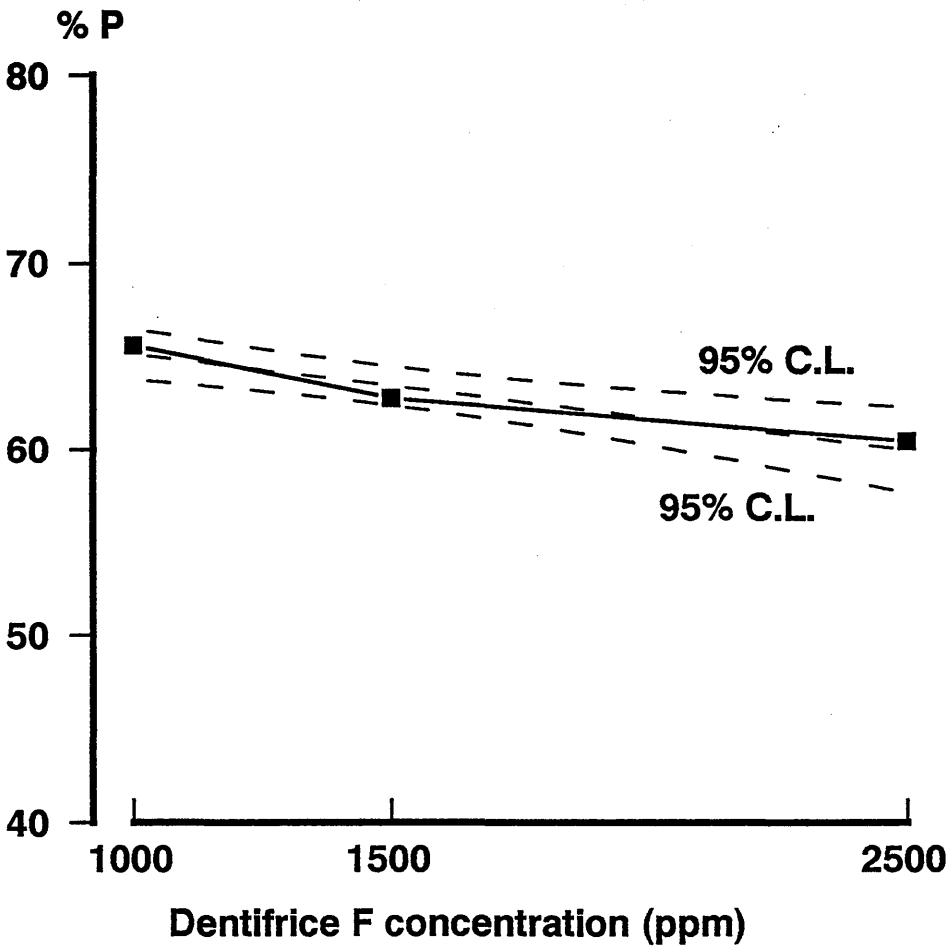


Figure 4.16 The percentage of surfaces which 'Progressed' (P), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

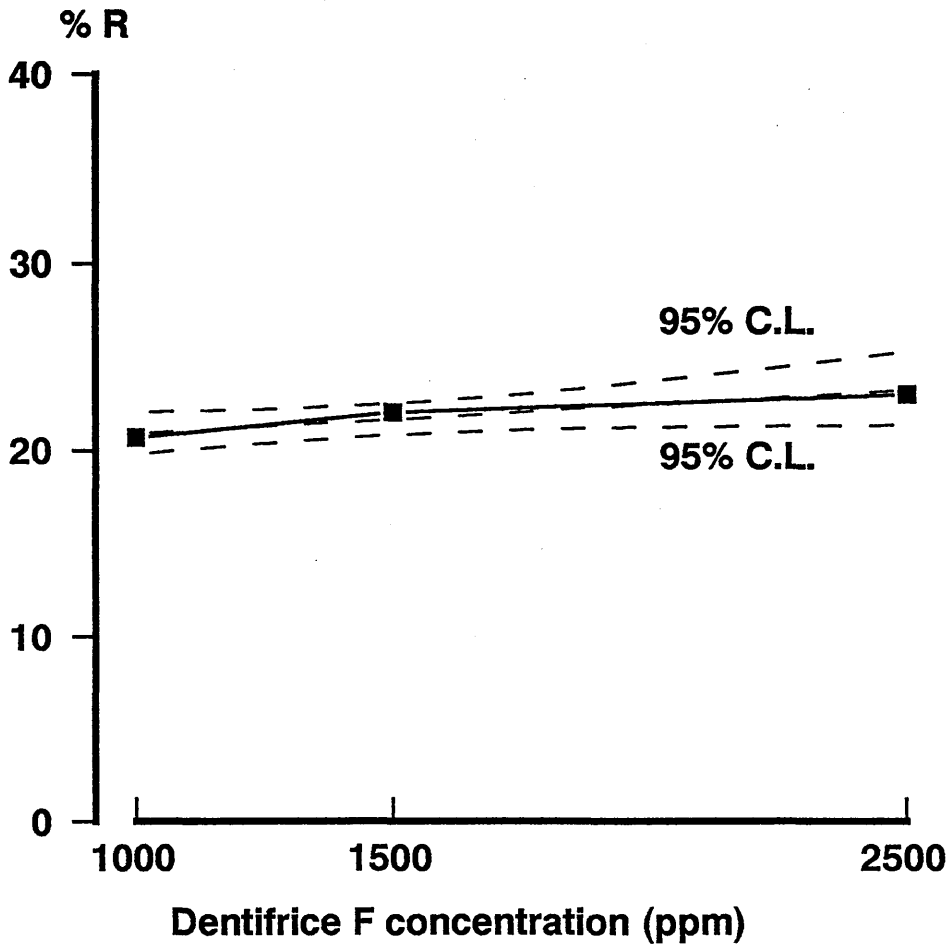


Figure 4.17 The percentage of surfaces which 'Reversed' (R), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

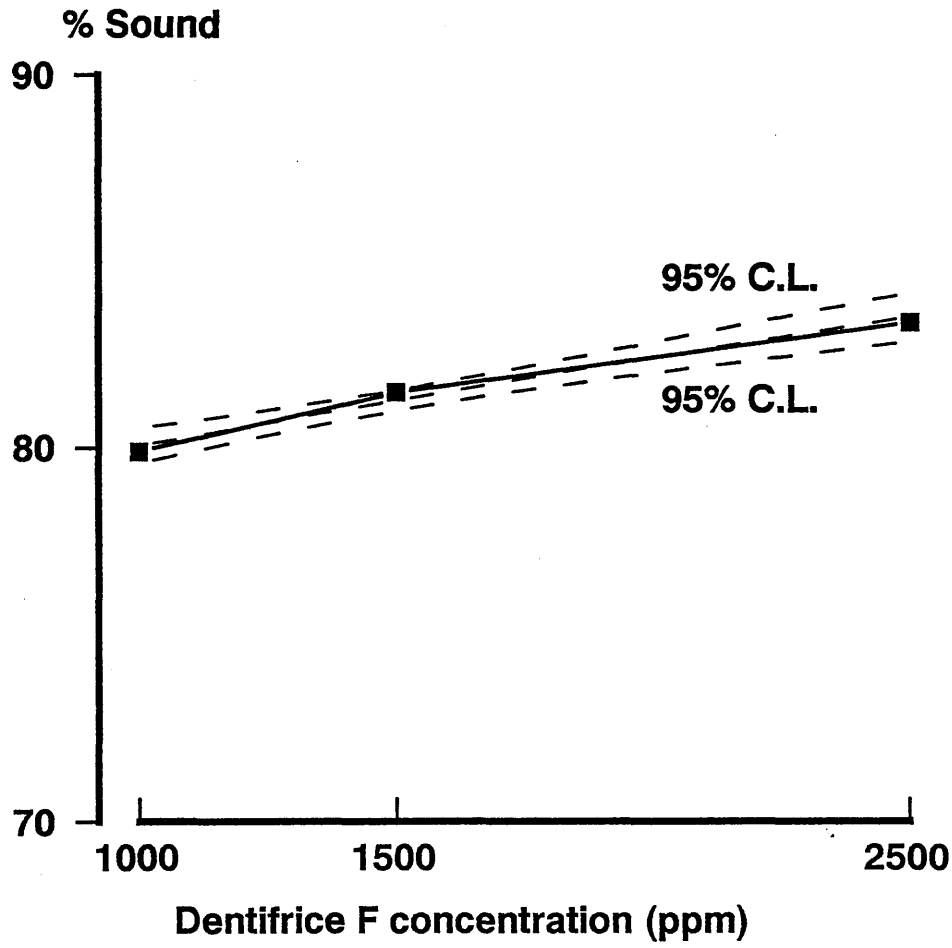


Figure 4.18 The percentage of surfaces which remained radiographically sound versus dentifrice fluoride concentration for zinc and non-zinc agents combined.
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

PROGRESSIVE SURFACES - FLUORIDE + ZINC

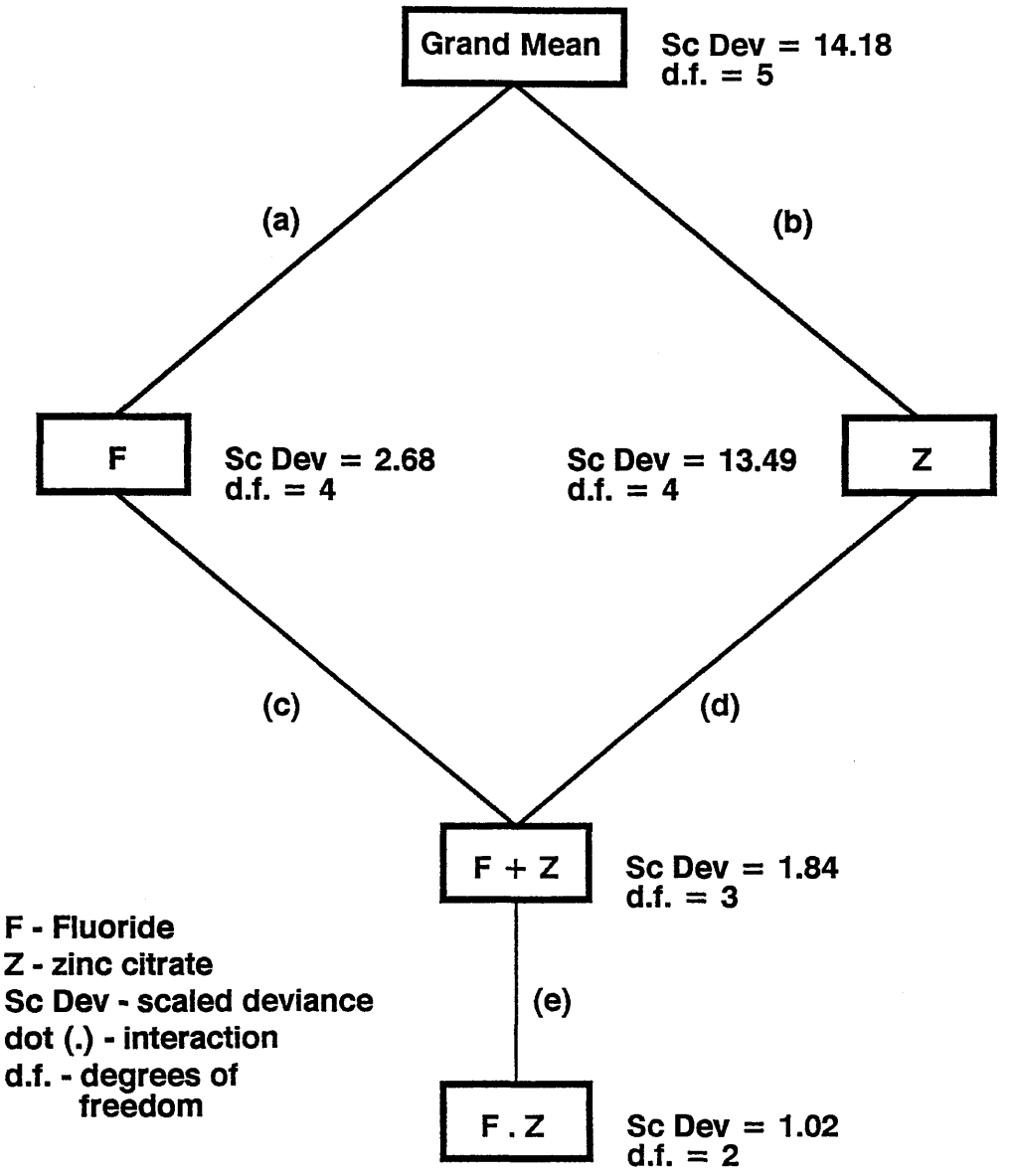


Figure 4.19 Diagramatic representation of the effect of modelling the covariates on the scaled deviance: (a) effect of fluoride, (b) effect of zinc, (c) adding the effect of zinc to that of fluoride, (d) adding the effect of fluoride to that of zinc, and (e) adding a fluoride / zinc interactive component, for surfaces which 'Progressed'.

showing that while the addition of zinc had no effect, the addition of fluoride did. Line (e) traces the addition of an interactive effect between zinc and fluoride to that of fluoride plus zinc. In this case the interaction was not significant. Again, the calculated parameters for the significant models are as shown in Table 4.13.

A similar diagram for surfaces which 'Reversed' (R) is shown in Figure 4.20. In this case, none of the pathways (a) - (e) were significant.

For surfaces which remained 'zero' at all four examinations (Figure 4.21), pathway (a), the addition of fluoride, was significant [X^2 (GLIM) = 47.35, d.f. = 1, $p < 0.001$] and pathway (d), the addition of fluoride to zinc, was also significant [X^2 (GLIM) = 47.35, d.f. = 1, $p < 0.001$].

4.6.2 Effect of sex

The percentages of surfaces in the four classifications (P, R, S & B) for each fluoride concentration are tabulated in Table 4.8 for both males and females. The percentages of surfaces which 'Progressed' (P) at each fluoride level are shown in Figures 4.22, and 4.23 for males and females respectively. At each fluoride level, zinc citrate and non-zinc data were combined. For males, the percentages of 'Progressive' surfaces at 1000, 1500 and 2500 ppm were 66.8 %, 66.8 % and 65.3 % respectively. No significant dose-response was noted [X^2 (GLIM) = 0.50].

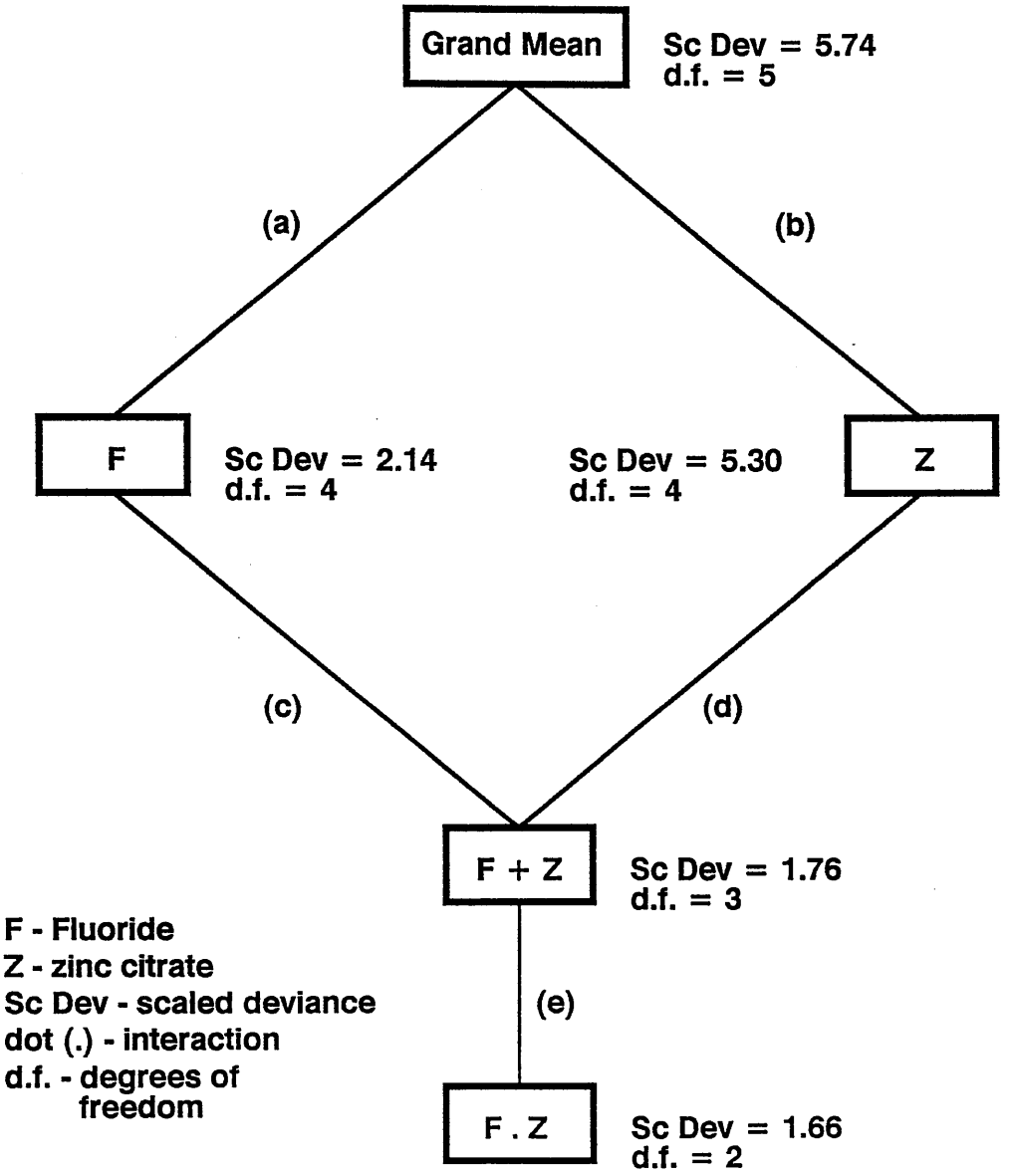


Figure 4.20 Diagramatic representation of the effect of modelling the covariates on the scaled deviance: (a) effect of fluoride, (b) effect of zinc, (c) adding the effect of zinc to that of fluoride, (d) adding the effect of fluoride to that of zinc, and (e) adding a fluoride / zinc interactive component, for surfaces which 'Reversed'.

SOUND SURFACES - FLUORIDE + ZINC

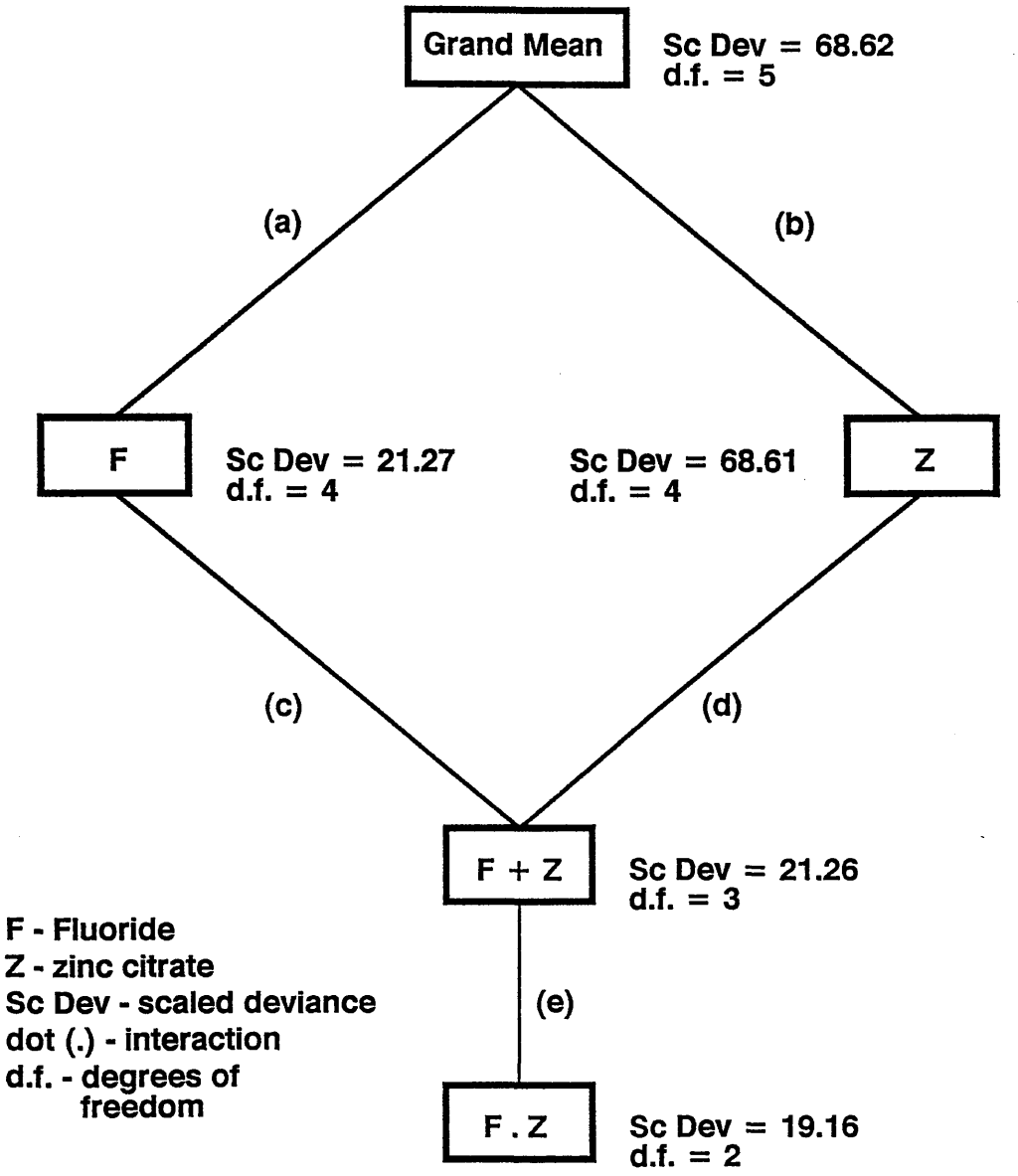


Figure 4.21 Diagramatic representation of the effect of modelling the covariates on the scaled deviance: (a) effect of fluoride, (b) effect of zinc, (c) adding the effect of zinc to that of fluoride, (d) adding the effect of fluoride to that of zinc, and (e) adding a fluoride / zinc interactive component, for surfaces which remained radiographically sound (i.e. '0000's).

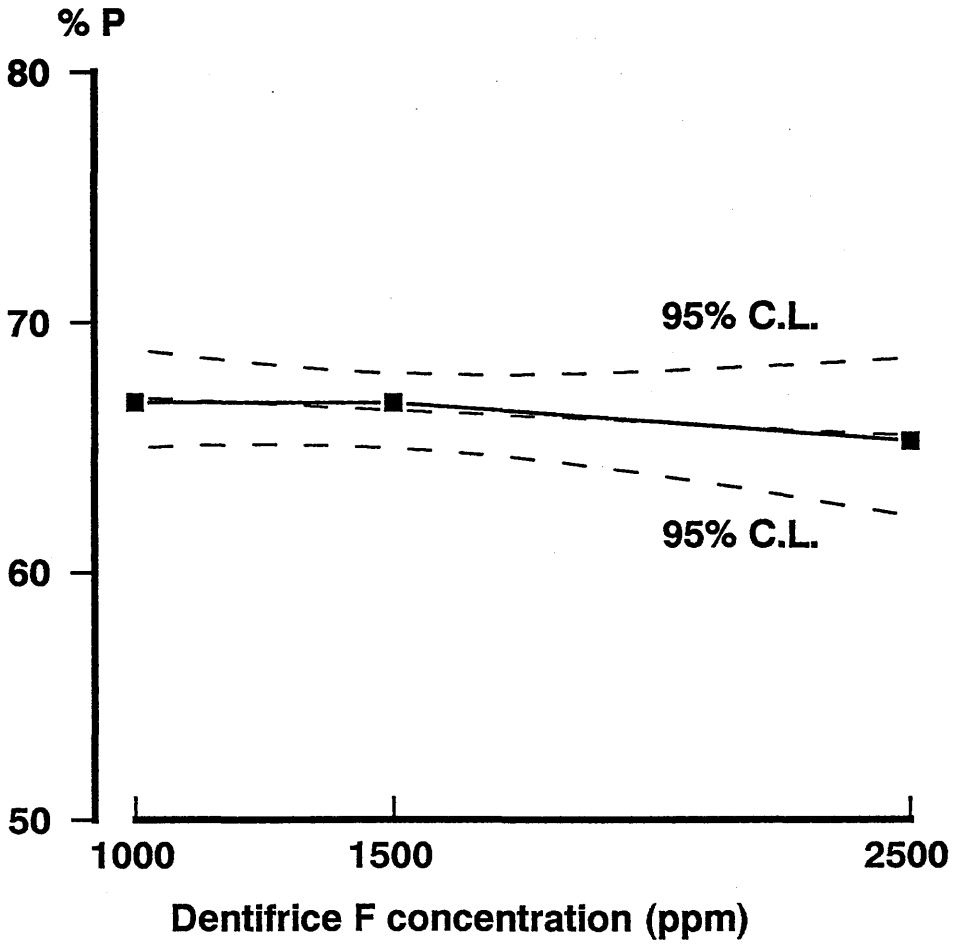


Figure 4.22 The percentage of surfaces which 'Progressed' (P), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for males. The central dotted line is the 'best fit' line.
95 % C.L. = 95 % Confidence Limits.

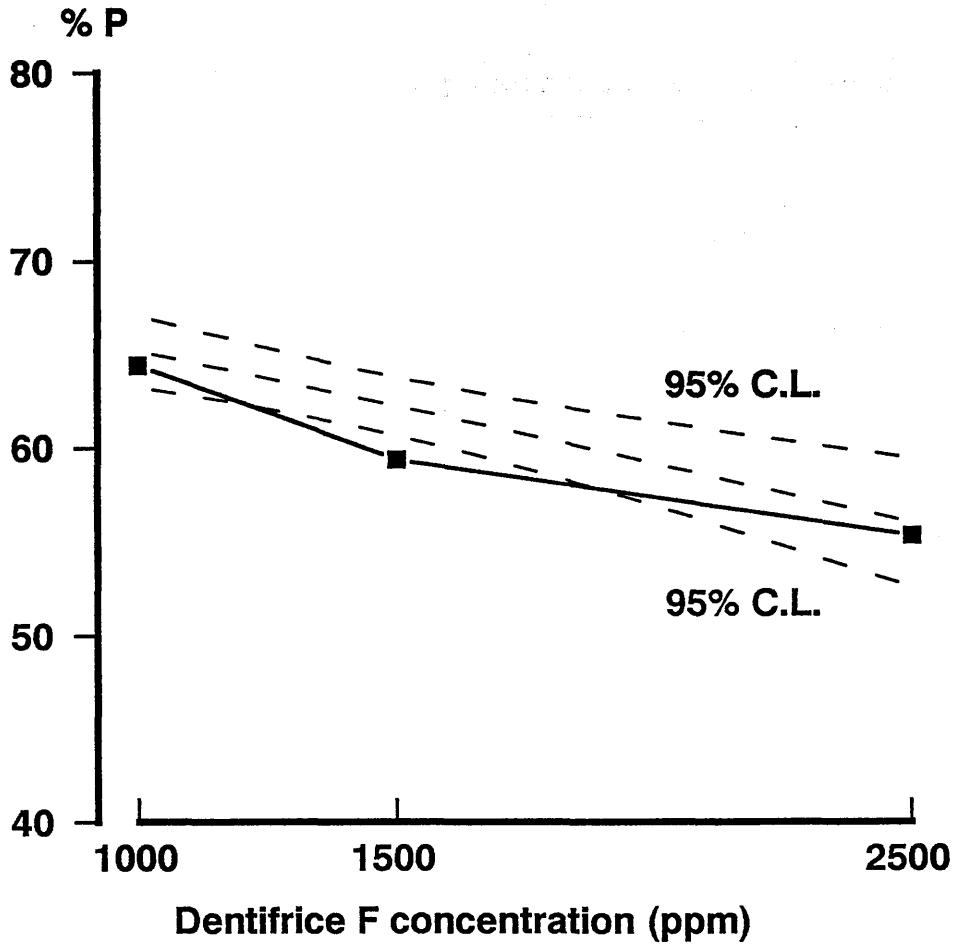


Figure 4.23 The percentage of surfaces which 'Progressed' (P), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for females. The central dotted line is the 'best fit' line.
95 % C.L. = 95 % Confidence Limits.

However, for females the corresponding values for the three dentifrices were 64.4 %, 59.4 %, and 55.4 %. This fall in the proportion of surfaces which 'Progressed' (P) was highly significant [X^2 (GLIM) = 17.73, d.f. = 1, $p<0.001$].

Similar graphs for the percentage of surfaces which 'Reversed' (R) are shown in Figures 4.24 and 4.25 for males and females respectively. Contrary to the situation above, the increase in the proportion of 'Reversals' with increasing fluoride level was significant for males [X^2 (GLIM) = 4.29, d.f. = 1, $p<0.05$], the percentage of 'Reversals' being 20.2 %, 19.6 % and 24.0 % at the three F^- levels. However, for females, the relationship between the corresponding values of 21.1 %, 24.2 % and 22.0 % respectively, and fluoride, was not significant [X^2 (GLIM) = 0.454]. The change in the percentages of surfaces which remained radiographically sound with fluoride concentration is shown in Figures 4.26 and 4.27 for males and females respectively. The increase was significant for males [X^2 (GLIM) = 12.6, d.f. = 1, $p < 0.001$], but not for females [X^2 (GLIM) = 3.55, d.f. = 1]. Again, the calculated parameters for the significant models are shown in Table 4.13.

The results of the three parameter model of fluoride and sex are shown in Figure 4.28 for surfaces which 'Progressed' (P). All pathways (a) - (e), resulted in significant X^2 values (Table 4.14), including that of the

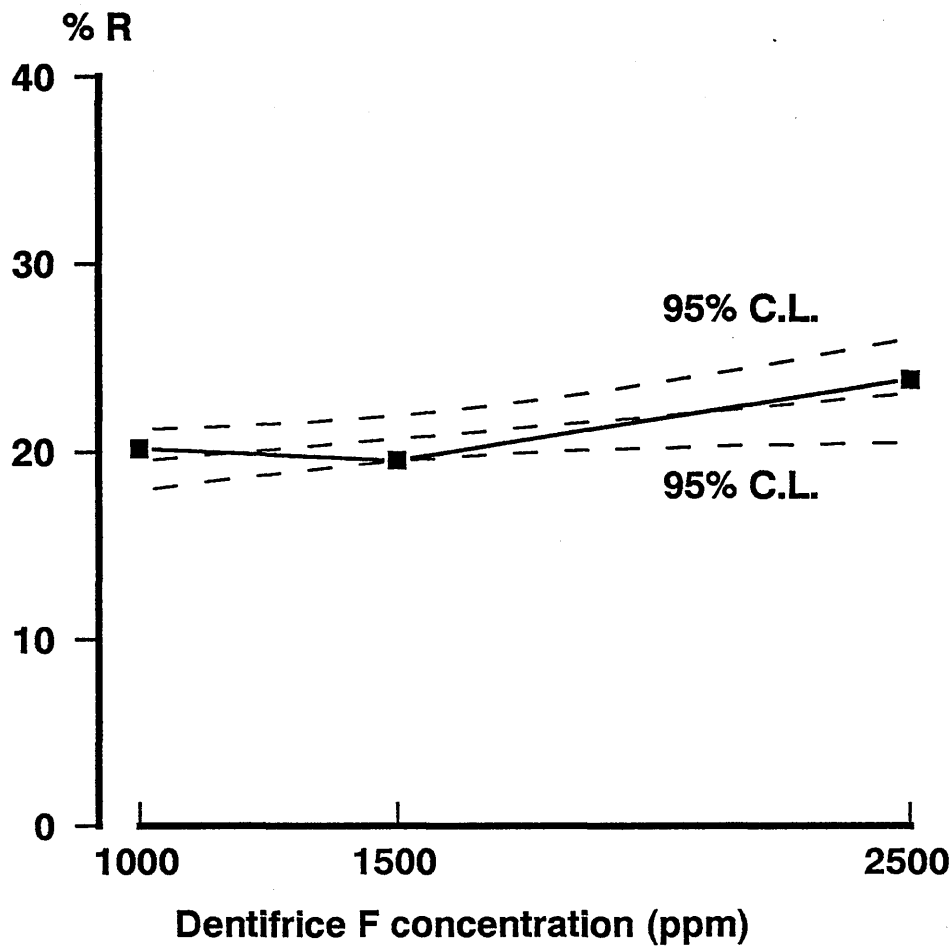


Figure 4.24 The percentage of surfaces which 'Reversed' (R), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for males. The central dotted line is the 'best fit' line.
95 % C.L. = 95 % Confidence Limits.

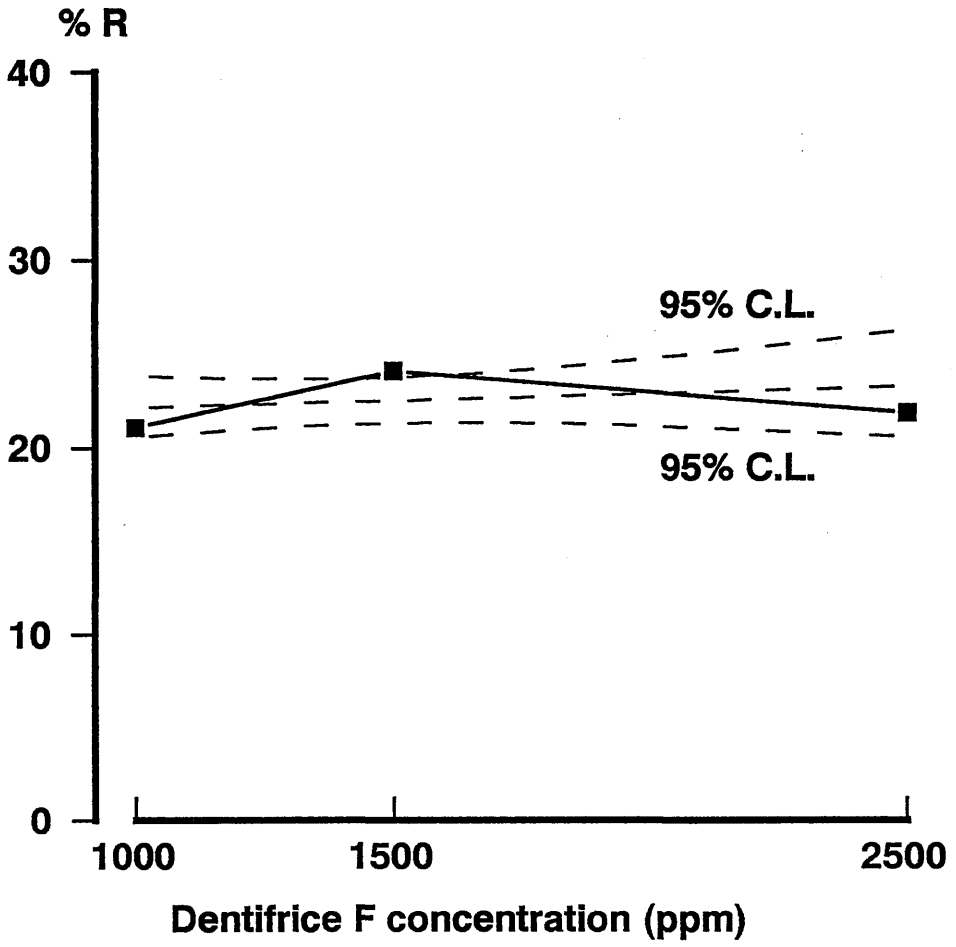


Figure 4.25 The percentage of surfaces which 'Reversed' (R), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for females. The central dotted line is the 'best fit' line.
95 % C.L. = 95 % Confidence Limits.

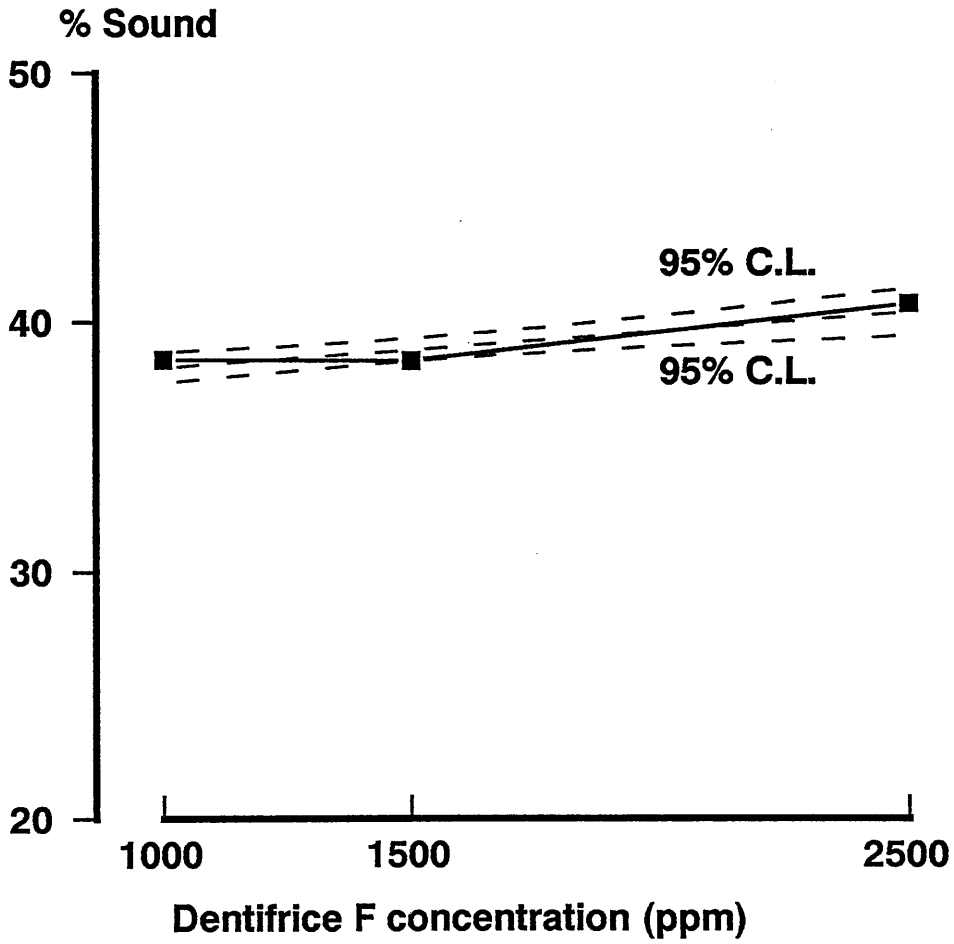


Figure 4.26 The percentage of surfaces which remained radiographically sound versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for males.
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

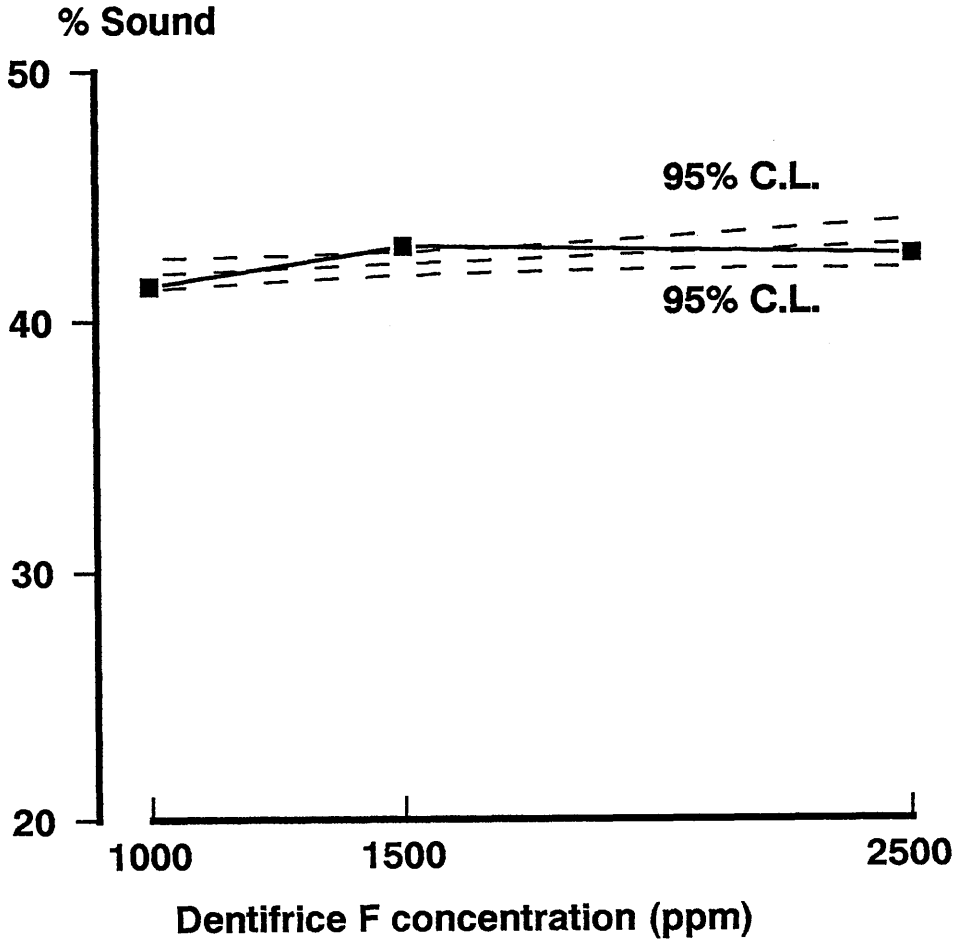


Figure 4.27 The percentage of surfaces which remained radiographically sound versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for females. The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

PROGRESSIVE SURFACES - FLUORIDE + SEX

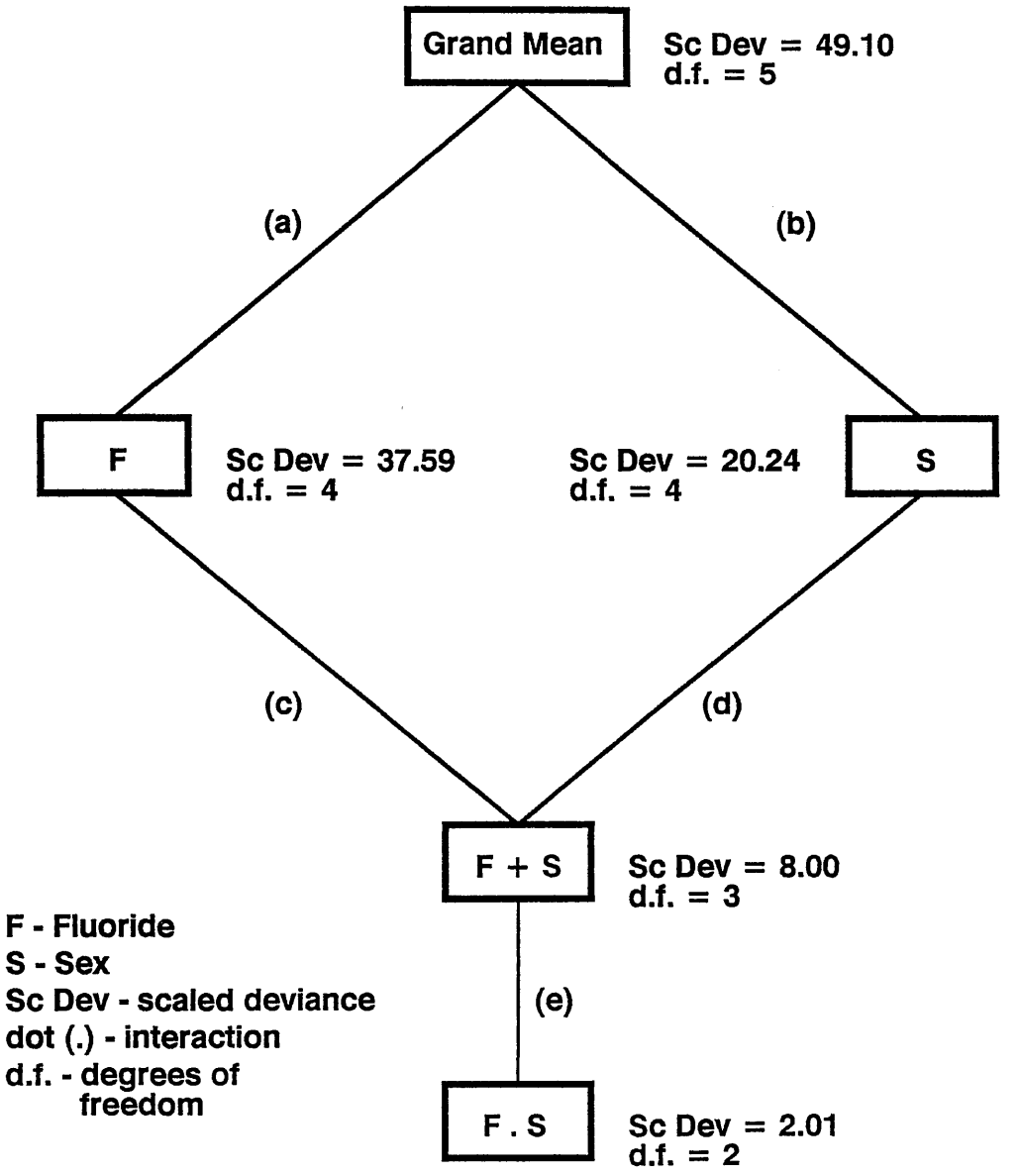


Figure 4.28 Diagramatic representation of the effect of modelling the covariates on the scaled deviance: (a) effect of fluoride, (b) effect of sex, (c) adding the effect of sex to that of fluoride, (d) adding the effect of fluoride to that of sex, and (e) adding a fluoride / sex interactive component, for surfaces which 'Progressed'.

Table 4.14 X^2 values from GLIM model of the effect of fluoride and sex on surfaces which 'Progressed'.

Pathway	Covariates	X^2	p
(a)	F	11.51	< 0.001
(b)	S	28.86	< 0.001
(c)	F+S	29.59	< 0.001
(d)	S+F	12.24	< 0.001
(e)	F.S	5.99	< 0.02

F - fluoride S - Sex
F+S - effect of adding sex to fluoride
S+F - effect of adding fluoride to sex
F.S - interaction between F and S.
Pathways (a - e) as per Figure 4.35.

addition of the interactive effect between fluoride and sex, to that of fluoride plus sex.

The corresponding diagram for surfaces which 'Reversed' (R) is shown in Figure 4.29. Only pathways (b) and (c), the effect of adding sex alone, and the effect of adding sex to fluoride respectively, were significant [X^2 (GLIM) = 4.16 & 4.31, d.f. = 1, $p < 0.05$].

In the case of surfaces which remained 'zero' at all four examinations (Figure 4.30), all pathways except (e), the interaction, were significant (Table 4.15).

4.6.3 Effect of baseline radiographic score

The percentages of surfaces in the four classifications (P, R, S & B) for each fluoride concentration are tabulated in Table 4.16 according to their radiographic score at the baseline examination. The variations in the percentage of surfaces which 'Progressed' (P) with dentifrice fluoride concentration are shown in Figures 4.31 and 4.32 for surfaces which had a radiographic score of '2' and '3' at baseline, respectively. Similar graphs for the percentage of surfaces which 'Reversed' are shown in Figures 4.33 and 4.34. In all cases, no significant dose-response was obtained, although there were so few surfaces with a baseline score of '3' (n = 0 - 147), that meaningful analysis was not possible.

Earlier in Section 4.6.1, it was shown that surfaces which

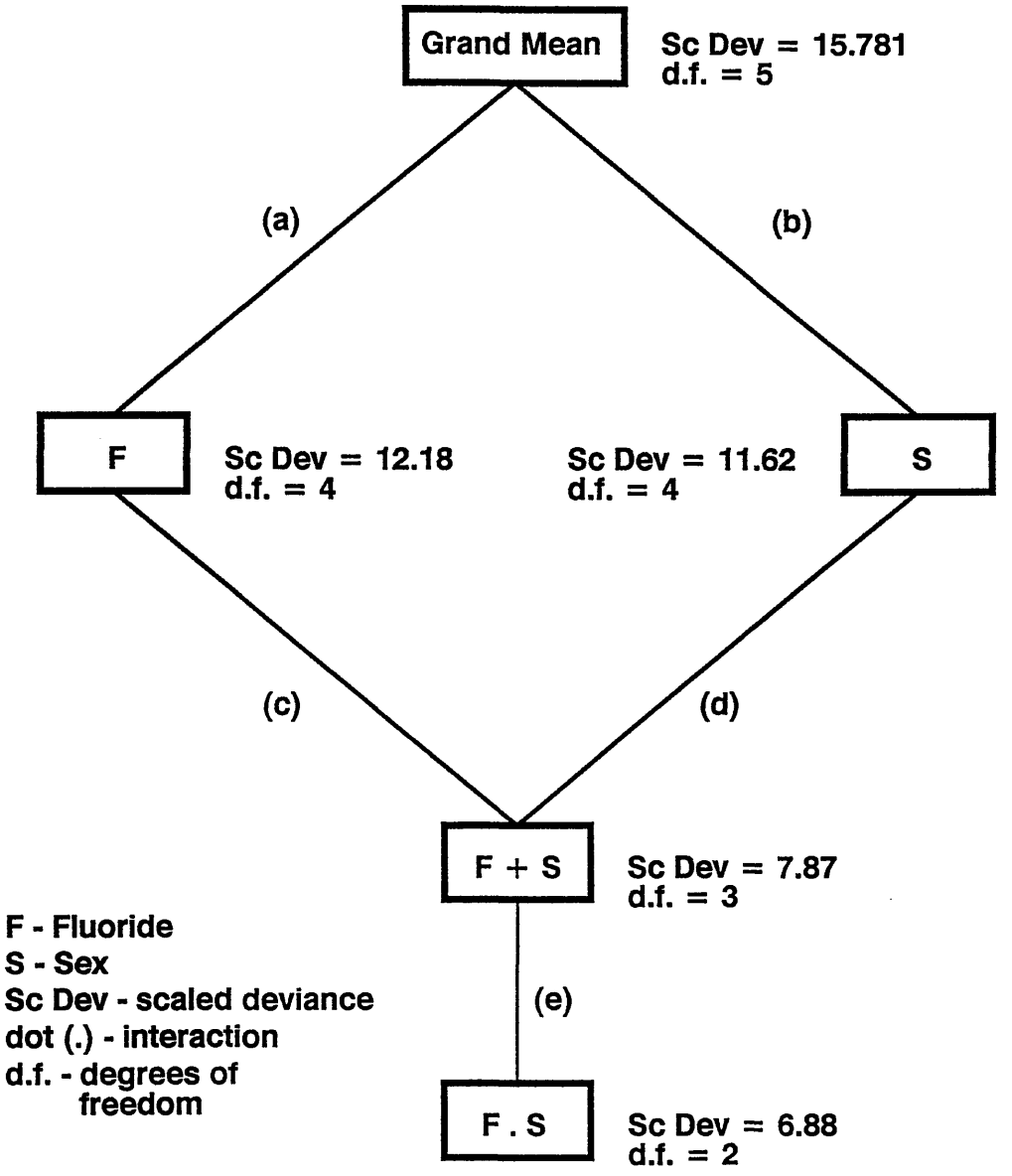


Figure 4.29 Diagramatic representation of the effect of modelling the covariates on the scaled deviance: (a) effect of fluoride, (b) effect of sex, (c) adding the effect of sex to that of fluoride, (d) adding the effect of fluoride to that of sex, and (e) adding a fluoride / sex interactive component, for surfaces which 'Reversed'.

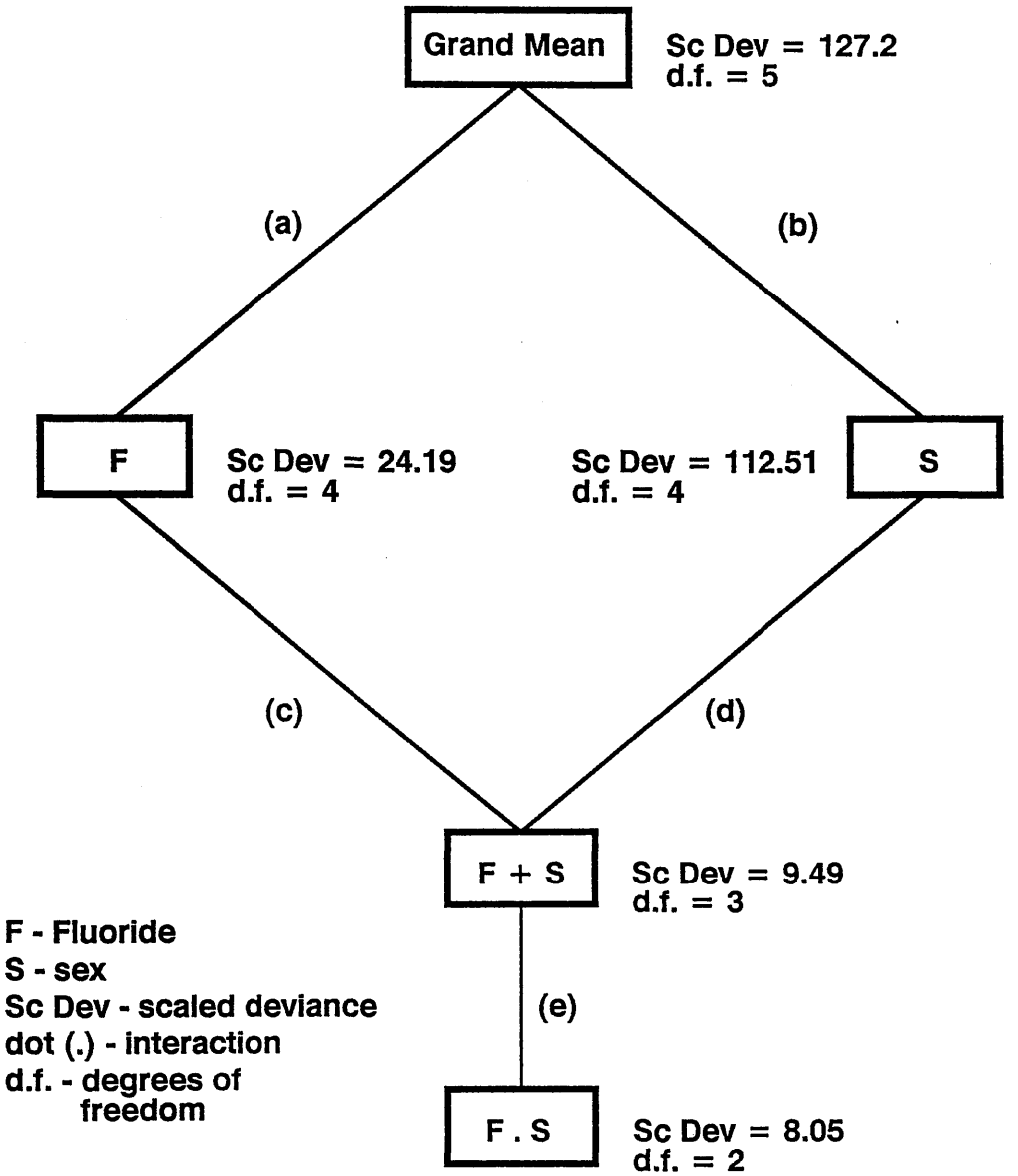


Figure 4.30 Diagramatic representation of the effect of modelling the covariates on the scaled deviance: (a) effect of fluoride, (b) effect of sex, (c) adding the effect of sex to that of fluoride, (d) adding the effect of fluoride to that of sex, and (e) adding a fluoride / sex interactive component, for surfaces which remained radiographically sound (i.e. '0000's).

Table 4.15 X^2 values from GLIM model of the effect of fluoride and sex on surfaces which were 'zero' at all four examinations.

Pathway	Covariates	X^2	p
(a)	F	103.0	< 0.001
(b)	S	14.69	< 0.001
(c)	F+S	14.70	< 0.001
(d)	S+F	103.0	< 0.001
(e)	F.S	1.44	N.S.

F - fluoride S - Sex
F+S - effect of adding sex to fluoride
S+F - effect of adding fluoride to sex
F.S - interaction between F and S.
Pathways (a - e) as per Figure 4.37.

Table 4.16 Number and percentage of surfaces which 'Progressed' (P), 'Reversed' (R), remained 'Stable' (S) and were 'Borderline' (B). Effect of baseline radiographic score. All surfaces.

Agent	P		R		S		B	
	n	%	n	%	n	%	n	%
Baseline Radiographic score = 0								
1 & 2	1932	75.5	545	21.3	18	0.1	63	2.5
3 & 4	1707	73.4	534	23.0	15	0.1	69	3.0
5 & 6	727	69.8	260	25.0	14	1.3	40	3.8
Baseline Radiographic score = 2								
1 & 2	329	45.1	151	20.7	223	30.5	27	3.7
3 & 4	326	43.2	159	21.1	237	31.4	33	4.4
5 & 6	138	44.8	64	20.8	92	29.8	14	4.5
Baseline Radiographic score = 3								
1 & 2	27	13.4	25	12.4	147	72.8	3	1.5
3 & 4	26	13.1	32	16.2	140	70.7	0	0
5 & 6	9	9.5	9	9.5	77	81.1	0	0

Agents 1 & 2: 1000 ppm F
Agents 3 & 4: 1500 ppm F
Agents 5 & 6: 2500 ppm F

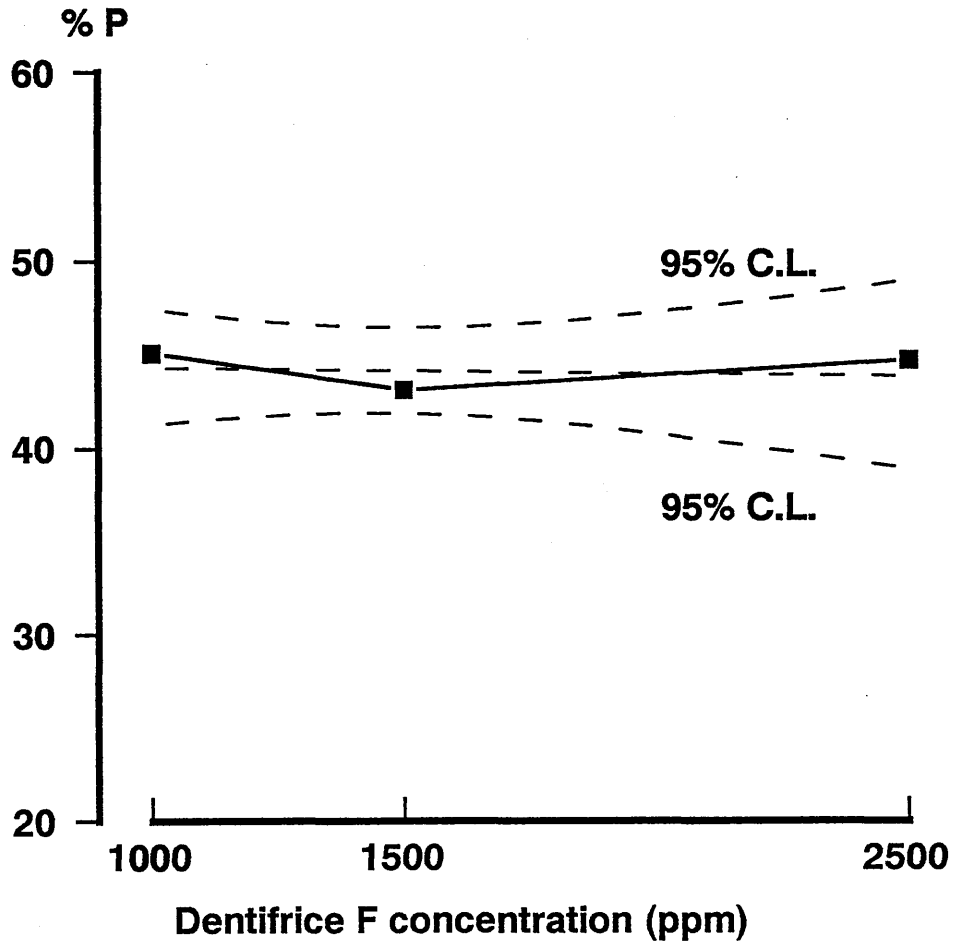


Figure 4.31 The percentage of surfaces which 'Progressed' (P), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for surfaces with a baseline radiographic score of '2'.
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

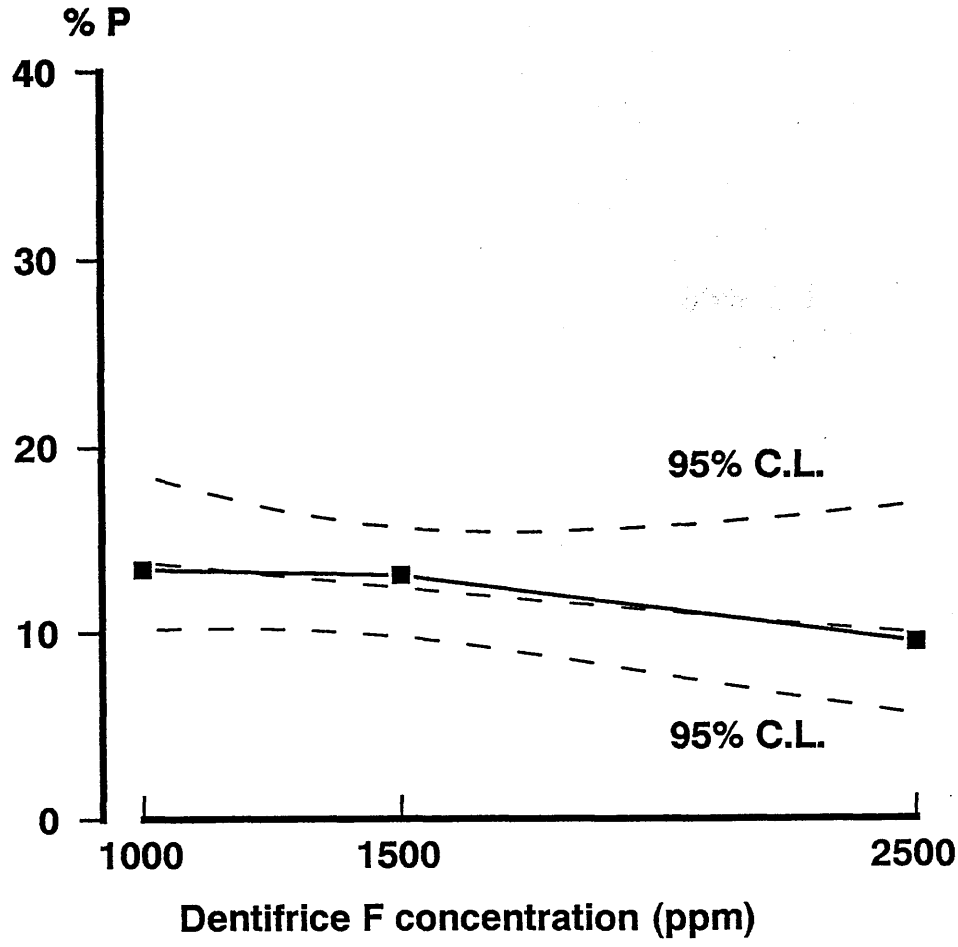


Figure 4.32 The percentage of surfaces which 'Progressed' (P), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for surfaces with a baseline radiographic score of '3'.
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

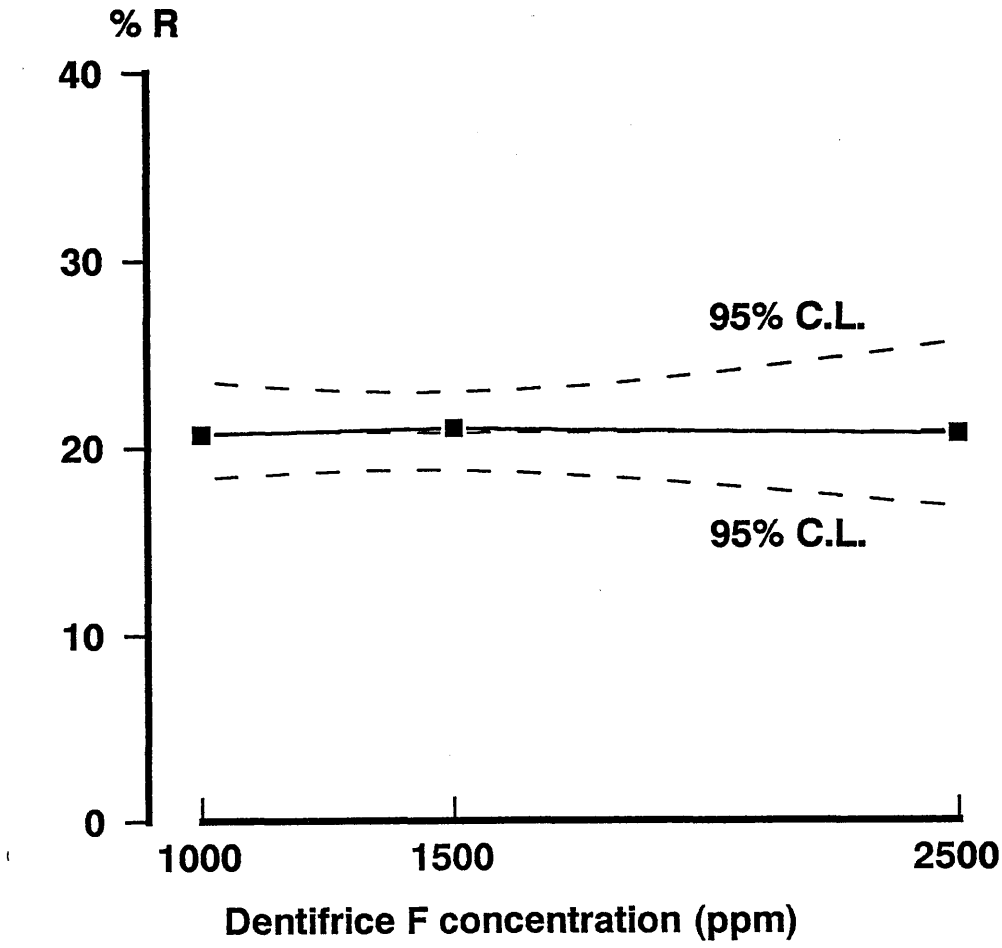


Figure 4.33 The percentage of surfaces which 'Reversed' (R), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for surfaces with a baseline radiographic score of '2'.
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

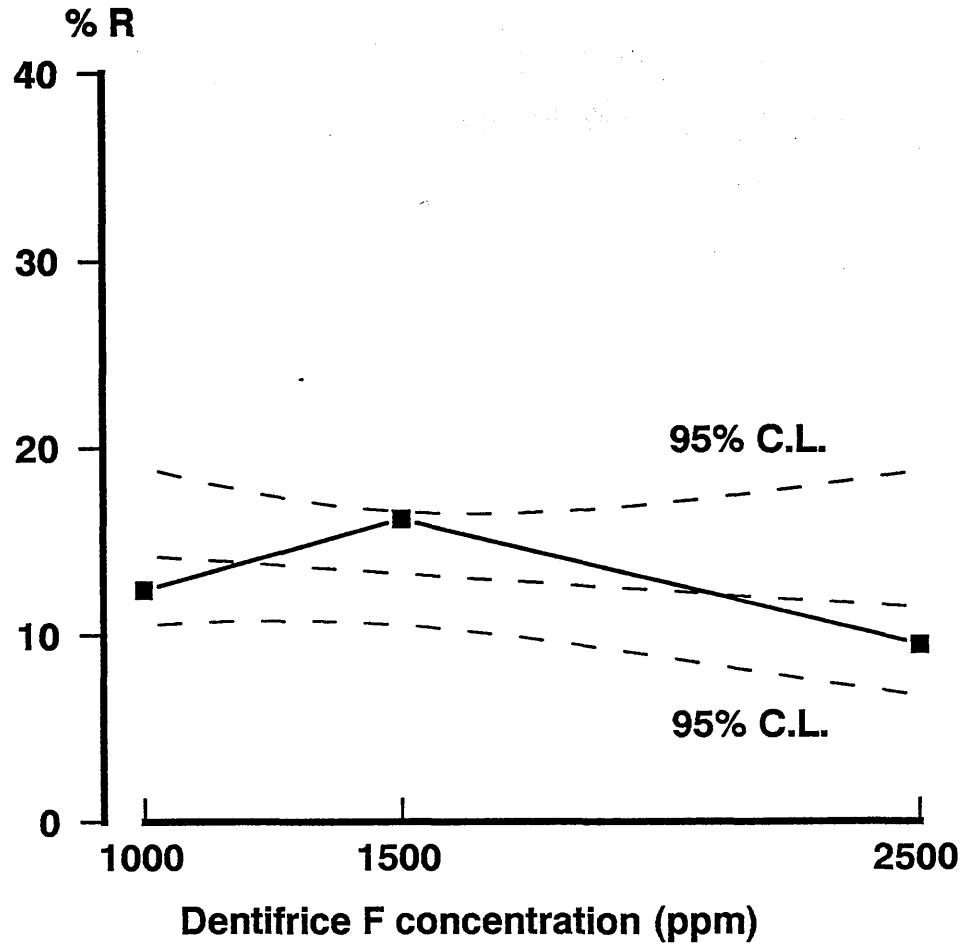
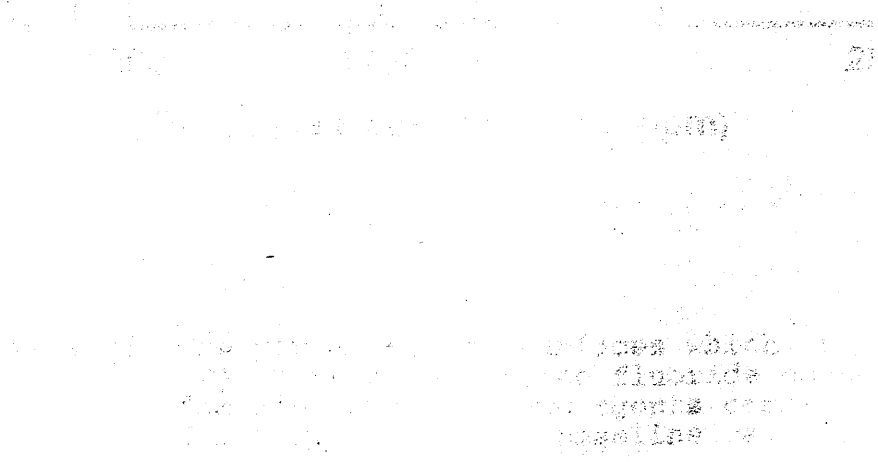


Figure 4.34 The percentage of surfaces which 'Reversed' (R), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for surfaces with a baseline radiographic score of '3'.
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

had a radiographic score of 'zero' at all four examinations had a significant fluoride dose-response (Figure 4.18). Figures 4.35 and 4.36 show the variation, with fluoride concentration, in the percentage of surfaces with a baseline score of 'zero', which 'Progressed' and 'Reversed'. The percentages were calculated without the inclusion of the '0000' data. In both cases, there was a significant dose-response, with $p < 0.001$ [X^2 (GLIM) = 12.3, d.f. = 1] for the surfaces which 'Progressed', and $p < 0.05$ [X^2 (GLIM) = 5.76, d.f. = 1] for surfaces which 'Reversed'.



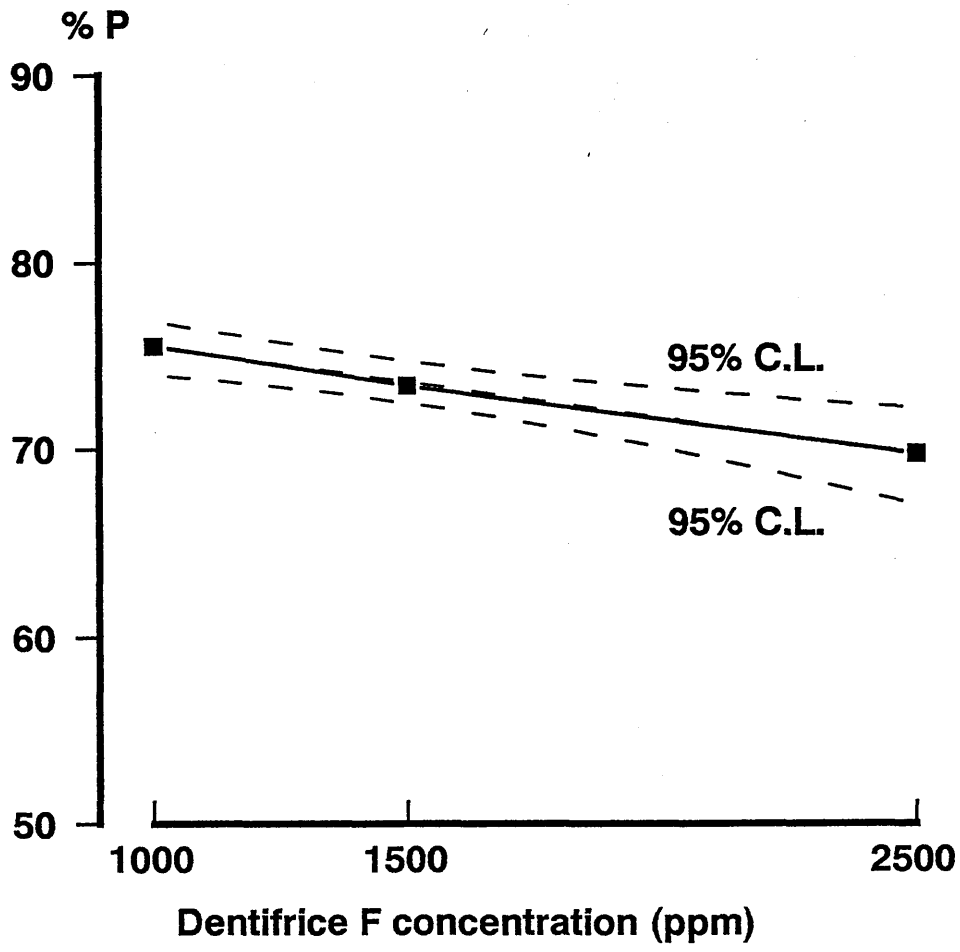


Figure 4.35 The percentage of surfaces which 'Progressed' (P), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for surfaces with a baseline radiographic score of '0'.
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

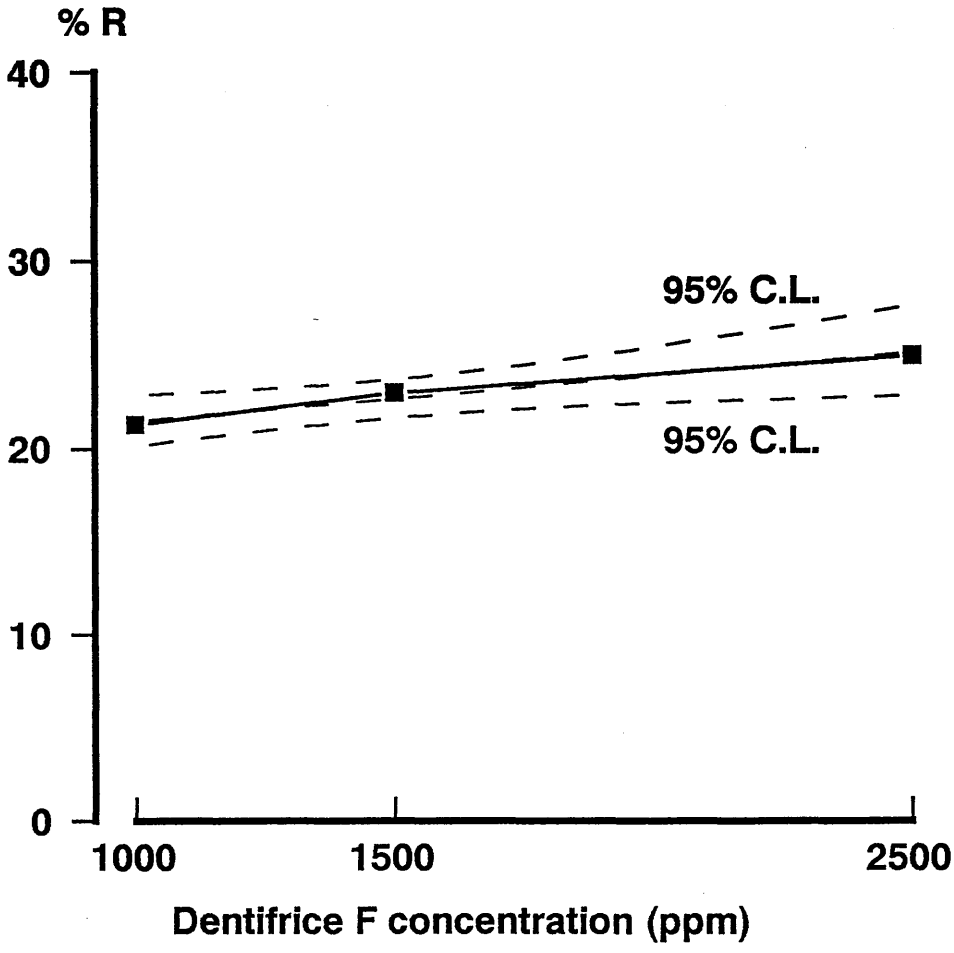


Figure 4.36 The percentage of surfaces which 'Reversed' (R), versus dentifrice fluoride concentration for zinc and non-zinc agents combined. Data for surfaces with a baseline radiographic score of '0'.
The central dotted line is the 'best fit' line. 95 % C.L. = 95 % Confidence Limits.

CHAPTER 5 DISCUSSION and CONCLUSIONS

5.1 Statistical methods and assumptions

In this thesis, two statistical methods were employed. k x n Chi-square tests were used for looking at differences between distributions (e.g. between males and females) or, in the case of a 1 x n tests, to test the hypothesis that one (or more) of the cells was significantly different from the others (eg site distributions). This is a non-parametric test, thus no assumptions have to be made regarding the normality of the data distribution. Although it proved to be useful in most circumstances, there were, however, occasional instances where the limitations of the test restricted its use. For example, it could not be used to test the differences between left- and right-handed subjects for individual agents, as some cells contained less than five elements. As such, there would be a distinct risk of a false-positive result. The usual method of overcoming this problem is to combine cells, but this may not always make physical sense. Furthermore, the statistical power of the Chi-square test cannot be established as there is no parametric equivalent (Siegel, 1956; Kirkwood, 1988).

To test the effect which various parameters had on the fluoride dose-response (Section 4.6), Generalised Linear Interactive Modelling (GLIM) was employed. This technique has been used in several medical (Murrells *et al.*, 1985; Machin *et al.*, 1986; Green *et al.*, 1988; Jenkinson *et al.*,

1988), and dental (Wallenstein, Fleiss & Chilton, 1981; Huntington, 1985) studies.

As the data in this study was in the form of counted proportions, a logit transformation was used to transform the data to the real line between minus and plus infinity. However, there is no theoretical reason why a logit link should produce a simple linear model for a set of counted proportions, though in practice it often seems to do so. Probit (or NED - nominal equivalent deviate) could be used instead. Fitted values with probit and logit links applied to the same data are almost identical. Very rarely is it necessary (or possible) to choose between the two (Healy, 1988). Logit has the advantage that it is easier to calculate, although with modern computing methods this advantage is reduced.

GLIM is a very flexible modelling tool, but it must be used with caution as several factors have to be considered :-

1. There is the usual problem associated with regression analysis, namely that a significant result does not necessarily imply a relation between the variables. They may only be correlated.
2. Even though a significant fit / model is obtained, this does not necessarily imply that the model is the best available. Where no theoretical relationship is known, the choice of model is empirical and it is usual to investigate the simplest case. In this thesis a linear

model was used, and significant results obtained in some cases. No attempt was made to investigate multiplicative models.

3. Another problem which can arise with GLIM occurs when data are derived from counts or proportions of very large samples. Here, extremely small deviations from the model can be detected, but often so small as to be of no practical importance although they do produce statistically significant results (Evans, 1988). The difference between clinical and statistical significance is further complicated by the fact that a small change may not be clinically significant for an individual, but may still be important on a population basis. This would certainly apply to the results presented in this thesis.
4. It is generally advantageous to have a model with as few parameters as possible. A model with the same number of parameters as data-points, does not reduce complexity. Also, if by the addition of extra parameters, a model fits the data too well, then the scope of the model will be reduced such that, when it is applied to other data, it will not be able to encompass the necessary changes (McCullagh & Nelder, 1983).
5. The level of significance is obtained by equating the differences in scaled deviance with X^2. This is not valid when the numbers are low. However, theory does not give a lower limit of validity (Armitage & Berry, 1987; Healy, 1988), and this was certainly a problem

when analysing data for those surfaces which had an initial radiographic score of '3'.

6. The effect of unmeasured variables is unpredictable, and their absence can lead to wholly incorrect conclusions with regard to the effect of the measured variables (Evans, 1988).

The major assumption made in the use of these statistical methods was that each surface is an independent variable. It could be argued that a subject's mouth is the true independent variable and that surfaces in a given mouth are not independent. However, there are several points which support this assumption:-

1. If the mouth is the true independent variable, then it might be assumed that adjacent interproximal surfaces, sharing the same environment, should behave similarly. However, in Section 4.2, it was shown that for those surfaces which had a classification of P, R, S or B, only 10.3 % of adjacent surfaces (in the same mouth) had identical radiographic combinations. Although this analysis did not take into account different eruption times, it does show there is no strong dependence between adjacent sites.
2. Weatherell *et al.* (1988), have shown there are large variations in fluoride concentrations within the oral cavity following a mouthrinse. For example, the concentration was higher in the upper anterior sulcus than in the lower anterior sulcus, and in the lower jaw, the posterior levels were higher than the anterior

levels. They explained this site difference by variations in salivary turnover, and the distance from the parotid duct orifices. Similar site-specific differences were also found for glucose (Weatherell *et al.*, 1989), and these workers stated that such differences vary from individual to individual (Weatherell *et al.*, 1986).

3. Creanor, Strang & Stephen (1989) found there was a significant difference in the extent of mineral loss in artificially created lesions at different parts of the same enamel surface. Here, cervical lesions had lower mineral loss than incisal lesions. On the other hand, ten Cate *et al.* (1988), found the opposite. In addition, Weatherell, Robinson & Hallsworth (1972); Weatherell, Hallsworth & Robinson (1973), and Athanassouli *et al.* (1988) have shown that the fluoride distribution from the incisal to the cervical region varies, not only from one surface to another, but also with age. Thus, these studies demonstrate there are variations, even within a single tooth, to de- and remineralisation processes.
4. In Section 4.3, it was shown there were significant differences between sites in the proportion of surfaces which 'Progressed', 'Reversed', remained 'Stable' or were 'Borderline'.

Hence, strictly speaking, while the mouth is the true independent variable, the above points indicate there are many variations within an individual's mouth and that treating the surface as the independent variable is

acceptable. This assumption has also been made by others studying longitudinal changes in individual surfaces e.g. Haugejorden & Slack (1975), and Zamir *et al.* (1976).

The final point which should be remembered regarding the use of statistics, is that there is always a danger when many tests are being undertaken, of a false-positive result occurring by chance. If the 95% level of probability is taken as a measure of significance, there is a 5 % chance of a false-positive outcome. As the number of tests performed increases, so the probability of a false result rises. For example, if tests are undertaken on 20 sets of data which are truly the same, then the probability that none of the twenty tests will be significant is 0.95^{20} i.e. 0.36. Thus the probability of at least one significant result occuring in these truly non-different sets of data, is [1 - 0.36], i.e. 0.64 (Bland, 1987).

5.2 Errors

The validity of the results of the studies presented in this thesis are dependent upon the accuracy of the data. In Chapter 1, the errors associated with bitewing radiography were discussed. However, the inter- and intra-examiner reliability coefficients for the trial data were all above 0.92 (Stephen *et al.*, 1988).

The results are also dependent on the categorisation of the radiographic combinations into surfaces which

'Progressed, 'Reversed', remained 'Stable' or were 'Borderline'. Although this task was performed by a clinician with considerable experience of bitewing radiographic interpretation, it must be obviously subjective. To try and minimise this subjectiveness, it was decided that certain X-ray sets should be re-read longitudinally. In addition to those surfaces which had originally been awarded individual scores that resulted in an 'illogical' combination, some surfaces were also re-read to confirm the subjective classifications e.g. the classification of the combination '0220' as a 'Reversal'. The results of re-reading 671 such combinations were presented in Chapter 3, and no 'illogical' combinations were obtained. This result would suggest that reading X-rays longitudinally is more accurate than the original cross-sectional method employed. However, two factors must also be considered. Firstly, a different examiner re-read the radiographs, and secondly, the lack of 'illogical' results does not necessarily imply greater accuracy. Haugejordan (1974), in a large study into the effect of different reading methods on bitewing radiographic scoring, found the two methods had only minor effects on DFS and DMFS experience and incidence. Nevertheless, as discussed in Section 3.2.3, the assumptions regarding the classification of combinations must still be treated with caution due to possible errors arising from such factors as beam angulation (Section 1.4.2). Hence the conclusions stated in this thesis might also be regarded cautiously.

There are two other sources of error which may affect the

results presented. Teeth extracted during the trial were excluded from the analysis. Although, the reason for extraction could be established accurately in some circumstances, e.g. as a result of trauma, or for orthodontic purposes, it was not possible to distinguish whether teeth extracted for caries were lost due to caries on the occlusal, smooth or interproximal surfaces. While further information may have been obtained from preceding X-rays, this would have required additional re-reading (again supporting longitudinal perusal), or by considering previous radiographic scores. However, occlusal caries was only scored radiographically at Examination 3 (Creanor *et al.*, 1990), and smooth surface caries cannot be accurately assessed by radiography alone. Thus, it was decided this aspect could not be pursued further. As a result, the exclusion of all teeth deemed as 'extracted due to caries' gave an underestimation of the proportion in which caries progressed.

The other possible source of error, was the inclusion of data from teeth erupting during the period of the clinical trial. The number of surfaces erupting between the different examinations, for the different dentifrices, was shown in Table 4.5. A total of 6360 surfaces erupted during the trial, with 3836, 1872 and 652 surfaces erupting between Examinations 1 & 2, 2 & 3 and 3 & 4 respectively. This compares with 43795 surfaces included in the analysis (Table 4.4). Not surprisingly, the erupting surfaces were significantly biased towards those

which remained radiographically sound, with the proportion varying between 94 and 99 %, as compared to approximately 79 % in the main data.

When analysed by toothpaste group, it was shown that for surfaces remaining radiographically caries-free, there was a significant fluoride dose-response for surfaces erupting between Examinations 2 & 3, and an almost significant response for those erupting between Examinations 1 & 2. Obviously, the few surfaces which erupted between Examinations 3 & 4 were not subjected to the oral environment, nor the effects of the dentifrices, for a sufficient period of time to produce significant data.

Although, in retrospect, it may have been advisable to have excluded teeth erupting during the trial from the analysis, the numbers involved are relatively small (14.5 %). While their inclusion resulted in a bias towards surfaces which remained sound, a fluoride dose-response was still obtained for the main data. In addition, ignoring the surfaces which remained sound, there was, as a result of the reduced exposure time, a bias towards lesions which 'Progressed'. To some extent, this would compensate for the underestimation of the proportion of 'Progressive' surfaces arising from the exclusion of extracted teeth.

5.3 Results

5.3.1 Site Variation and Handedness

In view of the work reported by Weatherell *et al.* (1988), regarding oral site-specific variations in fluoride distribution, it is perhaps not surprising that no consistent differences were found in this study, between quadrants in right- and left-handed brushers.

5.3.2 Fluoride dose-response

Here, the results of the combined zinc and non-zinc pastes will be discussed. In Section 4.6.1, it was shown there was a significant decrease in the proportion of surfaces where lesions 'Progressed' as the dentifrice fluoride concentration increased. There was a corresponding increase in the number of 'Reversals', although the trend just failed to achieve significance. However, this analysis, i.e. the calculation of the proportion of 'Progressives' etc, ignored those surfaces which remained radiographically sound throughout the trial. Because of this, it was mathematically possible that the proportion of surfaces which 'Progressed', calculated in the manner above, decreased, while the total number of 'Progressive' surfaces actually increased. This would only occur if the number of surfaces which remained sound decreased, with increasing dentifrice fluoride concentration. However, analysis of those surfaces which did remain radiographically sound, also gave a significant fluoride dose-response, showing that the proportion of sound surfaces increased

with increasing fluoride. Therefore, it can be concluded that increasing the fluoride concentration of MFP dentifrices from 1000 ppm F to 2500 ppm F, results in significantly more surfaces remaining sound, and fewer lesions progressing.

This outcome is in agreement with the analysis of the combined clinical and radiographical DMFS values from the clinical trial (Stephen *et al.*, 1988). These authors reported that the mean (S.D.) DMFS decreased from 6.8 (6.22) for the 1000 ppm F paste, to 6.33 (5.72) for the 1500 ppm F paste, to 5.71 (5.6) for the 2500 ppm F paste. Results of other studies looking at a fluoride dose-response have been reviewed recently by Mellberg (1990) and have been summarised in Table 1.3.

5.3.3 Effect of 0.5 % (w/w) zinc citrate

Zinc salts have been known to have an anti-plaque and anti-calculus action (Saxton, Harrap & Lloyd, 1986; Stephen *et al.*, 1987). However, Mellberg & Chomicki (1983) reported that zinc inhibited the remineralising capability of fluoride *in vitro*. In addition, White & Faller (1987) suggested that the presence of zinc reduced the uptake of sodium monofluorophosphate into demineralised enamel.

In Section 4.5 it was shown that the addition of 0.5 % (w/w) zinc citrate to the dentifrice significantly changed the proportion of lesions which 'Progressed', 'Reversed', remained 'Stable', or were 'Borderline' for the 1500 ppm F

paste, but not for the other two dentifrices. The only differences between Agents 3 and 4 were in the proportions of 'Reversals' and 'Stables'. For the proportion of lesions which remained 'zero', there was no difference between the two 1000 ppm F pastes. However, for the higher fluoride agents, there were significant differences. At 1500 ppm F, the non-zinc paste had a lower percentage of lesions which remained sound, whereas for the 2500 ppm F paste, the situation was reversed with the zinc-containing paste having the lower number.

In Section 4.6.1, it was shown that a significant fluoride dose-response was noted for the proportion of lesions which 'Progressed', for the zinc citrate-containing pastes (Agents 2, 4 & 6) but not for the non-zinc pastes (Agents 1, 3 & 5). In addition, a significant fluoride dose-response was obtained for the proportion of lesions which remained radiographically sound, for both non-zinc and zinc-containing pastes. The difference in the fluoride dose-response for the proportion of lesions which 'Progressed' between the two groups of agents is not great, despite one being significant. The figures in Table 4.11 show, for the non-zinc paste, 64.6 % at 1000 ppm F, falling to 62.5 % at 1500ppm and 61.0 % at 2500 ppm. The corresponding values for the zinc-containing pastes were 66.5 %, 63.2 % and 60.1 %. Although, there were no significant differences in the proportions of the two 1000 ppm agents, the higher 1000 ppm level for the zinc-containing paste (66.5 %) may have enabled the

fluoride dose-response to be significant. Combining both sets of data also showed a significant dose-response.

It is therefore concluded that the addition of 0.5 % (w/w) zinc citrate to the dentifrice had no major effect on the anti-caries activity of the dentifrice. This supports the finding reported on the combined clinical and radiographic data from this trial (Stephen *et al.*, 1987a,c, 1988) and is in conflict with earlier suggestions that zinc had an inhibitory effect.

5.3.4 Effect of sex

Males were found to have a significantly higher proportion of lesions which 'Progressed' than females, in both the 1500 and 2500 ppm F groups. This was also true when all pastes were combined. In addition, the proportion of 'Progressive' lesions decreased significantly with increasing dentifrice concentration for females, but not for males. At first inspection, this consistent advantage for females was contradicted by the significant increase in the proportion of 'Reversals' for males but not for females. However, when the data for both 'Reversals' and 'Stables' were combined, there was a significant fluoride dose-response in females [X^2 (GLIM) = 9.66, d.f. = 1, $p < 0.01$], but not in males ($X^2 = 0.76$). For the proportion of lesions which remained radiographically sound, a significant increase, with increasing fluoride concentration, was found for males, but not for females. Nonetheless, it should be noted that the percentage of

sound lesions, for males, in the highest fluoride group (40.8 %), was still lower than the value (41.4 %) for females in the lowest fluoride group. This overall result, that girls of this age-group show a better response than boys from dentifrice usage, is in agreement with that obtained by Hodge *et al.* (1980).

The conclusion from this study was that females in the Lanarkshire region of Scotland have better oral habits than males, a finding also obtained from mean DMFS results calculated from combined clinical and radiographic data (Stephen *et al.*, 1988). In addition, girls showed the fluoride dose-response more clearly. Backer-Dirks (1961) found that boys had more proximal lesions involving dentine, but fewer total lesions between the ages of 12.5 and 15 years. In 1966, he reported that boys had 10 % more proximal lesions and 35 % more buccal cavities than girls (Backer-Dirks, 1966). Conversely, several epidemiological studies have shown a consistent, but small, increase in caries experience in permanent teeth of females, as compared to males of the same age (Todd & Whitworth, 1974; Brunelle & Carlos, 1982; Nikiforuk, 1985). This has usually been explained by the earlier eruption of permanent teeth in girls (Carlos & Gittelsohn, 1965), but this hypothesis has been challenged (Sloman, 1941; Backer-Dirks, 1961). Sloman (1940) and Hodge *et al.* (1980) stated that the oral habits of girls were superior to those of boys.

5.3.5 Effect of initial radiographic score on fluoride dose-response

In Section 4.6.3, it was shown there was a significant fluoride dose-response in surfaces which had a baseline score of'zero'. This was true for both the proportion of surfaces which 'Progressed' and 'Reversed'. It was also shown (Section 4.6.1) that the proportion of surfaces which remained sound throughout the period of the trial had a significant dose-response. However, no significant dose-responses were found from lesions with a baseline score of'2' or '3', although the numbers of lesions with an initial score of '3' were too small to allow statistical evaluation.

Haugejorden & Slack (1975) also analysed changes in interproximal radiographic scores in terms of initial lesion size. They reported that over a one year period, two out of 73 lesions initially penetrating less than half the enamel became apparently sound. For lesions penetrating more than half-way into enamel, but not involving the amelo-dentinal junction, three out of 27 lesions reversed. In addition, two out of 22 surfaces initially involving dentine also were reported to have reversed, but no analysis in terms of preventive measures was mentioned.

It is generally accepted that a large proportion of lesions with a radiographic score of '3', i.e. a radiolucency in enamel and dentine not involving the pulp,

will have surface breakdown (Mileman, Purdell-Lewis & van der Weele, 1983). Thus it is not surprising that a fluoride dose-response was not apparent, as it is also accepted that fluoride is of little use in such circumstances. What is slightly surprising is that remineralisation was recorded in 66 lesions which had a baseline value of '3'. However, it should be remembered in 38 of these lesions, that the radiographic combination was '3000' and it was assumed that the initial score of '3' should probably have been accorded a '2'. Nevertheless, there were several confirmed 'Reversals' from those surfaces which were re-read. Presumably these were non-cavitated lesions.

It is well established that radiographs underestimate lesion depth (Gwinnett, 1971; Bille & Thylstrup, 1982; Kidd, 1983), thus lesions with a radiographic score of '2' are relatively large compared to the early white spot lesion normally associated with remineralisation, which is not visible on bitewing radiographs (Kidd, 1984). Therefore a proportion of surfaces, initially scored as 'sound' will, in fact, have demineralised enamel. Hence it is not surprising that the reported dose-response was indeed observed.

5.3.6 GLIM Models

In the GLIM models, fluoride was always the most important predictive parameter, zinc having no such effect. The addition of sex (Figures 4.28 - 4.30) also had a

significant effect for 'Progressives', 'Reversals' and '0000's. For the 'Progressives', there was also a significant interactive effect between fluoride and sex. However, no information on the nature of this interaction is available.

5.4 Other similar studies

Several studies have been published on longitudinal changes in interproximal surfaces using bitewing radiographs. Backer-Dirks (1966) reported on alterations occuring over an eight year period, in the mesial surfaces of upper and lower first permanent molars of 100 children. He was surprised by the large numbers of lesions which did not progress, 26 % over the eight year span. He also mentioned that 37 out of 72 clinically diagnosed white spot lesions on buccal surfaces of upper first molars became sound over that time. Interestingly, as early as 1966,Backer-Dirks attributed these changes to remineralisation, and not to examiner error.

In 1975, Haugejorden & Slack (1975) published results of a study to determine the value of a bitewing radiograph scoring system. The changes over a 12 month period in 122 carious interproximal surfaces of 40 subjects were described. Approximately 24 % of the lesions progressed over the year, 56 % remained unchanged, 7 % reversed and 13 % had been restored. However, ten years after Backer-Dirks' (1966) paper, these authors attributed the 'reversal' of their nine surfaces to both examiner error

and remineralisation effects, with no preventive measures being mentioned.

Zamir *et al.* (1976) studied 96 approximal carious lesions in 51 patients, each having had six bitewing radiographs taken over a four year period. They found that (a) 12 % of the lesions had not changed after 36 months, (b) less than 20 % had reached dentine after 24 months, and (c) the average rate of spread of the lesion from the tooth surface to the amelo-dentinal junction was 26.4 months for 14 - 15 year olds, and 32.3 months for 21 - 24 year olds. No mention was made of lesions which reversed, or of any preventive measures taken by the patients.

The changes in individual proximal surfaces in 204 children, three and six years after ceasing school-based preventive dental treatment, were investigated by Grondahl *et al.* (1977b) and by Grondahl & Hollander (1979). Lesions were assessed using bitewing radiographs and classified on a 12 point scale (Grondahl *et al.*, 1977a). They found that intact surfaces, and those with small lesions, were more resistant to changes than others and, generally, the progress of caries was slow. Again no mention was made of any lesion remineralising. In a later study, Shwartz *et al.*, (1984) found similar results for the progression rates in Swedish and American children.

Pitts (1983) reviewed 19 radiographic studies of approximal lesion progression. Most showed that progression was slow and emphasised the need for longer trials and more longitudinal studies to allow 'the evolution of rational decision strategies for the timing of restorative intervention'.

Finally, Bjarnason, Finnbogason & Kluppel (1989) compared the effect of two sodium fluoride dentifrices (250 & 1000 ppm F) on the fate of enamel lesions over a three year period. They noted no significant differences in the

proportion of lesions which remained unchanged or progressed. This finding is in agreement with results of the present study which found a fluoride dose-response was only apparent for surfaces which were initially rated as radiographically 'sound'. Hence it would seem, at least in countries / communities where fluoride is generally available via dentifrice etc, that radiographic (or equivalent) techniques will assume greater importance in the caries clinical trials of the future.

5.5 Future Studies

Although the classification into different X-ray lesion groups used in this thesis was, of necessity, subjective, the methods employed proved to be useful and provided information on the fate of individual tooth surfaces. An alternative approach, might have been to consider the radiographic changes for individual surfaces, on a year-to-year basis, e.g. the combination '0200' (a 'Reversal' overall) would have then been considered as consisting of '02' (a 'Progressive'); '20' (a 'Reversal') and '00' (a 'Stable'). Although, this may have assisted the removal of the subjective nature of the overall classifications, it is highly likely that, unless the bitewings had also been read longitudinally and previous errors corrected, an increased level of 'noise' would have resulted from such annual sub-divisions.

Further radiographic-based analyses which could be carried out with this data, would be to consider the

effects of such factors as oral hygiene and brushing frequency (which were collected during the trial field-work) on the fluoride dose-response.

APPENDIX 1: Classification of radiographic surface codes and numbers in each dentifrice group (before re-reading - See Section 3.2.4, p55). (P - Progression, R - Reversal, S - Stable B - Borderline, */** - combinations re-read).

CODES	CLASS	Dentifrice 1	2	3	4	5	6	TOTAL
0002	P	183	183	182	164	57	58	827
0003	P	29	31	24	25	10	8	127
0004	P	2	0	4	3	0	3	12
0005	P	27	34	35	33	17	19	165
0020	R	122	136	132	144	59	75	668
0022	P	158	160	147	137	61	69	732
0023	P	26	32	17	18	7	11	111
0025	P	13	7	10	8	1	7	46
0030	*	17	21	17	17	11	7	90
0032	P	5	4	7	7	2	4	29
0033	P	21	23	14	14	12	8	92
0034	P	0	0	2	0	0	0	2
0035	P	10	6	11	5	0	10	42
0040	*	2	0	0	0	0	0	2
0043	P	1	0	0	0	0	0	1
0044	P	2	0	2	1	0	0	5
0050	*	8	7	6	8	3	7	39
0052	*	2	1	0	0	1	0	4
0053	*	0	1	0	0	0	0	1
0055	P	31	54	38	30	31	19	203
0200	R	64	66	56	41	30	37	294
0202	B	21	23	24	20	8	14	110
0203	*	6	3	8	1	4	2	24
0204	P	1	0	0	0	0	0	1
0205	P	6	2	5	2	0	0	15
0220	**(R)	39	25	40	37	22	28	191
0222	P	108	110	95	83	31	49	476
0223	P	17	16	20	10	6	9	78
0225	P	11	10	8	11	2	1	43
0230	*	4	4	5	4	4	0	21
0232	S	11	6	7	4	9	4	41
0233	P	23	20	24	19	10	7	103
0234	P	0	0	0	0	1	0	1
0235	P	9	11	7	9	1	5	42
0245	P	0	0	1	0	0	0	1
0250	*	1	0	1	2	0	0	4
0252	*	0	1	1	0	0	0	2
0255	P	26	25	16	11	6	10	94
0300	*	7	10	7	8	1	6	39
0302	S	0	1	1	1	0	0	3
0303	*	2	0	2	1	1	0	6
0304	*	0	0	0	1	0	0	1

APPENDIX 1: (continued)

CODES	CLASS	Dentifrice 1	2	3	4	5	6	TOTAL
0305	*	5	2	0	1	0	0	8
0320	*	2	0	0	1	0	1	4
0322	P	2	3	2	0	1	3	11
0323	P	1	1	2	1	0	2	7
0325	P	0	0	0	1	0	0	1
0330	*	2	3	5	2	2	3	17
0332	P	1	0	1	1	1	2	6
0333	P	10	8	15	10	3	9	55
0335	P	10	3	1	3	2	2	21
0343	P	0	0	0	0	1	0	1
0344	P	1	0	1	0	0	0	2
0350	*	2	0	0	0	0	0	2
0353	P	0	0	1	0	0	0	1
0355	P	11	10	11	5	4	4	45
0404	*	0	0	0	3	0	0	3
0433	P	0	0	0	1	0	0	1
0443	P	0	0	0	1	0	0	1
0444	P	0	2	1	1	1	0	5
0500	*	4	0	1	0	0	0	5
0502	*	1	0	0	0	0	0	1
0505	*	3	4	4	7	0	0	18
0522	*	3	1	0	0	0	0	4
0534	P	0	1	0	0	0	0	1
0550	*	2	1	0	0	0	0	3
0552	*	0	0	1	0	1	0	2
0555	P	35	46	38	39	6	27	191
2000	R	27	25	29	25	10	9	125
2002	B	2	5	3	5	1	3	19
2003	*	2	5	1	0	0	1	9
2005	*	0	1	1	2	0	0	4
2020	B	8	4	9	9	3	3	36
2022	S	7	4	16	7	3	5	42
2023	S	2	2	1	0	1	1	7
2025	P	2	1	1	0	0	1	5
2030	*	3	2	2	0	0	0	7
2032	S	1	3	2	0	0	0	6
2033	P	1	3	4	1	0	2	11
2035	P	0	3	1	4	0	0	8
2050	*	0	0	1	0	0	0	1
2052	*	0	0	0	1	0	0	1
2053	P	0	0	0	0	1	0	1
2055	P	3	0	2	2	0	3	10

APPENDIX 1: (continued)

CODES	CLASS	Dentifrice 1	2	3	4	5	6	TOTAL
2200	R	11	10	22	14	8	3	68
2202	S	16	11	10	10	6	5	58
2203	S	1	1	2	2	0	1	7
2205	P	1	0	1	2	2	0	6
2220	R	20	14	15	18	7	9	83
2222	S	62	63	104	52	24	25	330
2223	P	13	11	11	10	7	4	56
2225	P	8	6	14	9	3	4	44
2230	*	0	3	6	4	2	1	16
2232	**(R)	12	10	10	13	6	5	56
2233	P	19	19	26	20	2	9	95
2234	P	0	0	1	0	0	0	1
2235	P	17	7	8	15	3	4	54
2250	*	0	0	0	1	0	0	1
2255	P	20	16	15	9	3	4	67
2303	*	1	0	0	1	0	0	2
2305	*	0	1	0	1	0	0	2
2320	R	2	0	0	2	0	1	5
2322	**	5	5	5	3	0	2	20
2323	S	4	3	4	1	1	1	14
2325	P	0	0	4	0	0	1	5
2330	R	0	1	0	0	0	0	1
2332	**(R)	7	2	5	1	3	1	19
2333	P	22	24	23	10	11	9	99
2334	P	2	0	0	1	0	0	3
2335	P	14	5	14	11	5	5	54
2350	*	0	0	1	0	1	0	2
2352	*	1	0	0	0	0	0	1
2355	P	17	18	18	5	8	9	75
2433	S	1	0	0	0	0	0	1
2505	*	0	0	1	0	0	0	1
2522	*	0	0	0	1	0	1	2
2550	*	0	1	0	0	0	0	1
2552	*	0	0	0	1	0	0	1
2553	S	1	0	1	0	0	0	2
2555	P	25	26	44	25	11	16	147
3000	R	6	6	9	11	2	4	38
3002	*	0	0	1	0	2	0	3
3003	*	2	1	2	0	0	1	6
3005	*	0	1	0	0	0	0	1
3020	B	0	3	0	0	0	0	3
3022	S	1	0	1	1	1	0	4
3023	S	0	2	0	0	0	0	2
3025	*	0	1	0	0	0	0	1
3030	*	1	1	1	2	1	0	6

APPENDIX 1: (continued)

CODES	CLASS	Dentifrice 1	2	3	4	5	6	TOTAL
3032	S	0	0	2	1	0	0	3
3033	S	3	2	1	0	1	1	8
3034	P	1	0	0	0	0	0	1
3035	P	2	1	0	0	0	0	3
3053	*	0	1	0	0	0	0	1
3055	P	3	1	2	3	1	1	11
3200	R	1	0	0	2	0	1	4
3203	*	1	0	0	0	0	0	1
3205	P	0	0	0	0	1	0	1
3220	R	2	1	1	0	0	0	4
3222	S	2	2	3	0	0	1	8
3223	S	0	0	1	1	0	1	3
3225	P	0	1	0	0	0	0	1
3230	*	0	0	0	0	0	1	1
3232	S	0	1	1	2	0	1	5
3233	S	2	3	3	0	2	1	11
3235	P	1	0	0	4	1	0	6
3253	S	0	0	0	0	1	0	1
3255	P	1	4	3	0	0	2	10
3300	R	2	2	0	1	2	0	7
3303	*	1	1	1	1	1	0	5
3305	P	3	2	1	3	0	2	11
3320	R	0	0	0	1	0	0	1
3322	**(R)	0	1	0	1	0	0	2
3323	S	0	0	0	0	1	1	2
3330	*	1	2	4	1	0	1	9
3332	**	0	1	0	1	3	0	5
3333	S	10	16	11	8	5	6	56
3334	P	0	2	0	1	0	0	3
3335	S	10	2	10	7	2	5	36
3343	S	0	1	0	0	0	0	1
3344	P	1	0	0	2	0	0	3
3350	*	0	2	0	0	0	0	2
3353	S	1	0	0	0	0	0	1
3355	S	14	18	17	12	8	1	70
3404	P	0	0	0	1	0	0	1
3420	*	0	0	1	0	0	0	1
3430	*	1	0	0	0	0	0	1
3444	P	2	2	1	1	0	0	6
3455	P	0	0	0	0	1	0	1
3505	*	0	1	2	3	2	1	9
3530	*	0	1	0	0	0	0	1
3535	S	0	0	0	0	1	0	1
3550	*	0	0	1	0	0	0	1
3555	S	31	26	25	30	13	20	145

APPENDIX 2: The number of surfaces in each radiographic category P, R, S and B for each surface and each agent.
(P - Progression, R - Reversal, S - Stable
B - Borderline).

(a) Agent 1 (1000 ppm F)

Surface	Number of surfaces P	R	S	B	Total
UR7M	26	11	0	1	38
UR6M	61	28	23	4	116
UR6D	37	14	1	2	54
UR5M	51	19	11	0	81
UR5D	79	17	16	1	113
UR4M	20	4	1	0	25
UR4D	43	20	10	1	74
UL4M	16	7	1	0	24
UL4D	52	11	4	2	69
UL5M	42	14	12	1	69
UL5D	81	12	11	1	105
UL6M	56	28	27	5	116
UL6D	50	14	4	1	69
UL7M	27	9	1	0	37
Total	641	208	122	19	990
LR7M	53	9	6	4	72
LR6M	40	17	13	4	74
LR6D	57	11	11	2	81
LR5M	20	7	2	3	32
LR5D	60	12	10	1	83
LR4M	8	7	0	0	15
LR4D	16	9	3	2	30
LL4M	6	14	0	0	20
LL4D	23	7	4	1	35
LL5M	20	14	6	1	41
LL5D	64	13	6	2	85
LL6M	32	10	13	1	56
LL6D	57	11	10	1	79
LL7M	40	18	6	2	66
Total	496	159	90	24	769
Grand Total	1137	367	212	43	1759

APPENDIX 2: (continued)

(b) Agent 2 (1000 ppm F + zinc citrate)

Surface	Number of surfaces P	R	S	B	Total
UR7M	25	6	0	1	32
UR6M	46	28	20	6	100
UR6D	44	20	6	0	70
UR5M	38	18	9	0	65
UR5D	59	13	9	5	86
UR4M	13	9	0	1	23
UR4D	55	8	5	1	69
UL4M	11	6	2	0	19
UL4D	50	18	4	1	73
UL5M	51	9	10	1	71
UL5D	77	15	3	3	98
UL6M	73	24	11	6	114
UL6D	57	10	2	2	71
UL7M	29	10	0	1	40
Total	628	194	81	28	931
LR7M	42	15	6	0	63
LR6M	50	17	8	3	78
LR6D	70	8	8	0	86
LR5M	28	13	9	2	52
LR5D	65	12	9	4	90
LR4M	2	4	0	1	7
LR4D	23	10	4	3	40
LL4M	5	1	1	1	8
LL4D	19	6	2	0	27
LL5M	23	11	6	0	40
LL5D	58	17	12	1	88
LL6M	37	27	17	3	84
LL6D	58	9	12	1	80
LL7M	43	10	1	3	57
Total	523	160	95	22	800
Grand Total	1151	354	176	50	1731

APPENDIX 2: (continued)

(c) Agent 3 (1500 ppm F)

Surface	Number of surfaces P	R	S	B	Total
UR7M	19	12	0	1	32
UR6M	57	29	22	4	112
UR6D	44	14	4	2	64
UR5M	40	20	7	1	68
UR5D	71	14	12	2	99
UR4M	16	8	0	0	24
UR4D	50	10	9	2	71
UL4M	14	4	2	0	20
UL4D	40	7	11	0	58
UL5M	39	7	10	1	57
UL5D	67	16	13	2	98
UL6M	48	35	27	6	116
UL6D	43	12	11	1	67
UL7M	18	8	2	3	31
Total	566	196	130	25	917
LR7M	49	18	16	4	87
LR6M	41	20	13	5	79
LR6D	60	10	7	5	82
LR5M	21	13	9	1	44
LR5D	70	10	5	1	86
LR4M	4	2	0	0	6
LR4D	18	5	6	0	29
LL4M	4	9	0	1	14
LL4D	18	13	0	1	32
LL5M	18	15	5	2	40
LL5D	58	16	16	1	91
LL6M	43	19	16	0	78
LL6D	69	12	4	2	87
LL7M	44	11	7	0	62
Total	517	173	104	23	817
Grand Total	1083	369	234	48	1734

APPENDIX 2: (continued)

(d) Agent 4 (1500 ppm F + zinc citrate)

Surface	Number of surfaces P	R	S	B	Total
UR7M	27	5	1	0	33
UR6M	54	23	17	6	100
UR6D	41	13	1	0	55
UR5M	35	11	12	1	59
UR5D	60	20	4	2	86
UR4M	14	8	2	0	24
UR4D	34	6	10	2	52
UL4M	11	8	0	0	19
UL4D	46	10	2	2	60
UL5M	37	11	5	1	54
UL5D	52	24	9	3	88
UL6M	48	31	23	6	108
UL6D	41	15	4	2	62
UL7M	22	6	3	1	32
Total	522	191	93	26	832
LR7M	44	12	1	4	61
LR6M	37	12	11	2	62
LR6D	52	6	4	7	69
LR5M	15	12	5	0	32
LR5D	50	14	9	1	74
LR4M	5	2	1	1	9
LR4D	22	8	1	0	31
LL4M	4	3	1	0	8
LL4D	16	12	5	2	35
LL5M	22	12	3	2	39
LL5D	50	19	6	2	77
LL6M	36	21	8	2	67
LL6D	54	16	7	2	79
LL7M	47	16	3	3	69
Total	454	165	65	28	712
Grand Total	976	356	158	54	1544

APPENDIX 2: (continued)

(e) Agent 5 (2500 ppm F)

Surface	Number of surfaces P	R	S	B	Total
UR7M	9	2	0	0	11
UR6M	22	14	10	0	46
UR6D	15	4	2	0	21
UR5M	13	5	3	0	21
UR5D	22	2	4	1	29
UR4M	4	4	0	0	8
UR4D	14	2	5	0	21
UL4M	11	5	1	0	17
UL4D	19	4	5	1	29
UL5M	19	6	4	4	33
UL5D	26	6	6	1	39
UL6M	19	10	11	2	42
UL6D	16	6	5	1	28
UL7M	9	3	1	0	13
Total	218	73	57	10	358
LR7M	20	5	2	1	28
LR6M	13	11	4	0	28
LR6D	21	6	3	1	31
LR5M	12	2	2	0	16
LR5D	22	7	4	2	35
LR4M	2	3	0	0	5
LR4D	10	6	1	0	17
LL4M	2	4	0	1	7
LL4D	8	2	0	0	10
LL5M	11	4	3	0	18
LL5D	19	13	3	2	37
LL6M	14	8	5	1	28
LL6D	23	8	4	1	36
LL7M	18	3	1	1	23
Total	195	82	32	10	319
Grand Total	413	155	89	20	677

APPENDIX 2: (continued)

(f) Agent 6 (2500 ppm F + zinc citrate)

Surface	Number of surfaces P	R	S	B	Total
UR7M	10	4	0	1	15
UR6M	20	17	8	2	47
UR6D	22	6	2	1	31
UR5M	20	4	2	1	27
UR5D	20	7	6	3	36
UR4M	6	3	1	1	11
UR4D	19	2	5	3	29
UL4M	8	2	1	1	12
UL4D	28	8	7	1	44
UL5M	20	11	4	1	36
UL5D	27	11	8	0	46
UL6M	19	17	12	3	51
UL6D	14	7	4	4	29
UL7M	11	8	0	1	20
Total	244	107	60	23	434
LR7M	20	6	1	0	27
LR6M	20	15	5	0	40
LR6D	22	5	4	0	31
LR5M	14	6	0	0	20
LR5D	27	3	3	0	33
LR4M	2	1	1	0	4
LR4D	7	4	1	0	12
LL4M	2	1	0	0	3
LL4D	10	3	4	0	17
LL5M	14	1	1	2	18
LL5D	22	10	5	1	38
LL6M	14	7	4	3	28
LL6D	27	3	1	2	33
LL7M	16	6	4	3	29
Total	217	71	34	11	333
Grand Total	461	178	94	34	767

REFERENCES

AASENDEN, R., DePAOLA, P.F. & BRUDEVOLD, F. (1972) Effects of daily rinsing and ingestion of fluoride solutions upon dental caries and enamel fluoride. *Archives of Oral Biology*, 17, 1705 - 1714.

AINAMO, J. (1980) Relative rates of toothbrushing, sucrose consumption and fluorides in the maintenance of oral health in children. *International Dental Journal*, 30, 54 - 66.

AINAMO, J. & PARVIAINEN, K. (1979) Occurrence of plaque, gingivitis and caries as related to self-reported frequency of toothbrushing in fluoride areas in Finland. *Community Dentistry and Oral Epidemiology*, 7, 142 - 146.

ALANEN, P. & TIEKSO, J. (1986) Problems in caries surveys on children and adolescents in Finland. *Proceedings of the Finnish Dental Society*, 82, 254 - 259.

ANDERSON, P.G., WILLIAMS, C.H.M., HALDERSON, H., SUMMERFELDT, C. & AGNEW, R.G. (1934) The influence of vitamin D in the prevention of dental caries. *Journal of the American Dental Association*, 21, 1349 - 1366.

ANDLAW, G.J. & TUCKER, G.T. (1975) A dentifrice containing 0.8 per cent sodium monofluorophosphate in an aluminium oxide trihydrate base. A 3-year clinical trial. *British Dental Journal*, 138, 426 - 432.

ARMITAGE, P. & BERRY, G. (1987) Statistical methods in medical research. Oxford: Blackwell.

ARNOLD, F.A., LIKINS, R.C., RUSSELL, A.L. & SCOTT, D.B. (1962) Fifteenth year of the Grand Rapids fluoridation study. *Journal of the American Dental Assosciation*, 65, 780 - 785.

ASHLEY, F.P., MAINWARING, P.J., EMSLIE, R.D. & NAYLOR, M.W. (1977) Clinical testing of a mouthrinse and a dentifrice containing fluoride. A two-year supervised study in school children. *British Dental Journal*, 143, 333 - 338.

ATHANASSOULI, T., STRONG, M., PANAGOPOULOS, H. & WEATHERELL, J.A. (1988) Patterns of fluoride distribution on the surface of a tooth fragment after clinical treatment with fluoride gel. *Caries Research*, 22, 134 - 138.

AXELSSON, P., & LINDHE, J. (1974) The effect of a preventive programme on dental plaque, gingivitis and caries in schoolchildren. Results after one and two years.
Journal of Clinical Periodontology, 1, 126 - 138.

BACKER-DIRKS, O. (1961) Longitudinal dental caries study in children 9 - 15 years of age.
Archives of Oral Biology, 6, Special Suppl., 94 - 108.

BACKER-DIRKS, O. (1966) Posteruptive changes in dental enamel.
Journal of Dental Research, 45, Suppl. 3, 503 - 511.

BACKER-DIRKS, O. (1967) The relationship between fluoridation of water and dental caries experience.
International Dental Journal, 17, 582 - 605.

BACKER-DIRKS, O., AMERONGEN, van J. & WINKLER, K.C. (1951) A reproducible method for caries evaluation.
Journal of Dental Research, 30, 346 - 359.

BARLAGE, B., BUHE, H., & BUTTNER, W. (1981) A 3-year clinical dentifrice trial using different fluoride levels: 0.8 and 1.2 percent sodium monofluorophosphate.
Caries Research, 15, 185.

BARNHART, W.E., HILLER, K., LEONARD, G.J. & MICHAELS, S.E. (1974) Dentifrice usage and ingestion among four age groups.
Journal of Dental Research, 53, 1317 - 1322.

BARTHELD, F. von (1958) Decalcification in initial caries.
Tijdschrift voor Tandheelkunde, 65, 76 - 88.

BERENIE, J., RIPA, L.W. & LESKE, G. (1973) The relationship of frequency of toothbrushing, oral hygiene, gingival health and caries experience in schoolchildren.
Journal of Public Health Dentistry, 3, 160 - 171.

BERGMAN, G. & LINDEN, L. (1969) The action of the explorer on incipient caries.
Svensk Tandlakare Tidskrift, 62, 629 - 634.

BERMAN, D.S. & SLACK G.L. (1973) Caries progression and activity in approximal tooth surfaces - a longitudinal study.
British Dental Journal, 134, 51 - 57.

BIBBY, B.G., WILKINS, E. & WITOL, E. (1955) A preliminary study of the effects of fluoride lozenges and pills on dental caries.
Oral Surgery, 8, 213 - 216.

BILLE, J. & THYLSTRUP, A. (1982) Radiographic diagnosis and clinical tissue changes in relation to treatment of approximal carious lesions.
Caries Research, 16, 1 - 6.

BJARNASON, S., FINNBOGASON, S.Y. & KLUPPEL, H.J. (1989) Different fluoride levels in dentifrice and progression of proximal carious lesions.
Journal of Dental Research, 68, 982.

BJELKHAGEN, H., SUNDSTROM, F., ANGMAR-MANSSON, B., & RYDEN, H. (1982) Early detection of enamel caries by the luminescence excited by visible laser light.
Swedish Dental Journal, 6, 1 - 7.

BLAND, M. (1987) An introduction to medical statistics. Oxford: Oxford University Press.

BODECKER, H.W.C & BODECKER, C.F. (1912) The diagnosis of hidden caries by means of radiographs.
Dental Review, 26, 379 - 380.

BRINKMAN, J., BOSCH, J.J. ten. & BORSBOOM, P.C.F. (1988) Optical quantitation of natural caries in smooth surfaces of extracted teeth.
Caries Research, 22, 257 - 262.

BRUNELLE, J.A., & CARLOS, J.P. (1982) Changes in the prevalence of dental caries in US schoolchildren, 1961 - 1980.
Journal of Dental Research, 61, 1346 - 1351.

BUHE, H., BUTTNER, W. & BARLAGE, B. (1984) Three-year clinical tooth cream test with toothpastes of varying fluoride content: 0.8 and 1.2 sodium monofluorophosphate.
Quintessence, 35, 103 - 111.

CAHEN, P.M., FRANK, R.M., TURLOT, J.C., & JUNG, M.T (1982) Comparative unsupervised clinical trial on caries inhibition effect of monofluorophosphate and amine fluoride dentifrices after 3 years in Strasbourg, France.
Community Dentistry & Oral Epidemiology, 10, 238 - 241.

CARLOS, J.P., GITTELSOHN, A.M. (1965) Longitudinal studies of the natural history of caries - II. A life-table study of caries incidence in the permanent teeth.
Archives of Oral Biology, 10, 739 - 751.

CARLOS, J.P., GITTELSOHN, A.M. & HADDON, W. (1962) Caries in deciduous teeth in relation to maternal ingestion of fluoride.
Public Health Report, 77, 658 - 660.

CARLOS, J.P. & SENNING, R.S. (1968) Error and bias in dental clinical trials.
Journal of Dental Research, 47, 142 - 148.

CATE, J.M. ten. & ARENDS, J. (1977) Remineralisation of artificial enamel lesions *in vitro*.
Caries Research, 11, 277 - 286.

CATE, J.M. ten. & REMPT, H.E. (1986) Comparison of the *in vivo* effect of a 0 and 1500 ppmF MFP toothpaste on fluoride uptake, acid resistance and lesion remineralization.
Caries Research, 20, 193 - 201.

CATE, J.M. ten., TIMMER, K., SHARIATI, M. & FEATHERSTONE, J.D.B. (1988) Effect of timing of fluoride treatment on enamel de- and remineralization *in vitro*: a pH cycling study.
Caries Research, 22, 20 - 26.

CHURCHILL, H.V. (1931) Occurrence of fluorides in some waters of the United States.
Journal of Industrial and Engineering Chemistry, 23, 996 - 998.

COHEN, J. (1960) A coefficient of agreement for nominal scales.
Educational and Psychological Measurement, 20, 37 - 46.

COHEN, L. & HOLLIDAY, M. (1983) Statistics for Social Scientists.
London: Harper & Row.

CONTI, A.J., LOTZKAR, S., DALEY, R., CANCRO, L., MARKS, R.G. & McNEAL, D.R. (1988) A 3 year clinical trial to compare efficacy of dentifrices containing 1.14 % and 0.76 % sodium monofluorophosphate.
Community Dentistry & Oral Epidemiology, 16, 135 - 138.

CREANOR, S.L., RUSSELL, J.I., STRANG, D.M. & STEPHEN, K.W. (1989) Prevalence of clinically undetected occlusal dentine caries in Scottish adolescents.
Caries Research, 23, 446 - 447.

CREANOR, S.L., RUSSELL, J.I., STRANG, D.M. & STEPHEN, K.W. (1990) Prevalence of clinically undetected occlusal dentine caries in Scottish adolescents.
British Dental Journal, In press.

CREANOR, S.L. & STRANG, R. (1989) A quantitative assessment of early enamel lesion remineralisation from fluoridated dentifrices.
Dental Update, 16, 9 - 17.

CREANOR, S.L., STRANG, R. & STEPHEN, K.W. (1989) Demineralisation in acidifed gelatin at different sites on the same enamel surface.
Caries Research, 23, 345 - 347.

DAHLBERG, G. (1940) Statistical methods for medical and biological students. pp 122 - 132. London: Allan and Unwin.

DALE, J.W. (1969) Toothbrushing frequency and its relationship to dental caries and periodontal disease. *Australian Dental Journal*, 14, 120 - 123.

DAMATO, F.A., STRANG, R., & STEPHEN, K.W. (1988) Comparison of solution- and gel-prepared enamel lesions - an *in vitro* pH-cycling study. *Journal of Dental Research*, 67, 1122 - 1125.

DEAN, H.T. (1933) Distribution of mottled enamel in the United States. *Public Health Report*, Washington, 48, 704 - 734.

DEAN, H.T. (1934) Classification of mottled enamel diagnosis. *Journal of the American Dental Association*, 21, 1421 - 1426.

DEAN, H.T. (1936) Chronic endemic dental fluorosis (mottled enamel). *Journal of the American Dental Association*, 107, 1269 - 1272.

DEAN, H.T., ARNOLD, F.A. & ELVOVE, E. (1942) Domestic water and dental caries. V. Additional studies of the relation of fluoride domestic waters to dental caries experience in 4,425 white children aged 12 - 14 years of 13 cities in 4 States. *Public Health Report*, 57, 1155 - 1179.

DePAOLA, P.F. (1983) Clinical studies of monofluorophosphate dentifrices. *Caries Research*, 17, (Suppl. 1), 119 - 135.

DIODATI, R.R., TRIOL, C.W., KRANY, S.M., KORN, L.R. & VOLPE, A.R. (1986) Clinical anticaries efficacy of various fluoride dentifrices. *Journal of Dental Research*, 65, 198.

DOWNER, M.C. & O'MULLANE, D.M. (1975) A comparison of the concurrent validity of two epidemiologic diagnostic systems for caries evaluation. *Community Dentistry & Oral Epidemiology*, 3, 20 - 24.

DUCKWORTH, R. (1963) Fluoride dentifrices. *The Dental Practitioner and Dental Record*, 14, 93 - 101.

EKSTRAND, J., KOCH, G., & PETERSSON, L.G. (1983) Plasma fluoride concentrations in pre-school children after ingestion of fluoride tablets and toothpaste. *Caries Research*, 17, 379 - 384.

ELDERTON, R.J. (1985) Assessment and clinical management of early caries in young adults. Invasive versus non-invasive methods.
British Dental Journal, 158, 440 - 444.

ELDERTON, R.J., NUTTALL, N.M., EDDIE, S. & DAVIES, J.A. (1985) Dental health services research in Scotland: a review of some 5-year results.
Community Dentistry & Oral Epidemiology, 13, 249 - 252.

ERICSSON, Y., & FORSMAN, B. (1969) Fluoride retained from mouthrinses and dentifrices in preschool children.
Caries Research, 3, 290 - 299.

ERICSSON, Y., & WEI, S.H.Y. (1979) Fluoride supply and effects in infants and young children.
Pediatric Dentistry, 1, 44 - 54.

ESPELID, I. & TVEIT, A.B. (1984) Radiographic diagnosis of mineral loss in approximal enamel.
Caries Research, 18, 141 - 148.

EVANS, S.J.W. (1988) Uses and abuses of multivariate methods in epidemiology.
Journal of Epidemiology & Community Health, 42, 311 - 315.

ETTY, E.J., LOOK, M., VINGERLING, P.A., WOLTGENS, J.H.M., EGGINK, C.O. (1988) Comparison of the development of approximal caries with occlusal or smooth surface caries within 1 year.
Caries Research, 22, 109.

FANNING, E.A., GOTJAMANOS, R. & VOWLES, N.J. (1968) The use of fluoride dentifrices in the control of dental caries: methodology and results of a clinical trial.
Australian Dental Journal, 13, 201 - 206.

FEATHERSTONE, J.D.B., CUTRESS, T.W., RODGERS, B.E. & DENNISON, P.J. (1982) Remineralization of artificial caries-like lesions *in vivo* by a self-administered mouthrinse or paste.
Caries Research, 16, 235 - 242.

FEDERATION DENTAIRE INTERNATIONAL (1990) Salt fluoridation programme in Costa Rica.
Federation Dentaire International News, 169, 7.

FEDERATION DENTAIRE INTERNATIONAL / WORLD HEALTH ORGANISATION (1985) Changing patterns of oral health and implications for oral health manpower : Part 1
International Dental Journal, 35, 235 - 251.

FEHR, F.R. von der., LOE, H. & THEILADE, E. (1970) Experimental caries in man.
Caries Research, 4, 131 - 148.

FEHR, F.R. von der. & MOLLER, I.J. (1978) Caries-Preventive fluoride dentifrices.
Caries Research, 12, (Suppl. 1), 31 - 37.

FEJERSKOV, O., THYLSTRUP, A., & LARSEN, M.J. (1977) Clinical and structural features and possible pathogenic mechanisms of dental fluorosis.
Scandinavian Journal of Dental Research, 85, 510 -534.

FISCHMAN, S., CANCRO, L., & D'AGOSTINO, R. (1987) Effect of anticaries dentifrices on orthodontic subjects.
Journal of Dental Research, 66, 258.

FLEISS, J.L., FISCHMAN, S.L., CHILTON, N.W., & PARK, M.H. (1979a) Reliability of discrete measurements in caries trials.
Caries Research, 13, 23 - 31.

FLEISS, J.L., SLAKTER, M.J., FISCHMAN, S.L., PARK, M.H., & CHILTON, N.W. (1979b) Inter-examiner reliability in caries trials.
Journal of Dental Research, 58, 604 - 609.

FOGELS, H.R., MEADE, J.J., GRIFFITHS, J., MIRAGLIUOLO, R. & CANCRO , L.P. (1988) A clinical investigation of a high-level fluoride dentifrice.
Journal of Dentistry for Children, 55, 210 - 215.

FORSMAN, B. (1974) Studies on the effect of dentifrices with low fluoride content.
Community Dentistry & Oral Epidemiology, 2, 166 - 175.

FORWARD, G.C. (1980) Action and interaction of fluoride in dentifrices.
Community Dentistry & Oral Epidemiology, 8, 257 - 266.

FRAZIER, P.J. (1978) A new look at dental health education in community programmes.
Dental Hygiene, 52, 176 - 186.

GARDNER, D.E., SMITH, F.A., HODGE, H.C., OVERTON, D.E. & FELTMAN, R. (1952) The fluoride content of placental tissue as related to the fluoride content of drinking water.
Science, 115, 208 - 212.

GLASS, R.L. (1968) Criteria for selected variables in clinical trials.
In: Proceedings of the Conference on the clinical testing of cariostatic agents. pp 89 - 92. Chicago: American Dental Association.

GLASS, R.L. (1981) Caries reduction by a dentifrice containing sodium monofluorophosphate in a calcium carbonate base. Partial explanation for diminishing caries prevalence.
Clinical Preventive Dentistry, 3, 6 - 8.

GLASS, R.L., PETERSON, J.K. & BIXLER, D. (1983) The effects of changing caries prevalence and diagnostic criteria on clinical caries trials.
Caries Research, 17, 145 - 151.

GLASS, R.L. & SHIERE, F.R. (1978) A clinical trial of a calcium carbonate base dentifrice containing 0.76% sodium monofluorophosphate.
Caries Research, 12, 284 - 289.

GOAZ, P.W., McELWAINE, L.P., BISWELL, H.A. & WHITE, W.E. (1963) Effect of daily applications of sodium monofluorophosphate solution on caries rate in children.
Journal of Dental Research, 42, 965 - 972.

GRAF, H. & MUHLEMANN, H.R. (1969) Oral telemetry of fluoride ion activity.
Archives of Oral Biology, 14, 259 - 263.

GRANATH, L., MARTINSSON, T., MATSSON, L., NILSSON, G., SCHRODER, U. & SODERHOLM, B. (1979) Intraindividual effect of daily supervised flossing on caries in schoolchildren.
Community Dentistry & Oral Epidemiology, 7, 147 - 150.

GREEN, J., MONTASSER, M., LOW, H.C. & WOODROW, J.C. (1988) Investigation of the associations of a number of HLA antigens with psoriasis and psoriatic arthritis.
Statistics in Medicine, 7, 443 - 450.

GROENVELD,A. & BACKER-DIRKS, O. (1988) Fluoridation of drinking water, past, present and future.
In : Fluoride in dentistry. Ed. Ekstrand, J., Fejerskov, O. & Silverstone, L.M., pp 229 - 251, Copenhagen: Munksgaard.

GRON, P., BRUDEVOLD, F. & AASENDEN, R. (1971) Monofluorophosphate interaction with hydroxyapatite and intact enamel.
Caries Research, 5, 202 - 214.

GRONDAHL, H.G. (1979) Some factors influencing observer performance in radiographic caries diagnosis.
Swedish Dental Journal, 3, 157 - 172.

GRONDAHL, H.G. & HOLLENDER, L. (1979) Dental caries and restorations. IV. a six - year longitudinal study of the caries increment of proximal surfaces.
Swedish Dental Journal, 3, 47 - 55.

GRONDAHL, H.G., HOLLENDER, L., MALMCRONA, E. & SUNDQUIST, B. (1977a) Dental caries and restorations in teenagers. I. Index and score system for radiographic studies of proximal surfaces.
Swedish Dental Journal, 1, 45 - 50.

GRONDAHL, H.G., HOLLENDER, L., MALMCRONA, E. & SUNDQVIST, B. (1977b) Dental caries and restorations in teenagers. II. A longitudinal radiographic study of the caries increment of proximal surfaces among urban teenagers in Sweden.
Swedish Dental Journal, 1, 51 - 57.

GUSTAFSSON, B.E., QUESNEL, C.E., LANKE, L.S., LUNDQUIST, C., GRAHNEN, C.H. BONOW, B.E. & KRASSE, B. (1954) The Vipeholm dental caries study. The effect of different levels of carbohydrate intake on caries activity in 436 individuals observed for five years.
Acta Odontologica Scandinavica, 11, 232 - 388.

GWINNET, A.I. (1971) A comparison of proximal carious lesions as seen by clinical radiography, contact microradiography and light microscopy.
Journal of the American Dental Association, 83, 1078 - 1080.

HACKETT, A. & STEPHEN, K.W. (1983) Diet and the fall in caries prevalence.
British Dental Journal, 155, 6.

HARGREAVES, J. A. & CHESTER, C.G. (1973) Clinical trial among Scotish children of an anti-caries dentifrice containing 2 per cent sodium monofluorophosphate.
Community Dentistry & Oral Epidemiology, 1, 47 - 57.

HARRIS,R. (1959) Observations on the effect of topical sodium fluoride on caries incidence in children.
Australian Dental Journal, 4, 247 - 260.

HAUGEJORDEN, O. (1974) A study of the methods of radiographic diagnosis of dental caries in epidemiological investigations.
Acta Odontologica Scandinavica, 32, Suppl 65.

HAUGEJORDEN, O. & SLACK, G.L. (1975) Progression of approximal caries in relation to radiographic scoring codes.
Acta Odontologica Scandinavica, 33, 211 - 217.

HEALY, M.J.R. (1988) Glim: An introduction. Oxford: Clarendon Press.

HODGE, H.C., HOLLOWAY, P.J, DAVIES, T.G.H. & WORTHINGTON, H.V. (1980) Caries prevention by dentifrices containing a combination of sodium monofluorophosphate and sodium fluoride. Report of a 3-year clinical trial.
British Dental Journal, 149, 201 - 204.

HOROWITZ, H.S. (1968) Inter- and intra-examiner variability. In: Proceedings of the Conference on the Clinical Testing of Cariostatic Agents. Ch. 2. Chicago: American Dental Association.

HOROWITZ, H.S. & DOYLE, J. (1971) The effect on dental caries of topically applied acidulated phosphate-fluoride: results after three years.
Journal of the American Dental Association, 82, 359 - 365.

HOWAT, A.R., HOLLOWAY, P.J. & DAVIES, T.G.H. (1978) Caries prevention by daily supervised use of a MFP dentifrice. report of a 3-year clinical trial.
British Dental Journal, 145, 233 - 235.

HUNT, R.J. (1986) Percent agreement, Pearson's Correlation, and Kappa as measures of inter-examiner reliability.
Journal of Dental Research, 65, 128 - 130.

HUNTINGTON, E. (1985) Increasing the sensitivity of caries clinical trials by applying logistic modelling to specific teeth.
Community Dentistry & Oral Epidemiology, 13, 264 - 267.

INGRAM, G.S. (1977) Reaction between apatite and monofluorophosphate: modification by fluoride and condensed phosphate.
Caries Research, 11, 30 - 38.

JAMES, P.M.C., ANDERSON, R.J., BEAL, J.F & BRADNOCK, G. (1977) A 3-year clinical trial of a dentifrice containing 2% sodium monofluorophosphate.
Community Dentistry & Oral Epidemiology, 5, 67 - 72.

JENKINSON, M.L., FITZPATRICK, R., STREETE, P.J. & VOLANS, G.N. (1988) The relationship between plasma ibuprofen concentrations and toxicity in acute ibuprofen overdose.
Human Toxicology, 7, 319 - 324.

JULIANO, G.F., YROALA, B., CANO-AREVALO, M., TRIOL, C.W. & VOLPE, A.R. (1985) Clinical study comparing the anticaries effect of two fluoride dentifrices.
Journal of Dental Research, 64, 189.

KAILIS, D.G., TAYLOR, S.R., DAVIS, G.B., BARTLETT, L.G., FITZGERALD, D.J., GROSE, I.J., & NEWTON, P.D. (1968) Fluoride and caries: observations on the effects of prenatal and postnatal fluoride on some Perth pre-school children.
The Medical Journal of Australia, 2, 1037 - 1040.

KALSBEEK, H. (1982) Evidence of decrease in prevalence of dental caries in the Netherlands: an evaluation of epidemiological caries surveys on 4-6 and 11-15 year old children between 1965 and 1980.
Journal of Dental Research, 61, (Special Issue), 1321 - 1326.

KARJALAINEN, S. & HANNULA, P. (1988) Variation of reproducibility and agreement in radiographic caries diagnosis among dental teachers.
Proceedings of Finnish Dental Society, 84, 70 - 78.

KIDD, E.A.M. (1983) The histopathology of enamel caries in young and old permanent teeth.
British Dental Journal, 155, 196 - 198.

KIDD, E.A.M. (1984) The diagnosis and management of the early carious lesion in the permanent teeth.
Dental Update, 11, 69 - 81.

KING, N.M. & SHAW, L. (1979) Value of bitewing radiographs in detection of occlusal caries.
Community Dentistry & Oral Epidemiology, 7, 218 - 221.

KINKEL, H.J., & RAICH, R. (1974) Die Karieshemmung ein Na_2FPO_3-Zahnpaste nach 4 Jahren Applikation.
Schweiz Mschr Zahnheilk, 84, 226 - 229.

KINKEL, H.J. & STOLTE, G. (1968) On the effect of a sodium monofluorophosphate and bromochlorophene-containing toothpaste in a chronic animal experiment and on caries during a two-year period of supervised use.
Deutsche Zahnarztliche Zeitschrift, 22, 455 - 460.

KINKEL, H.J., STOLTE, G. & WESTRATE, J. (1974) Etude d'efficacite d'une pate dentifrice au fluorophosphate sur la denture des enfants.
Schweiz Mschr Zahnheilk, 84, 577 - 589.

KNUTSON. J.W. (1948) Sodium fluoride solutions: technic for application to the teeth.
Journal of the American Dental Association, 36, 37 - 39.

KIRKWOOD, B.R. (1988) Essentials of medical statistics.
Oxford: Blackwell.

KOCH, G. (1982) Evidence for declining caries prevalence in Sweden.
Journal of Dental Research, 61, (Special Issue), 1340 - 1345.

KOCH, G. & LINDHE, J. (1970) The state of the gingivae and the caries-increment in school-children during and after withdrawal of various prophylactic measures.
In: Dental Plaque, ed. McHugh, W.D, 271 - 281, Edinburgh: Livingstone.

KOCH, G., PETERSSON, L-G. & GLEERUP, A. (1982) Kinetics of fluorine in deciduous enamel after application of fluoride-containing varnish (Duraphat).
Swedish Dental Journal, 6, 39 - 44.

KOCH, G., PETERSSON, L-G., KLING, E. & KLING, L. (1982) Effect of 250 and 1000 ppm fluoride dentifrice on caries.
Swedish Dental Journal, 6, 233 - 238.

KOULOURIDES, T., CUETO, H. & PIGMAN, W. (1961) Rehardening of softened enamel surfaces of human teeth by solutions of calcium phosphates. *Nature*, 189, 226 - 227.

LEIJON, G. (1969) Initial approximal primarkaries i rontgenbilden Del I. *Swedish Dental Journal*, 6, 227 - 237.

LEVERETT, D.H. & CURZON, M.E.J. (1988) Clinical trial of a dentifrice containing 2000 ppm fluoride as monofluorophosphate. *Journal of Dental Research*, 67, 171.

LIND, O. P., MOLLER, J.J., VON DER FEHR, F.R. & LARSEN, N.J. (1974) Caries preventive effect of a dentifrice containing 2 per cent sodium monofluorophosphate in a natural fluoride area in Denmark. *Community Dentistry & Oral Epidemiology*, 2, 104 - 113.

LOESCHE, W.J., MURRAY, R.J. & MELLBERG, J.R. (1973) The effect of topical acidulated phosphate fluoride on percentage of Streptococcus mutans and Stretococcus sanguis in interproximal plaque samples. *Caries Research*, 7, 283 - 296.

LOESCHE, W.J., SYED, S.A., MURRAY, R.J. & MELLBERG, J.R. (1975) Effect of topical acidulated phosphate fluoride on percentage of Streptococcus mutans and Stretococcus sanguis in plaque. II Pooled occlusal and pooled approximal samples. *Caries Research*, 9, 139 - 155.

LONGBOTTOM, C., & PITTS, N.B. (1988) A preliminary comparison between conventional and endoscopic methods of caries diadnosis. *Journal of Dental Research*, 67, 663.

LOVIUS, B.B.J., & GOOSE, D.H. (1969) The effect of fluoridation of water on tooth morphology. *British Dental Journal*, 127, 322 - 324.

LU, K.H., RUHLMAN, C.D., CHUNG, K.S., STURZENBERGER, O.P. & LEHNOFF, R.W. (1987) A three-year clinical comparison of a sodium monofluorophosphate dentifrice with sodium fluoride dentifrices on dental caries in children. *Journal of Denistry for Children*, 54, 241 - 244.

McCALL, D.R., WATKINS, T.R., STEPHEN, K.W., COLLINS, W.J.N. & SMALL, M.J. (1983) Fluoride ingestion following APF gel application. *British Dental Journal*, 155, 333 - 336.

McCULLAGH, P. & NELDER, J.A. (1983) Generalized Linear Models. London: Chapman & Hall.

MacFADYEN, E.E., NEWMAN, P., STEPHEN, K.W., & GILLESPIE, F.C. (1977) Effect of sweeteners and fluoride rinses on intra-oral plaque pH measured using in-dwelling electrodes.
Caries Research, 11, 114.

McKAY, F.S. (1916) (In collaboration with Black, G.V.) Mottled teeth: an endemic developmental imperfection in the enamel of the teeth heretofore unknown in the literature of dentistry.
Dental Cosmos, 58, 477 - 484.

McKAY, F.S. (1933) Mottled enamel: the prevention of its further production through a change in the water supply at Oakley, Idaho.
Journal of the American Dental Association, 20, 1137 - 1149.

MACHIN, D., MURRELLS, T.J., CATFORD, J.C. & SMITH, T.M.F. (1986) The use of logit models to investigate social and biological factors in infant mortality. 1V: Post-neonatal mortality.
Statistics in Medicine, 5, 155 - 169.

MAINWARING, P.J. & NAYLOR, M.N. (1978) A three-year clinical study to determine the separate and combined caries inhibiting effect of sodium monofluorophosphate toothpaste and an acidulated phosphate-fluoride gel.
Caries Research, 12, 202 - 212.

MAINWARING, P.J. & NAYLOR, M.N. (1980) Anti-caries effects of a MFP/$CaCO_3$ toothpaste containing calcium glycerphosphate (CaGP) or sodium fluoride (NaF): a 4-year clinical study.
Journal of Dental Research, 60, 1091.

MARKEN, K.E. (1962) Studies of deviations between observers in clinico-odontological recordings.
Transactions of the Royal School of Dentistry, Stockholm and Umea.

MARTHALER, T.M. (1964) The examiners and the examinations.
Advances of Fluoride Research in Dental Caries Prevention, 2, 25 - 28.

MARTHALER, T.M. (1973) Rapidity of penetration of radiolucent areas through mesial enamel of first permanent molars.
Helvetica Odontologica Acta, 17, 19 - 26.

MARTHALER, T.M., MEJIA, R., TOTH, K. & VINES, J.J. (1978) Caries-preventive salt fluoridation.
Caries Research, 12, (Suppl 1), 15 - 21.

MELLBERG, J.R. (1990) Evaluation of topical fluoride preparations.
Journal of Dental Research In press.

MELLBERG, J.R., & CHOMICKI, W.G. (1983) Effect of zinc citrate on fluoride uptake by artificial caries lesions.
Journal of Dental Research, 62, 145 - 147.

MELLBERG, J.R., CHOMICKI, W.G., MALLON, D.E. & CASTROVINCE, L.A. (1985) Remineralization *in vivo* of artificial caries lesions by monofluorophosphate dentifrice.
Caries Research, 19, 126 - 135.

MELLBERG, J.R., NICHOLSON, C.R. & LAAKSO, P.V. (1967) The effect of a barrier coating on fluoride uptake by human tooth enamel.
Archives of Oral Biology, 12, 1177 - 1187.

MERGELE, M. (1968a) Report I. A supervised brushing study in state institution schools.
Builletin of the Academy of Medicine, N.J., 14, 247 - 250.

MERGELE, M. (1968b) Report II. An unsupervised brushing study on subjects residing in a community with fluoride in the water.
Builletin of the Academy of Medicine, N.J., 14, 251 - 255.

MILEMAN, P.A., PURDELL-LEWIS, D.J., & WEELE, L.T. van der. (1983) Effect of variation in caries diagnosis and degree of caries on treatment decisions by dental teachers using bitewing radiographs.
Community Dentistry and Oral Epidemiology, 11, 356 - 362.

MILEMAN, P.A., PURDELL-LEWIS, D.J., WEELE, L.T. van der, & LEERTOUWER, H.L. (1984) Diagnostic variation caused by differences in viewbox illumination and visual ability.
Dentomaxillofacial Radiology, 13, 51 - 58.

MILLMAN, C.K. (1984) Fluoride syndrome.
British Dental Journal, 157, 341.

MITROPOULOS, C.M., (1985a) The use of fibre-optic transillumination in the diagnosis of posterior approximal caries in clinical trials.
Caries Research, 19, 379 - 384.

MITROPOULOS, C.M., (1985b) A comparison of fibre-optic transillumination with bitewing radiographs.
British Dental Journal, 159, 21 - 23.

MITROPOULOS, C.M., HOLLOWAY, P.J., DAVIES, T.G.H. & WORTHINGTON, H.V. (1984) Relative efficacy of dentifrices containing 250 or 1000 ppm F in preventing dental caries - report of a 32-month clinical trial.
Community Dental Health, 1, 193 - 200.

MOLLER, I.J., HOLST, J.J. & SORENSEN, E. (1968) Caries-reducing effect of a sodium monofluorophosphate dentifrice.
British Dental Journal, 124, 209 - 213.

MUHLEMANN, H.R., SCHMID, H., & KONIG, K.G. (1957) Enamel solubility reduction studies with inorganic and organic fluorides.
Helvitia Odontological Acta, 1, 23 - 33.

MUHLER, J.C. (1956) Effect of fluorides and other solutions on solubility of powdered enamel in acid.
Proceedings of the Society of Experimental Biology and Medicine, 92, 849.

MURRAY, J.J. (1971) Adult dental health in fluoride and non-fluoride areas.
British Dental Journal, 131, 487 - 492.

MURRAY, J.J. & SHAW, L. (1975) Errors in diagnosis of approximal caries on bitewing radiographs.
Community Dentistry & Oral Epidemiology, 3, 276 - 282.

MURRAY, J.J. & SHAW, L. (1980) A 3-year clinical trial into the effect of fluoride content and abrasivity on the caries inhibitory properties of a dentifrice.
Community Dentistry & Oral Epidemiology, 8, 46 - 51.

MURRELLS, T.J., CATFORD, J.C., SMITH, T.M.F. & MACHIN, D. (1985) The use of logit models to investigate social and biological factors in infant mortality. 2: stillbirths.
Statistics in Medicine, 4, 189 - 200.

NAYLOR, M.N. (1982) The declining prevalence of dental caries. Report of an international conference.
British Dental Journal, 153, 151 - 152.

NAYLOR, M.N. & EMSLIE, R.D. (1967) Clinical testing of stannous fluoride and sodium monofluorophosphate dentifrices in London school children.
British Dental Journal, 123, 17 - 23.

NAYLOR, M.N. & GLASS, R.L. (1979) A 3-year clinical trial of a calcium carbonate dentifrice containing calcium glycerophosphate and sodium monofluorophosphate.
Caries Research, 13, 39 - 46.

NELDER, J.A. & WEDDERBURN, R.W.M. (1972) Generalized linear models.
Journal of the Royal Statistical Society, 135, 370 - 384.

NEWBRUN, E. (1986) Ed. Fluorides and Dental Caries.
Springfield: Charles C. Thomas.

NIKIFORUK, G. (1985) Understanding Dental Caries. Volume I: Etiology and Mechanisms. Basel: Karger.

NOMURA, H., ONOUE, Y. & NEMOTO, T. (1971) A preliminary report on the relation between electric resistance and pit or fissure in human tooth.
Bulletin of the Tokyo Dental College, 12, 77 - 83.

NUTTAL, N.M. (1984) General Dental Service treatment received by frequent and infrequent attenders in Scotland.
British Dental Journal, 156, 363 - 366.

NYSETHER, S. & HANSEN, B.F. (1983) Errors on dental bitewing radiographs.
Community Dentistry & Oral Epidemiology, 11, 286 -288.

OWEN, F. & JONES, R. (1987) Statistics.
2nd ed. London: Pitman.

PETERSON, J.K. (1979) A supervised brushing trial of sodium monofluorophosphate dentifrice in a fluoridated area.
Caries Research, 13, 68 - 72.

PETERSON, J.K. & WILLIAMSON, L.D. (1975) caries inhibition with MFP-calcium carbonate dentifrice in fluoridated area.
Journal of Dental Research, 54, L85.

PINCUS, P. (1951) A new method of examination of molar tooth grooves for the presence of dental caries.
Journal of Physiology, 113, 13 - 14.

PITTS, N.B. (1983) Monitoring of caries progression in permanent and primary posterior approximal enamel by bitewing radiography.
Community Dentistry & Oral Epidemiology, 11, 228 - 235.

PITTS, N.B. (1984) Systems for grading approximal carious lesions and overlaps diagnosed from bitewing radiographs. Proposals for future standardization.
Community Dentistry & Oral Epidemiology, 12, 114 - 122.

PITTS, N.B. (1986a) Approximal radiolucencies in partially overlapped enamel: the need for quantitation and a preliminary assessment of a computer-aided image analysis method.
Quintessence International, 17, 229 - 236.

PITTS, N.B. (1986b) Regression of approximal carious lesions diagnosed from serial standardised bitewing radiographs.
Caries Research, 20, 85 - 90.

PITTS, N.B. (1987) Monitoring the behaviour of posterior approximal carious lesions by image analysis of serial standardised bitewing radiographs.
British Dental Journal, 162, 15 - 21.

PITTS, N.B. & LONGBOTTOM, C. (1987a) The use of endoscopically viewed filtered fluorescence for the clinical diagnosis of carious lesions in dental enamel. *Medical Science Research*, 15, 535 - 536.

PITTS, N.B. & LONGBOTTOM, C. (1987b) Temporary tooth separation with special reference to the diagnosis and preventive management of equivocal approximal lesions. *Quintessence International*, 18, 563 - 573.

PITTS, N.B. & RENSON, C.E. (1986a) Image analysis of bitewing radiographs: a histologically validated comparison with visual assessments of radiolucency depth in enamel. *British Dental Journal*, 160, 205 - 209.

PITTS, N.B. & RENSON, C.E. (1986b) Further development of a computer-aided image analysis method of quantifying radiolucencies in approximal enamel. *Caries Research*, 20, 361 - 370.

POULSEN, S., BILLE, J. & RUGG-GUNN, A.J. (1980) Evaluation of a calibration trial to increase interexaminer reliability of radiographic diagnosis of approximal carious lesions. *Dental Oral Epidemiology*, 8, 135 - 138.

QUENZEL, C.E., GUSTAFSSON, B.E. & GRAHNEN, H. (1954) The Vipoholm dental caries study. Reliability of the method in determination of caries activity. *Acta Odontologica Scandinavica*, 11, 365 - 388.

RADIKE, A.W. (1968) Examiner error and reversals in diagnosis. In: Proceedings of the Conference on the Clinical Testing of cariostatic Agents. Chicago: American Dental Association.

REED, M.W. (1973) Clinical evaluation of three concentrations of sodium fluoride in dentifrices. *Journal of the American Dental Association*, 86, 1401 - 1403.

RIPA, L.W. (1981) Professionally (operator) applied topical fluoride therapy: a critique. *International Dental Journal*, 31, 105 - 120.

RIPA, L.W., LESKE, G.S. (1979) Two years' effect on the primary dentition of mouthrinsing with a 0.2% neutral NaF solution. *Community Dentistry & Oral Epidemiology*, 7, 151 - 153.

RIPA, L.W., LESKE, G.S., FORTE, A. & VARMA, A. (1988) Caries inhibition of mixed NaF-Na_2PO_3F dentifrices containing 1000 and 2500 ppmF: 3-year results. *Journal of the American Dental Association*, 116, 69 - 73.

RIPA, L.W., LESKE, G.S., SPOSATO, A. & VARMA, A. (1987) Clinical comparison of the caries inhibition of two mixed NaF-Na_2PO_3F dentifrices containing 1000 and 2500 ppmF compared to a conventional Na_2PO_3F dentifrice containing 1000 ppm F: Results after two years. *Caries Research*, 21, 149 - 157.

ROCK, W.P. & KIDD, E.A.M. (1988) The electronic detection of demineralisation in occlusal fissures. *British Dental Journal*, 164, 243 - 247.

RUGG-GUNN, A.J. (1972) Approximal carious lesions: a comparison of the radiological and clinical appearance. *British Dental Journal*, 133, 481 - 484.

RUGG-GUNN, A.J. & HOLLOWAY, P.J. (1974) Methods of measuring the reliability of caries prevalence and incremental data. *Community Dentistry & Oral Epidemiology*, 2, 287 - 294.

RUSOFF, L.I., KONIKOFF, B.S., FRYE, J.B., JOHNSTON, J.E. & FRYE, W.W. (1962) Fluoride addition to milk and its affect on dental caries in school children. *American Journal of Clinical Nutrition*, 11, 94 - 101.

RUSSELL, J.I. (1987) The relevance of microbiological tests in the prediction of caries in adolescents. Ph.D Thesis, University of Glasgow.

SAVARA, B., & SUHER, T. (1955) Dental caries in children one to six years of age as related to socioeconomic level, food habits and toothbrushing. *Journal of Dental Research*, 34, 870 - 875.

SAWLE, R.F. & ANDLAW, R.J. (1988) Has occlusal caries become more difficult to diagnose ? *British Dental Journal*, 164, 209 - 211.

SAXTON, C.A., HARRAP, G.J., & LLOYD, A.M. (1986) The effect of dentifrices containing zinc citrate on plaque growth and oral zinc levels. *Journal of Clinical Periodontology*, 13, 301 - 306.

SCHEI, O., WAERHAUG, J., LOVDAL, A. & ARNO, A. (1959) Alveolar bone loss as related to oral hygiene and age. *The Journal of Periodontology*, 30, 7 - 16.

SEDDON, R.P. (1986) A simple method of directly examining interproximal carious lesions by separating teeth using orthodontic elastomeric separating modules. *Journal of Dental Research*, 65, 514.

SEDDON, R.P. (1989) The detection of cavitation in carious approximal surfaces in vivo by tooth separation, impression and scanning electron microscopy. *Journal of Dentistry*, 17, 117 - 120.

SEWERIN, I.B. (1981) Influence of X-ray beam angulation upon the radiographic image of proximal carious lesions.
Community Dentistry & Oral Epidemiology, 9, 74 - 78.

SHEIHAM, A. (1984) Changing trends in dental caries.
International Journal of Epidemiology, 13, 142 - 147.

SHEIHAM, A., MAIZELS, J., CUSHING, A., & HOLMES, J. (1985) Dental attendance and dental status.
Community Dentistry & Oral Epidemiology, 13, 304 - 309.

SHIP, I.I., JONES, E.M. & LASTER, L.L. (1966) Errors, reversals and questionable dental caries diagnoses based on a longitudinal study in children.
Journal of Dental Research, 45, 323 - 331.

SHWARTZ, M., GRONDAHL, H.G., PLISKIN, J.S. & BOFFA, J. (1984) A longitudinal analysis from bite-wing radiographs of the rate of progression of approximal carious lesions through human dental enamel.
Archives of Oral Biology, 29, 529 - 536.

SIEGEL, S. (1956) Non parametric statistics for the behavioral sciences.
Tokyo: McGraw-Hill Kogakusha Ltd.

SILVERSTONE, L.M., WEFEL, J.S., ZIMMERMAN, B.H., CLARKSON, B.H. & FEATHERSTONE, M.J. (1981) Remineralization of natural and artificial lesions in human dental enamel *in vitro*. Effect of calcium concentration of the calcifying fluid.
Caries Research, 15, 138 - 157.

SLOMAN, E.G. (1941) Sex and age factors in the incidence of dental caries.
Journal of the American Dental Association, 28, 441 - 444.

SLOMAN, E.G. & SHARP, J.B. (1940) Extent of dental caries condition of teeth of San Francisco High School students.
Journal of the California Dental Association, 16, 89 - 120.

STEPHEN, K.W., BENNIE, W.M., STRANG, D.M., MILLER, S. & BURCHELL, C.K. (1989) Assessment of 2 year clinical trial bitewing and FOTI disagreements.
Journal of Dental Research, 68, 961.

STEPHEN, K.W., BOYLE, I.T., CAMPBELL, D., MCNEE, S., FYFFE, J.A., JENKINS, A.S. & BOYLE, P. (1981) A 4-year double-blind fluoridated school milk study in a Vitamin D - deficient area.
British Dental Journal, 151, 287 - 292.

STEPHEN, K.W., BURCHELL, C.K., HUNTINGTON, E., BAKER, A.G., RUSSELL, J.I., & CREANOR, S.L. (1987c) In vivo anticalculus effect of a dentifrice containing 0.5% zinc citrate trihydrate.
Caries Research, 21, 380 - 384.

STEPHEN, K.W. & CAMPBELL, D. (1978) Caries reduction and cost benefit after 3 years of sucking fluoride tablets daily at school.
British Dental Journal, 144, 202 - 206.

STEPHEN, K.W., CREANOR, S.L., RUSSELL, J.I., BURCHELL, C.K., HUNTINGTON, E. & DOWNIE, C.F.A. (1988) A 3-year oral health dose-response study of sodium monofluorophosphate dentifrices with and without zinc citrate: anti-caries results.
Community Dentistry & Oral Epidemiology, 16, 321 - 325.

STEPHEN, K.W., & MacFADYEN E.E. (1977) Three years of clinical caries preventiom for cleft palate children.
British Dental Journal, 143, 111 - 116.

STEPHEN, K.W., RUSSELL, J.I., CREANOR, S.L. & BURCHELL, C.K. (1987a) Effect of monofluorophosphate concentration and 0.5 % zinc citrate in toothpaste on caries increments.
Caries Research, 21, 162.

STEPHEN, K.W., RUSSELL, J.I., CREANOR, S.L. & BURCHELL, C.K. (1987b) Comparison of fibre optic transillumination with clinical and radiographic caries diagnosis.
Community Dentistry and Oral Epidemiology, 15, 90 - 94.

STOPPELAAR, J.D. De, HOUTE, J. van, & BACKER-DIRKS, O. (1969) The relationship between extracellular polysaccharide-producing streptococci and smooth surface caries in 13-year old children.
Caries Research, 3, 190 - 199.

STRANG, R., DAMATO, F.A., CREANOR, S.L. & STEPHEN, K.W. (1987) The effect of baseline mineral lesion mineral loss on *in situ* remineralisation.
Journal of Dental Research, 66, 1644 - 1646.

SVENSEON, B., GRONDAHL, H-G., PETERSSON, A. & OLVING, A. (1985) Accuracy of radiographic caries diagnosis at different kilovoltages and two film speeds.
Swedish Dental Journal, 9, 37 - 43.

THOMAS, A.E & JAMISON, H.C. (1970) Effect of a combination of two cariostatic agents on caries in children: Two-year clinical study of supervised brushing in children's homes.
Journal of the American Dental Association, 81, 118 - 124.

THYLSTRUP, A., & FEJERSKOV, O. (Editors) (1986) Textbook of Cariology. Copenhagen: Munksgaard.

TODD, J.E. & WHITWORTH, A. (1974) Adult dental health in Scotland 1972.
London: H.M.S.O.

TORELL, P. (1969) The use of fluoride toothpaste combined with fluoride rinsing every two weeks. *Sver. Tandlak Forb. Tidn*, 61, 873 - 875.

TORELL, P. & ERICSSON, Y. (1965) Two-year clinical tests with different methods of local caries-preventive fluorine application in Swedish school children. *Acta Odontologica Scandinavica*, 23, 287 - 321.

TOTH, K. (1976) A study of 8 years domestic salt fluoridation for prevention of caries. *Community Dentistry & Oral Epidemiology*, 4, 106 - 110.

TRIOL, C.W., GRAVES, R.C., WEBSTER, D.B. & CLARK, B.J. (1987) Anticaries effect of 1450 and 2000 ppm F dentifrices. *Journal of Dental Research*, 66, 216.

TUCKER, G. J.,ANDLAW, R.J., & BURCHELL, C.K. (1976) The relationship between oral hygiene and dental caries incidence in 11 year-old children. *British Dental Journal*, 141, 75 - 79.

UPDEGRAVE, W.J. (1967) Simplified and standarized bisecting-angle technic for dental radiography. *Journal of the American Dental Association*, 75, 1361 - 1368.

WAGGONER, W.F. & ASHTON, J.J. (1989) Predictability of cavitation based upon the radiographic appearance: comparison of two film types. *Quintessence International*, 20, 55 - 60.

WALLENSTEIN, S., FLEISS, J.L. & CHILTON, N.W. (1981) The logistic analysis of categorical data from dental and oral experiments. *Pharmacology and Therapeutics in Dentistry*, 6, 65 - 78.

WEATHERELL, J.A., HALLSWORTH, A.S. & ROBINSON, C. (1973) The effect of tooth wear on the distribution of fluoride in the enamel surface of human teeth. *Archives of Oral Biology*, 18, 1175 - 1189.

WEATHERELL, J.A., ROBINSON, C. & HALLSWORTH, A.S. (1972) Changes in the fluoride concentration of the labial enamel surface with age. *Caries Research*, 6, 312 - 324.

WEATHERELL, J.A., ROBINSON, C. RALPH, J.P. & BEST, J.S. (1984) Migration of fluoride in the mouth. *Caries Research*, 18, 348 - 353.

WEATHERELL, J.A., STRONG, M., RALPH, J.P. & ROBINSON, C. (1988) Availability of fluoride at different sites in the buccal sulcus. *Caries Research*, 22, 129 - 133.

WEATHERELL, J.A., STRONG, M., ROBINSON, C., NAKAGAKI, H. & RALPH, J.P. (1989) Retention of glucose in oral fluid at different sites in the mouth. *Caries Research*, 23, 399 - 405.

WEATHERELL, J.A., STRONG, M., ROBINSON, C. & RALPH, J.P. (1986) Fluoride distribution in the mouth after fluoride rinsing. *Caries Research*, 20, 111 - 119.

WELANDER, E. (1960) Partial recording of dental caries. *Acta Odontologica Scandinavica*, 18, 377 - 406.

WHITE, G.E., TSAMTSOURIS, A. & WILLIAMS, D.L. (1978) Early detection of occlusal caries by measuring the electrical resistance of the tooth. *Journal of Dental Research*, 57, 195 - 200.

WHITE, D.J. & FALLER, R.V. (1987) Fluoride uptake from anti-calculus dentifrices *in vitro*. *Caries Research*, 21, 40 - 47.

WHITE PAPER (1987) Promoting Better Health. The Government's programme for improving primary health care. Chapter 4: General and Community Dental Services. *British Dental Journal*, 163, 360 - 363.

WILLIAMS, J.E. (1968) Considerations for the use of film holding devices in radiographic examinations. In: Proceedings of the Conference on the clinical testing of cariostatic gents. Chicago: American Dental Association.

WRIGHT, G.Z., BANTING, D.W. & FEASBY, W.H. (1976) The Dorchester dental flossing study: preliminary report. *Caries Research*, 10, 379 - 385.

WRIGHT, G.Z., BANTING, D.W. & FEASBY, W.H. (1979) The Dorchester dental flossing study: final report. *Clinical Prevenitive Denistry*, 1, 23 - 26.

WRIGHT, G.Z., FEASBY, W.H. & BANTING, D.B. (1980) The effectiveness of interdental flossing with and without a fluoride dentifrice. *Pediatric Dentristry*, 2, 105 - 109.

ZACHERL, W.A. (1972).Clinica; evaluation of neutral sodium fluoride, stannous fluoride, sodium monofluorophosphate and acidulated fluoride-phosphate dentifrices. *Journal of the Canadian Dental Association*, 33, 35 - 38.

ZAMIR, T., FISHER, D., FISHEL, D. & SHARAV, Y. (1976) A longitudinal radiographic study of the rate of spread of human approximal dental caries. *Archives of Oral Biology*, 21, 523 - 526.