Dental Caries

The Disease and Its Clinical Management

Third Edition

Edited by
Ole Fejerskov, Bente Nyvad,
and Edwina Kidd

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Fluorides in caries control

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Introduction

The role of fluorides in the control of dental caries represents one of the most successful stories in general public health. However, as with many successful programs, this success is not without cost, and it is a story which at times has resulted in strong emotional debates within the dental profession that have not always been based on scientific evidence.

We will in this chapter base our views on what is currently known about the effects of fluorides on developing and erupted teeth to derive at a rational way of advocating the use of fluorides in contemporary populations. Fluoride (F^-) can have both beneficial and detrimental effects on the dentition. The beneficial effect is due primarily to the local (topical) effect of F^- on the tooth surfaces whenever these are covered by a biofilm after the teeth have erupted into the oral cavity (for mechanisms of action see later in this chapter and also Chapter 9). In contrast, the detrimental effects of F^- are due to its systemic absorption during tooth development, resulting in dental fluorosis, which is a hypomineralization of the enamel the degree of which is a direct reflection of F^- ingestion during tooth formation. If we can maximize the intraoral exposure throughout life and minimize systemic absorption during the period when the dentition is developing, F^- can be used to maximize the benefits of fluorides in caries control whilst at the same time minimizing the risk of fluorosis.

This chapter is divided into the following major headings:

- Fluoride in caries prevention and control
- Cariostatic mechanisms of fluoride
- Dental fluorosis and metabolism of fluoride
- The effectiveness of fluorides in the control of dental caries: evidence from systematic reviews
- Rational use of fluorides in caries control: recommendations

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HOWARD

Fluoride in caries prevention and control

It was in fact the detrimental effects of F^- on the appearance of tooth enamel (dental fluorosis) that prompted the initial detailed investigations and ultimately the discovery of its anticaries benefits [73]. Probably black, discolored teeth have been found as long as man has been living in areas with elevated F^- content in soil and water. For example, Galen (131–201 AD) noted that dental caries 'do not attack teeth having a dark yellow colour, although one would have expected the contrary' according to a translated text by late professor D Lambrou from Thessaloniki.

But the association between F^- and 'mottled enamel,' as it was first designated, became clear in the beginning of the 20th century thanks to two American dentists: Dr Fredrick McKay and US Public Health Officer H Trendley Dean. Subsequently, the positive association between elevated exposure to F^- and decreased prevalence of caries cavities became known. In Europe, however, Denninger in the latter part of the 19th century prescribed calcium fluoride (CaF_2) to children and pregnant women and observed 'great benefits' to their teeth [28].

In 1901, McKay worked in Colorado Springs, Colorado, USA, and noticed that some of his patients had what was locally known as 'Colorado brown stain.' In subsequent years he turned for help to Dr Greene Vardiman Black (see Chapter 19), one of America's most eminent experts on tooth enamel. His histological investigation of the condition 'Mottled teeth. An endemic imperfection of the enamel of the teeth heretofore unknown in the literature of dentistry' [17] drew the attention of the dental research community to the condition. One thing that puzzled both Black and McKay was that although mottled enamel was clearly hypocalcified, and therefore theoretically more susceptible to decay, this did not appear to be case [119]. Coincidentally, Ainsworth [2] in England made a similar observation.

It became clear that the condition was localized to children born in specific geographical areas and McKay suspected that the water supplies of these districts might be an important etiological factor. In Bauxite, changes to a water supply resulted in children having mottled enamel [99], and chemical analysis of the water supply revealed an unexpectedly high level of F^- in the drinking water (14.7 ppm F^-). These high levels were later confirmed in other towns where mottled enamel occurred [34]. These observations did not establish a cause-and-effect relationship. However, when McCollum *et al.* in 1925 reported that rats fed a diet with added F^- developed hypomineralized teeth, the etiology of mottled enamel was clearly established [117].

In the 1930s, systematic animal experiments and human epidemiological studies established both the association and cause–effect relationship between fluorides in drinking waters and mottled enamel (since referred to as dental fluorosis). The epidemiological studies were performed by a team led by Dean [44, 47, 48]. Dean was also interested in the apparent anomaly that although the enamel appeared to be hypomineralized it did not appear to be any more susceptible to decay. He initially undertook a small study involving 114 children who had used water containing 0.6–1.5 ppm F^- and found only 4% were caries free compared with 22% of 122 children in an area with drinking water containing 1.7–2.5 ppm F^- [45]. A further larger study suggested that caries experience in two cities with water supplies containing 1.7 and 1.8 ppm F^- was half that of two similar adjacent cities with only 0.2 ppm F^- in the drinking water [49].

The association between the F^- level in the drinking water and caries levels was then characterized in the '21 city study' (actually a series of studies [50, 51]. Children from cities with natural F^- concentrations in their drinking water ranging from around zero up to 2.6 ppm were examined and the results of this classic piece of epidemiological investigation of both fluorosis and caries experience are summarized in Figs 14.1 and 14.2 [46].

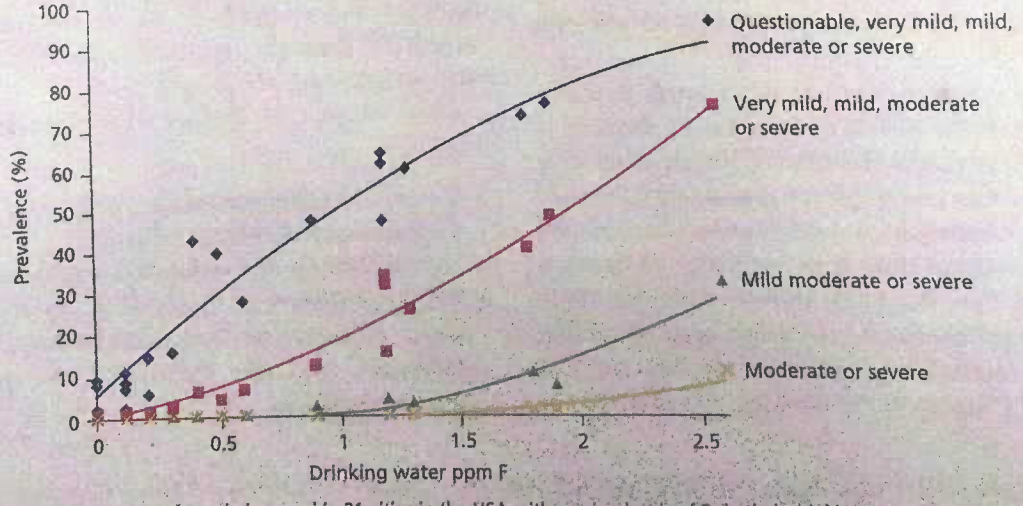

Figure 14.1 Prevalence and severity of mottled enamel in 21 cities in the USA with varying levels of F^- in their drinking water [46]. (Public domain.)

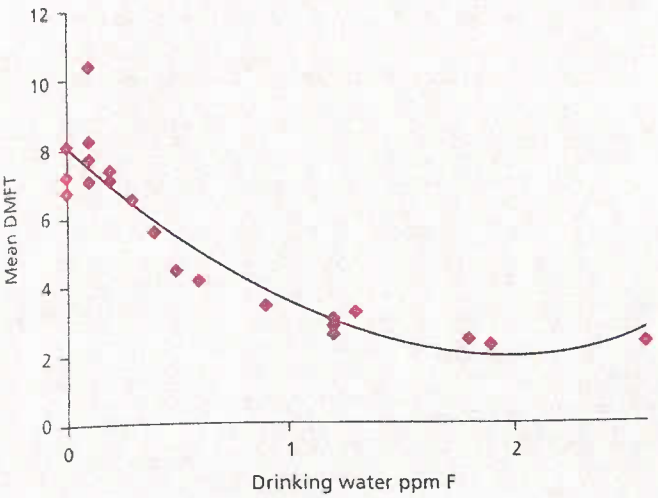

Figure 14.2 Mean number of decayed, missing, and filled teeth (DMFT) and F^- concentration of the drinking water from the 21 city study [46]. (Public domain.)

Dean's index [43, 45, 46] classifies fluorosis as questionable, very mild, mild, moderate, and severe. The prevalence of subjects with lesions of any severity is about 50% at the level of 1 ppm F^- or less in the drinking water (Fig. 14.1). However, it is also interesting to note that the less severe forms of fluorosis (questionable and very mild) account for most cases and there is a very clear dose–response relationship between the F^- level in the drinking water and the prevalence of fluorosis even at levels of F^- in the drinking water below 1 ppm. Therefore, even at low levels of F^- in the drinking water there was some risk attached to use of F^- (for details, see later in this chapter).

The use of the term 'questionable' to describe the earliest classification level in Dean's index has been the source of much controversy over the years as the dental profession has tried to eliminate this category, claiming that it reflected a variety of other types of enamel changes not caused by F^-. However, Fig. 14.1 clearly demonstrates that there is a strong dose–response relationship between this category of defects and the F^- concentration of the drinking water. Moreover, in 1983, Myers reviewed the available literature regarding the 'questionable' category of dental fluorosis and demonstrated that it was a distinct entity associated with F^- [124].

The association between F^- levels in the drinking water and dental caries in the 21 cities is shown in Fig. 14.2. At the time there was a dramatic reduction in caries as the F^- level in the drinking water increased up to 1 ppm. Beyond this level, the mean decayed, missing, and filled teeth (DMFT) continued to decrease but at a much lower rate. At the level of F^- of 1 ppm the average number of decayed, missing, or filled teeth had reduced by more than 50%. However, when studying this graph we should consider whether the apparent plateau is an artefact of the recording method or population observed. The recording method was DMFT, but the average DMFT (see Chapter 4) is a very crude measure and by its nature not able to reflect sensitively changes at the lower end of the scale. It only records caries when lesions have reached cavity level; as such, it is insensitive in identifying benefits in arresting enamel lesions.

Dean gave much thought to the question of what might constitute 'the optimum level of F^-' in drinking water supplies; that is, the concentration of F^- that would result in maximum 'caries protection' while causing minimal dental fluorosis. Based on his studies on 'the minimal threshold of chronic endemic dental fluorosis,' Dean concluded that 'amounts not exceeding 1 part per million expressed in terms of fluorine are of no public health significance' [47]. As was stressed when dealing with Fig. 14.1, Dean's personal assessment 'of no public health significance' was not synonymous with saying that no dental fluorosis occurs in the population. Also, the relationships between perceptions of dental appearance and oral health-related quality of life and dental fluorosis were not assessed at that time. Nevertheless, these reflections resulted in the widespread adoption of 1–1.2 ppm F^- in the USA as an 'optimal' level in the drinking water (for further discussion, see later).

The strong association between the F^- level in the drinking water and caries levels were based on cross-sectional study designs. Therefore, in order to establish a cause-and-effect relationship, intervention studies were required, and these commenced in the Lake Michigan area in 1944. Two towns were selected, Grand Rapids and Muskegon, and baseline caries levels in children aged 4–16 years were recorded. In addition, caries levels were recorded in Aurora, Illinois, an area with naturally occurring F^- in the drinking water at the level of 1.4 ppm. At the start of the study caries levels in the two Michigan cities were similar [52]. F^- at the level of 1 ppm was then added to the drinking water of the city of Grand Rapids in January 1945, and caries levels were recorded again after 6½ years of fluoridation. In 'non-fluoride' Muskegon the average number of teeth with decay experience was 5.7, compared with 3.0 in 'fluoridated' Grand Rapids [7]. The study was deemed so successful that it was decided to fluoridate the drinking water of Muskegon. After 15 years of fluoridation in Grand Rapids (Fig. 14.3) the number of teeth with cavities had fallen from 12.5 in 1944 to 6.2 in 1959, a reduction of approximately 50% [8]. Caries levels in Grand Rapids were now very similar to those experienced in Aurora, the naturally fluoridated city. This outcome was replicated in a number of studies throughout the USA and a few in other parts of the world. The Dutch Tiel–Culemborg studies by Otto Backer-Dirks and his collaborators were of particular importance [9] because the original data were available decades later when the artificial fluoridation of the drinking water had to cease. As we shall see, reanalyses of these data many years later confirmed the changed concepts on the mechanisms of F^- action.

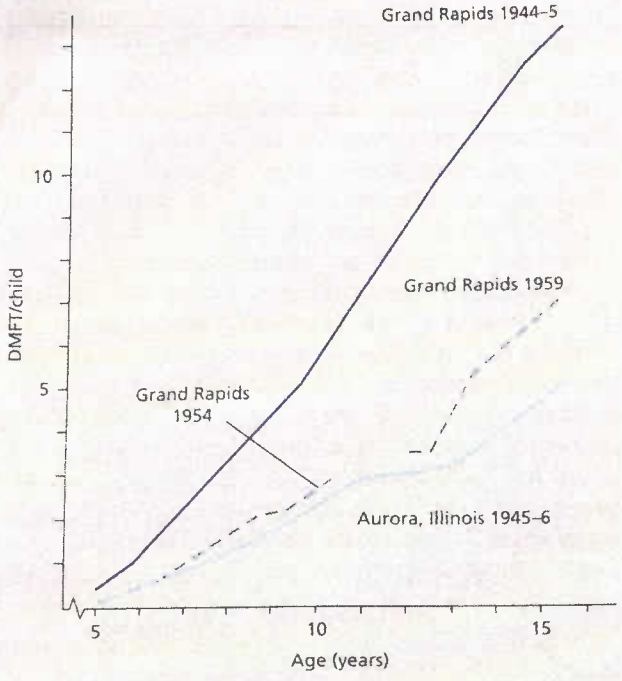

Figure 14.3 Dental caries in Grand Rapids children after 10 and after 15 years of fluoridation (– – – –), in Grand Rapids before fluoridation (——) and in the natural fluoride area Aurora (--------).

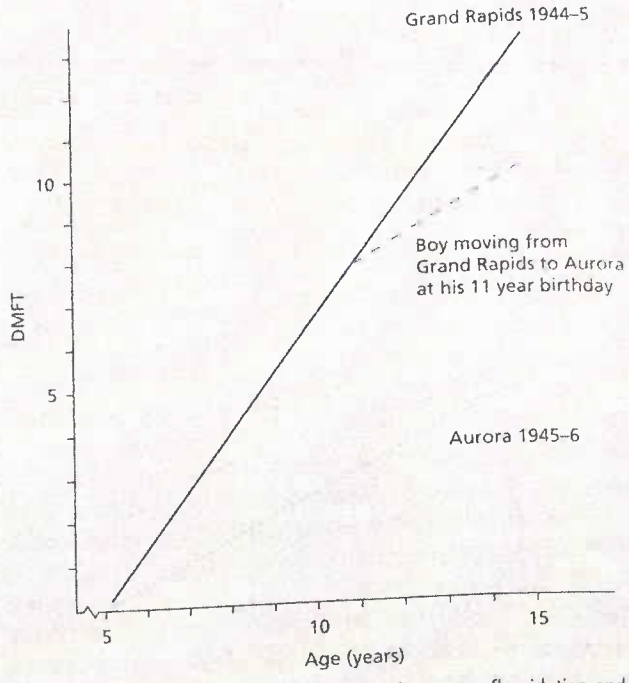

Figure 14.4 Dental caries in Grand Rapids before water fluoridation and in Aurora with fluoride in the water supply. The dashed line indicates caries progression in a boy moving from the non-fluoride to the fluoride area on his 11th birthday [107]. Reproduced with permission of John Wiley & Sons.

Although it is hard to think how these original studies in the USA could have been improved, some criticism can be made of the approach taken by Dean and his coworkers. Probably the most important is the possible bias introduced by the fact that the F^- level of the site investigated was known before the examinations were conducted (a problem which of course has been present in most other studies of the same kind). This might have resulted in a tendency to underscore fluorosis in later studies in different parts of the world, in particular when applying Dean's classification without including the 'questionable' category – or having had examiners not trained in the diagnostic characteristics of early signs of dental fluorosis. A similar bias could also be made in relation to the caries studies and the benefits may have been overestimated.

By the middle of the 20th century there was thus much enthusiasm about the possibilities for caries prevention using fluorides. During that period, in Europe in particular, the caries situation was overwhelming, with numerous tooth extractions amongst children, so attempts to introduce 'the American concept' of adding F^- to the water supplies were made in a few countries as exemplified in Holland. Similarly, it was introduced in Brazil. The concept of an 'optimum F^-' consumption was further advanced.

During these attempts, Hodge [91] presented the results of logarithmic transformations of Dean and coworkers' caries data and averaged index values of Dean's original scores of dental fluorosis (Fig. 14.4). It is now appreciated that this way of manipulating data is inappropriate (see later and Fig. 14.19). In a personal discussion (OF) with Hodge in 1982 he fully appreciated that, at the time, he was carried away when making this transformation of the data. However, from a public health point of view (and it appealed to the layman) it gave rise to a very convincing plot of data which indicated that children born and reared in areas with a F^- content in water supplies below 1 ppm would only experience a prevalence and severity of fluorosis that was considered of 'negligible biologic (aesthetic) significance.' Moreover, the mean caries experience recorded from the 21 city studies indicated that a maximum caries reduction was obtained around the concentration of about 1–1.2 ppm F^- in water supplies (Figs 14.5 and 14.6), so the 'optimum level' was determined as the level of concentration of F^- in water supplies that gave maximum caries reduction while causing minimal dental fluorosis of no concern from a public health point of view. This estimate of the optimal water F^- concentration was subsequently used to determine the amount of F^- that should be given in other systemic F^- regimens, such as tablets, vitamin drops, salt, and so on that became introduced in populations where health authorities would not allow artificial fluoridation of water supplies. For dose considerations and consequences, see later in this chapter.

The concept of the necessity of ingesting F^- was based on the belief that F^- exerted its anticariogenic effect predominantly by becoming incorporated into the crystals in

lesion progression. The more porous an enamel surface, the deeper the porosities where CaF_2 may form. These inaccessible microporous environments in enamel caries lesions may thus act as reservoirs for CaF_2 for prolonged periods (i.e., months) [22]. This slow-release mechanism probably explains the caries-reducing effect of concentrated topical F^- treatments provided by dental personnel.

We can conclude that to obtain a significant caries reduction using F^- the ion has to be present in the oral fluids at slightly elevated levels regularly during the day. This may be obtained from water, toothpastes, and several other vehicles – but remember, caries is not the result of F^- deficiency. F^- alone is not sufficient to obtain maximum caries control (see Chapters 9 and 16). Because F^- in toothpaste is applied concomitantly with removal/disturbance of the biofilms – if used appropriately, which is a major obstacle – it is the best possible way of obtaining maximum caries control. As will be apparent from the efficiency considerations later in this chapter, other vehicles (and protocols) may be chosen depending on the populations you are serving. *Therefore, there is not one – and only one – program to be recommended to all individuals, and in all communities.*

Dental fluorosis and metabolism of fluoride

In order to appreciate the clinical characteristics of dental fluorosis, it is important to understand the underlying histological features of the pathological changes in the tooth. The earliest manifestation of dental fluorosis is an increase in enamel porosity along the striae of Retzius [69]. With an increased exposure to F^- during tooth formation, the enamel exhibits an increased porosity in the tooth surface along the entire tooth surface (Fig. 14.10).

This porosity, which is a result of a hypomineralization of the enamel, can be seen in microradiographs, mainly in the subsurface enamel (Fig. 14.11). Hypomineralization is very different from hypoplasia. The normal structure of the enamel remains but the tissue is less well mineralized. The extent and degree of hypomineralization increases with increasing F^- exposure during tooth development. In humans, the most severe forms of the hypomineralized lesion extend throughout the enamel almost to the enamel–dentine junction in the cervical third of the crowns (Fig. 14.10c), whereas in the occlusal two-thirds of the teeth the band of hypomineralization extends more than halfway through the enamel. Such severely hypomineralized enamel will be very fragile; hence, when the tooth erupts, surface damage may occur due to mastication, attrition, and abrasion (Fig. 14.12). It is important to appreciate that in humans F^- has not been documented to cause true

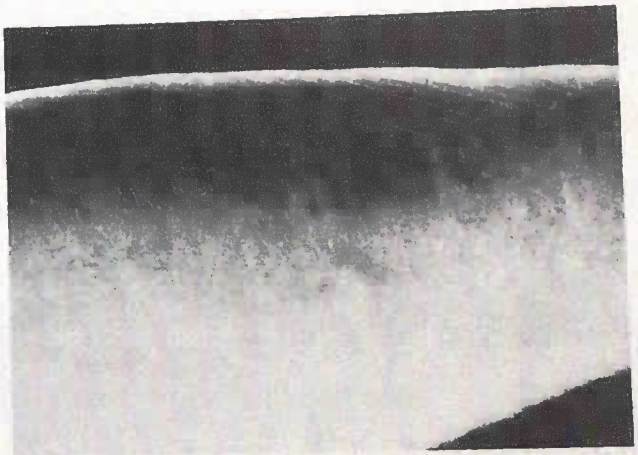

Figure 14.11 Microradiograph showing extensive hypomineralization of fluorosed enamel deep to a well-mineralized surface zone. Note incremental lines of Retzius. This represents a score of 4 according to the TF index.

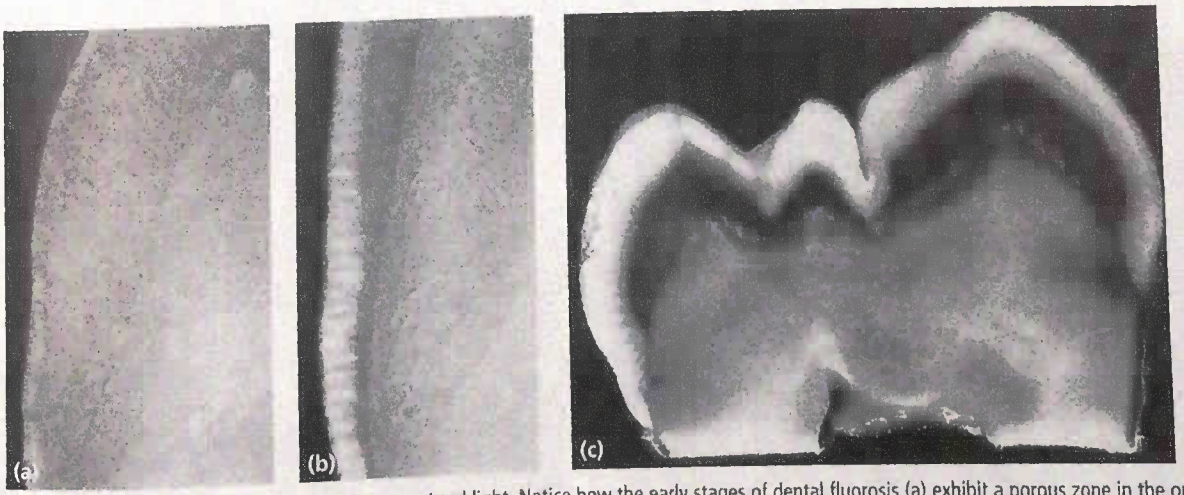

Figure 14.10 Ground sections of teeth examined in transmitted light. Notice how the early stages of dental fluorosis (a) exhibit a porous zone in the outermost enamel. With increasing severity this zone of porosity extends deeper into the enamel (b), and in very severe cases the porosity extends deep into the enamel tissue along the entire tooth crown (c) and in the cervical areas extends to the enamel–dentin junction.

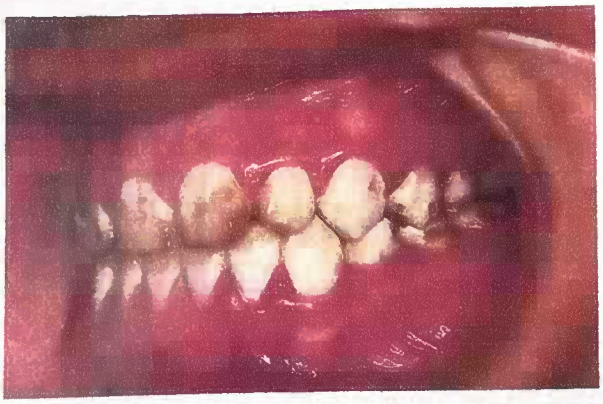

Figure 14.12 TF score 4 represents entirely white opaque enamel (see lower canine). As a reflection of the extension of subsurface hypomineralization, part of the surface enamel may break away posteruptively, creating TF scores 5–7. Brown discoloration of the porous enamel, which has occurred posteruptively, is also visible.

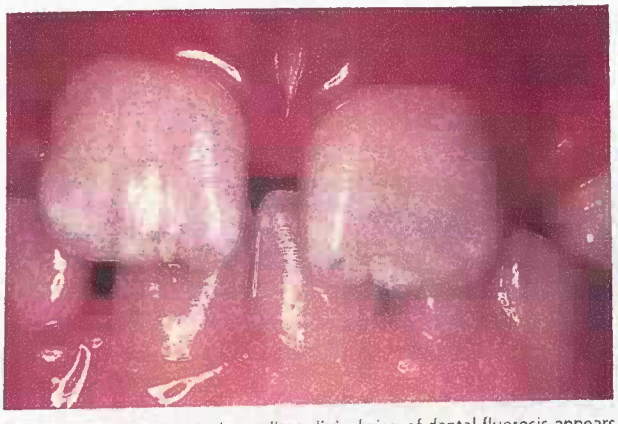

Figure 14.13 TF score 1: the earliest clinical sign of dental fluorosis appears as thin, white, opaque lines running across the tooth surface corresponding to the position of the perikymata.

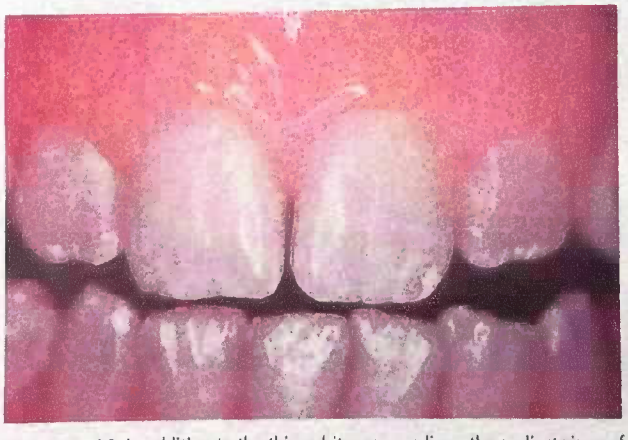

Figure 14.14 In addition to the thin, white, opaque lines, the earliest signs of dental fluorosis may include small, opaque, white areas along cusp tips, incisal edges, or marginal ridges.

hypoplastic changes; the characteristic pits, bands, and loss of extensive areas of enamel occur posteruptively and are not true hypoplasias.

Clinically, the porosity of the fluorosed enamel reflects itself as opacity of the enamel. Thus, F^--induced enamel changes at tooth eruption range from thin, white, opaque lines corresponding to the perikymata running across the tooth surface, to an entirely chalky white surface (Figs 14.13, 14.14, and 14.15). Depending upon the degree of hypomineralization, this chalky white enamel may then change posteruptively, due to mechanical damage, resulting in the more severe forms of fluorosis.

Dean's way of classifying dental fluorosis was based entirely on his interpretation of clinical appearance. In 1978, Thylstrup and Fejerskov proposed a way of recording dental fluorosis (TF-index) based on the histopathological features of the various degrees of dental fluorosis [169]. It is important to stress that the TF-index is a logical extension of the classification principles originally proposed by Dean; but, as would be expected, with a greater understanding of the underlying pathology, it is a more precise description of how to record early signs of fluorosis, as well as the more severe grades. Thylstrup and Fejerskov have ranged the severity of fluorosis in scores from 0 to 9 (Table 14.3 and Fig. 14.16).

This so-called TF-index represents a measurement on an ordinal scale and, therefore, should be considered only as an arbitrary point along a continuum of changes of the enamel. It is useful to compare the description found in Table 14.3 with the illustrations in Figs 14.12, 14.13, 14.14, 14.15, 14.17, and 14.18, where we can see that each score encompasses a small spectrum of fluorotic changes. It should be appreciated that if a child has been exposed to highly varying levels of F^- during the long-lasting period of tooth development, the intraoral distribution of fluorosis severity will be different to one who has been exposed to more constant F^- levels throughout the first 10–12 years of life [73, 102, 170]. The TF-index is the most appropriate

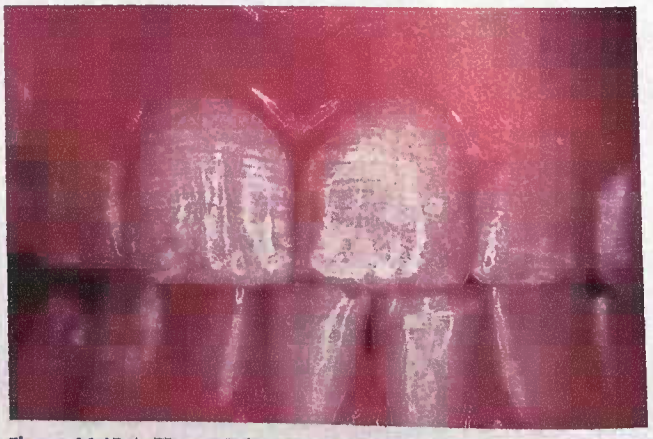

Figure 14.15 In TF score 2 the opaque white lines are more pronounced and frequently merge to form wider bands.

Table 14.3 The Thylstrup–Fejerskov index.

TF score	
0	The normal translucency of the glossy creamy-white enamel remains after wiping and drying of the surface
1	Thin white lines are seen running across the tooth surface. Such lines are found on all parts of the surface. The lines correspond to the position of the perikymata. In some cases, a slight 'snowcapping' of the cusps/incisal edges may also be seen
2	The opaque white lines are more pronounced and frequently merge to form small cloudy areas scattered over the whole surface. 'Snowcapping' of the incisal edges and cusp tips is common
3	Merging of the white lines occurs, and cloudy areas of opacity occur spread over many parts of the surface. In between the cloudy areas, white lines can also be seen
4	The entire surface exhibits a marked opacity, or appears chalky white. Parts of the surface exposed to attrition or wear appear to be less affected
5	The entire surface is opaque, and there are round pits (focal loss of the outermost enamel) that are less than 2 mm in diameter
6	The small pits may frequently be seen merging in the opaque enamel to form bands that are less than 2 mm in vertical height. In this class are also included surfaces where cuspal and facial enamel has chipped off, and the vertical dimension of the resulting damage is less than 2 mm
7	There is a loss of the outermost enamel in irregular areas, and less than half the surface is so involved. The remaining intact enamel is opaque
8	The loss of the outermost enamel involves more than half the enamel. The remaining intact enamel is opaque
9	The loss of the major part of the outer enamel results in a change of the anatomical shape of the surface/tooth. A cervical rim of opaque enamel is often noted

From Fejerskov *et al.* [73], as modified from the original work by Thylstrup and Fejerskov [169].

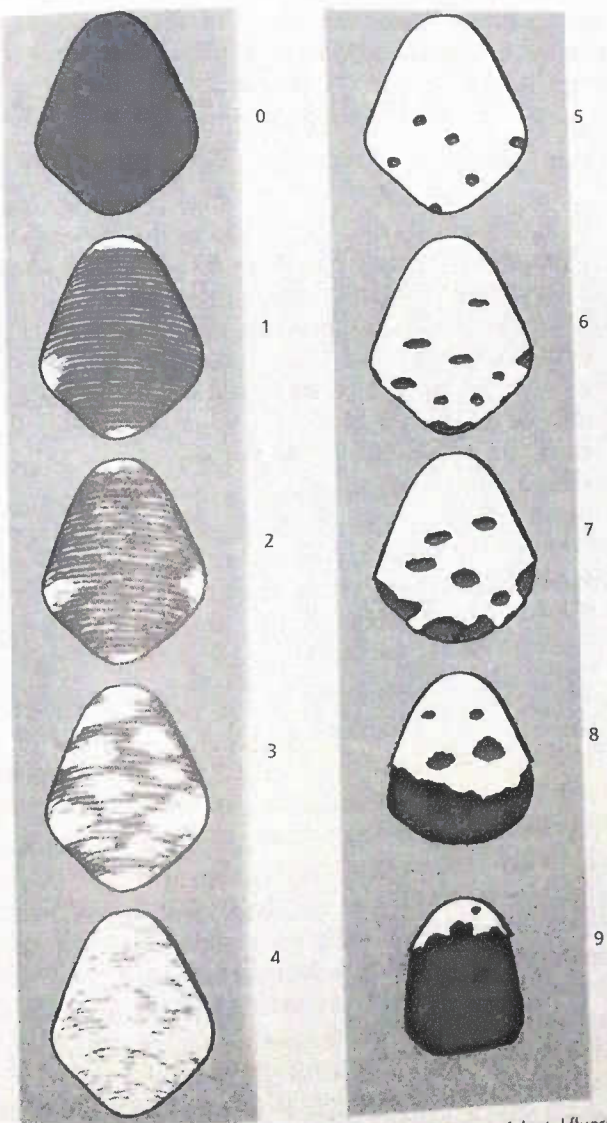

Figure 14.16 Diagrammatic illustration of the clinical features of dental fluorosis from the mildest form (TF 1) to the most severe (TF 9). Compare with Table 14.3.

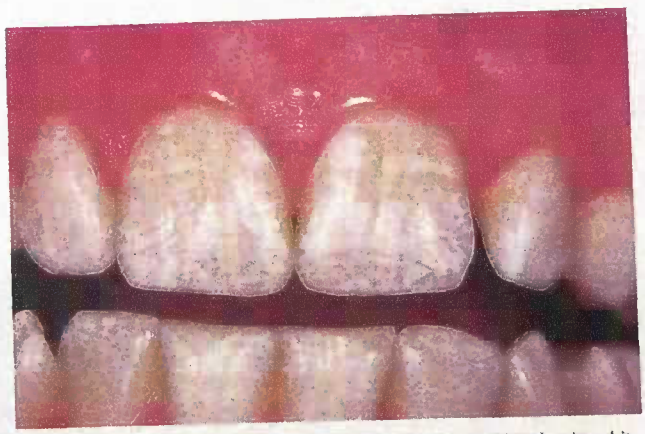

Figure 14.17 In TF score 3 the entire tooth surface exhibits cloudy, white, opaque areas between which accentuated perikymata lines are evident.

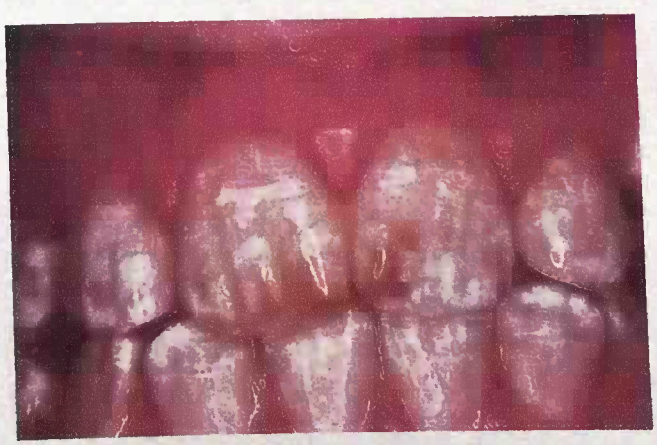

Figure 14.18 Another example of TF score 3 with the addition of posteruptive staining of the porous enamel.

way to classify the *biological severity* of fluorosis as it accurately reflects past F^- exposure. In a later section of this chapter on effectiveness of fluorides, the term *fluorosis of aesthetic concern* is introduced. This is highly subjective and reminiscent of the days where Dean talked about 'no public concern.' What is considered an aesthetic concern varies extensively from country to country – and often it is different in girls and boys. Therefore, when included in reviews it may give doubtful information which may lead to later misinterpretation and debates which should be prevented. An example: once, the first author was invited to a department of pediatric dentistry in the USA to calibrate the staff on how to record dental fluorosis – which the staff claimed was very rare in the county. He took with him a small handbook for health-care workers [73], and when the staff was looking at the pictures one said: 'we thought that it was natural to have these white teeth because everyone here looks like this – if this is the case we are having a high prevalence!'

Fluoride dose and dental fluorosis

It is remarkable that Dean's original data showed that the systemic effects of F^- on dental enamel were manifest even in communities exposed to concentrations of F^- below 1 ppm. Thus, the claim that water F^- concentrations around 1 ppm are 'of no public health significance' was for Dean not synonymous with saying that no dental fluorosis occurs in such populations.

Generally, any pharmaceutical product should be prescribed in relation to the body weight of the individual if its effect is systemic, but this does often not apply to F^- because its *anticaries* effect is local and not immediately concentration dependent, although the higher the concentrations in a toothpaste the longer time elevated F^- concentrations prevail (see 'Cariostatic mechanisms of fluoride' section). However, the F^- effect causing *fluorosis* is systemic and a dose–response effect would be expected. The use of water F^- concentrations has made attempts to produce valid estimates of a dose–response relationship between F^- ingestion and dental fluorosis difficult if weight and consumption are not considered. An accurate estimate of fluorosis severity can only be made in children when the permanent dentition erupts; hence, there is a considerable time lag between the F^- exposure during tooth formation and the measurement of the effect (dental fluorosis). In addition, no firm agreement exists as to how much F^- ingested from foods is in fact absorbed [166]. The bioavailability of F^- once ingested is relatively uncertain since the F^- compound in question and the contents of the stomach will determine the relative absorption of F^- by the organism. Therefore, the data about dose (expressed as mg F^-/day per kilogram body weight) for children from diet or dentifrice are dose of ingestion and do not reveal the fraction of F^- ingested that is in fact absorbed (bioavailable fraction). Furthermore, the suggested recommendation of 0.05–0.07 mg F^-/day per kilogram body weight [25] to give the anticaries benefit and minimize fluorosis has been shown not to be useful [116, 177].

However, despite all these difficulties, it is highly relevant to make use of the epidemiologic studies throughout the world which have shown a positive relationship between the water F^- content and severity of dental fluorosis [26, 46, 103, 108, 148, 169]. In an attempt to derive at an estimate of average water intake, daily consumption of water was related to air temperature, and Galagan and coworkers developed an equation that could describe the average water intake in relation to body weight in children as a function of air temperature [79–81]. For details on how to use these equations and calculate daily dose of F^- from drinking water, F^- tablets, and so on, the reader is referred to Fejerskov *et al.* [76]. When data from three large American epidemiological surveys conducted in the 1940s, 1960s, and 1980s are presented in such a way that the relationship between the average fluorosis score and daily F^- dose is calculated, a clear dose–response relationship is seen (Fig. 14.19) – for details concerning calculations, see [74, 75]. The following can be seen:

- Regardless of the source of the data, the regression of the fluorosis community index F_{ci} (Dean's way of averaging) on the daily dose of F^- from drinking water clearly demonstrates that even with very low F^- intake from water a certain level of dental fluorosis will be found.
- The dose–response relationship is clearly linear and the data indicate that for every increase of the dose of 0.0 mg F^- per kilogram body weight we can anticipate an increase in dental fluorosis in a population. Thus, there exists no 'critical' value for the F^- intake below which the effect on dental enamel will not be manifest.
- When the data originating from three distinctively different generations in the USA are examined – and hence a very different exposure to diet, commodities, and F^--containing dental products – there is no indication that the additional sources of F^- occurring until the mid 1980s have led to an upward shift of the dose–response curve.

When these data are kept in mind, it is to be expected that whenever more F^- is ingested in the form of tablets, salt, drops, toothpaste, and so on that both the prevalence and severity of dental fluorosis in a population will increase. Such an increase is not to be blamed, for example, on the F^- content per se in toothpastes, but is a simple reflection that dental fluorosis is a result of the total ingestion of fluorides during tooth development *irrespective of the source of the* F^-. The consequence of this, of course, is that if the water in any given area contains above 0.5 ppm F^- it is not acceptable uncritically to add further F^- for systemic use in such a population (e.g., salt). Furthermore, the estimation of an 'optimal F^- concentration' based on daily temperature

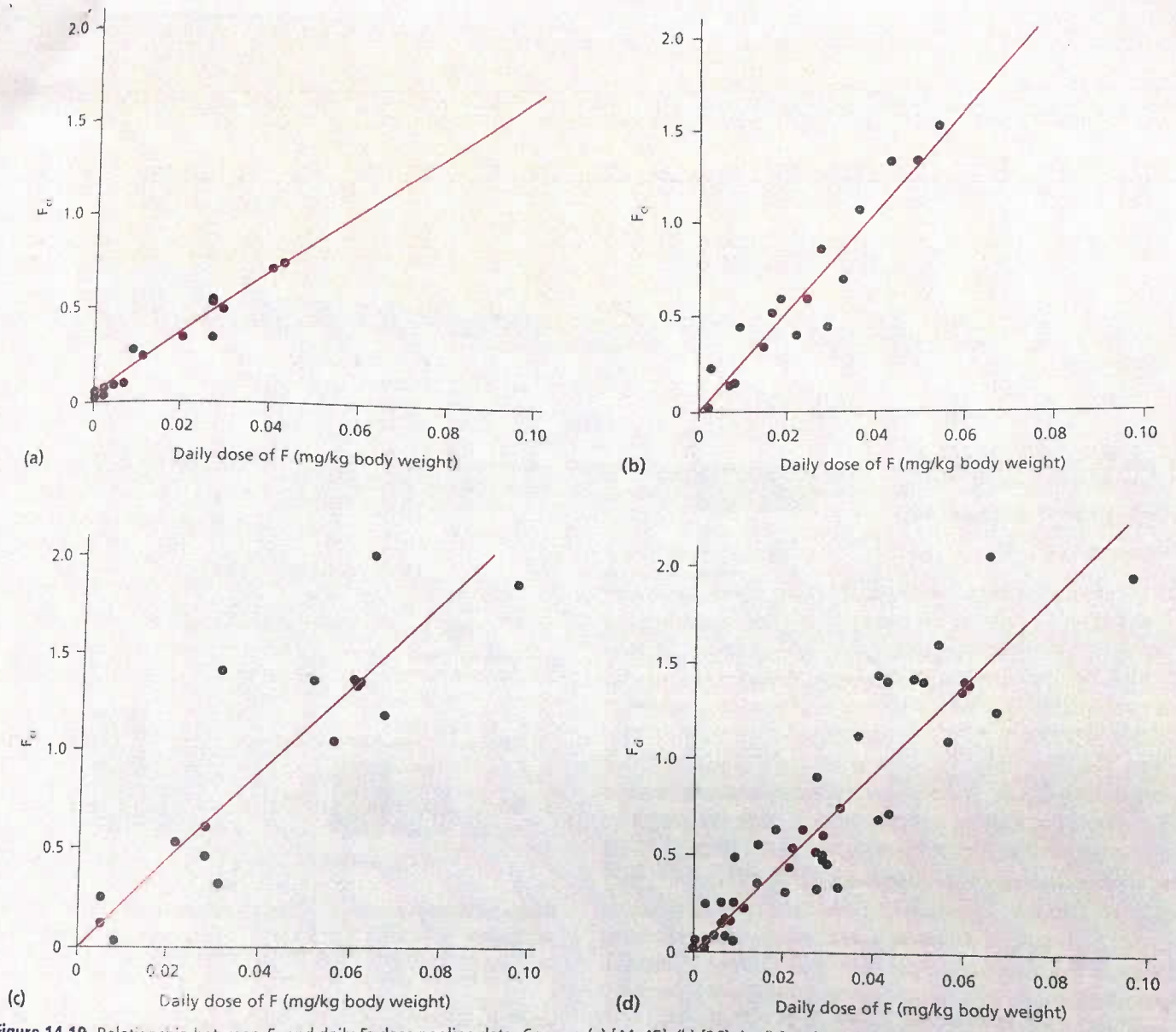

Figure 14.19 Relationship between F_{di} and daily F^- dose pooling data. *Sources:* (a) [44, 45]; (b) [26]; (c, d) [148]. All data sets pooled as presented by Fejerskov *et al.* [74, 75].

seems not to be valid for tropical regions when additional fluids are consumed and higher daily F^- intake is estimated [106]. Therefore, in tropical countries having water with natural F^- concentration as low as 0.5 ppm, a higher prevalence and severity of dental fluorosis should be expected if the population simultaneously is using fluoridated salt; Colombia is a good example.

Calculations of this type are useful, for example, when interpreting the effect of giving F^- tablets to a population. Thus, when considering the effect of different F^- tablet dose regimes in the USA [1] and in Sweden [86], it is apparent that, had these dose–response curves been generated at the time when the F^- tablet regimes were developed, it would have been possible to predict the subsequent level of fluorosis.

It is also important to understand that, if we assume a constant dose of F^-, the effects of F^- are cumulative; hence, the longer the teeth undergo mineralization the more severe the fluorosis will be. Figure 14.20 shows data from a very low F^- area [101]. The highest prevalence and severity of fluorosis is seen in the second molar teeth, whilst the prevalence and severity in the first molars erupting 6 years earlier is much lower.

Figure 14.19 shows the linear relationship between daily F^- dose and fluorosis prevalence, over the dose range 0–0.1 mg per kilogram body weight. Therefore, even very low levels of F^- ingestion (0.02 mg F per kilogram body weight) constitute a small risk of fluorosis. We can also see that an ingestion of 0.1 mg F^- per kilogram body weight per day would almost certainly result in a significant risk of

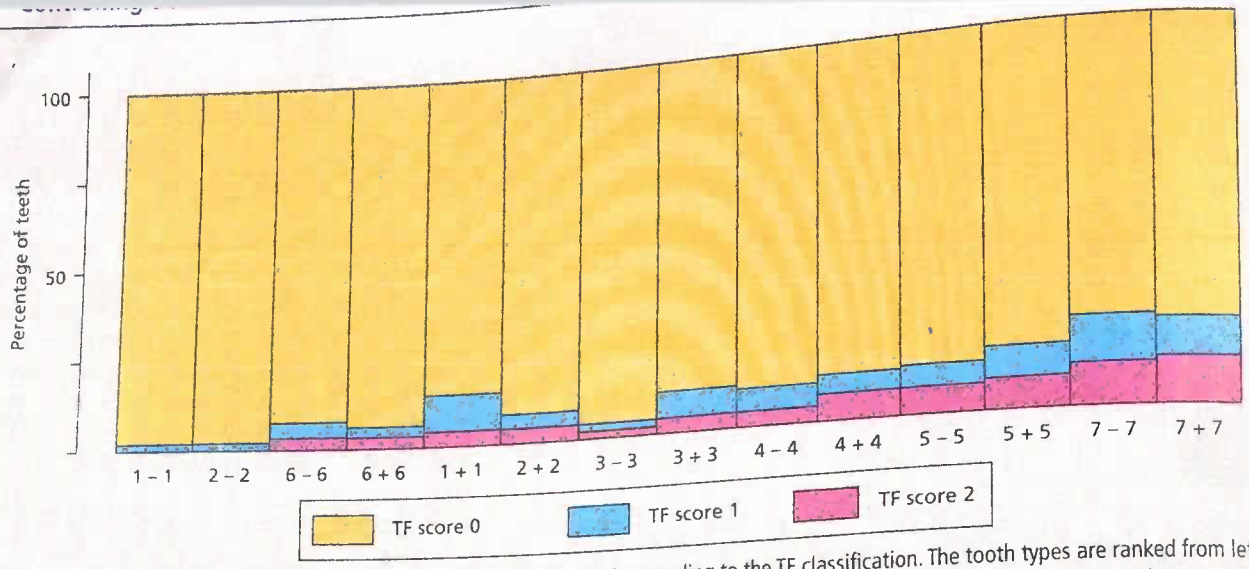

Figure 14.20 Diagram showing the percentage of teeth exhibiting dental fluorosis according to the TF classification. The tooth types are ranked from left to right in the order of mineralization. The data originate from children born and raised in an area of Denmark with less than 0.1 ppm F^- in the drinking water [101]. +: maxillary teeth; –: mandibular teeth.

developing the more aesthetically compromising forms. There is *only* a risk of developing dental fluorosis when the dentition is developing (from before birth to almost 20 years of age). From a cosmetic point of view, the permanent upper central incisors are particularly at risk between the ages of 15 and 30 months [67]. This can be explained when considering the data from Richards *et al.* [145] suggesting that dental fluorosis in humans results predominantly from a disturbance of enamel maturation. Although the weight of young children is highly variable, a 2-year-old child might be expected to weigh approximately 12 kg. We can therefore estimate that a F^- ingestion of 1.2 mg/day would constitute a very high risk of developing aesthetically compromising forms of fluorosis for a 2-year-old. As infants get older and heavier, the risk of fluorosis moves to the more posterior teeth, and because of the greater body weight the dose of F^- required to be ingested would be more. For example, a 5–6-year-old weighing approximately 20 kg would need to ingest approximately 2.0 mg. But at the same time, it should be remembered that the steady-state level of F^- in plasma will increase with age; so, if a child has been exposed to F^- from birth then such a child is likely to be more at risk than a child of the same weight who has not been lifelong exposed.

Calculations of F^- ingestion, although useful, are subject to many errors and must be treated with caution. Figure 14.21 represents the amounts of toothpaste (grams) required to be *ingested* to constitute an intake of 0.1 mg F^- per kilogram body weight for 12 and 20 kg children. Covering the head of a child's toothbrush would constitute an application of approximately 0.5–1 g of paste, and for a standard-head toothbrush it would be approximately 1–1.5 g of paste. It can be seen, therefore, that children brushing twice daily may be in contact with sufficient F^- to constitute a risk of dental fluorosis, particularly when using

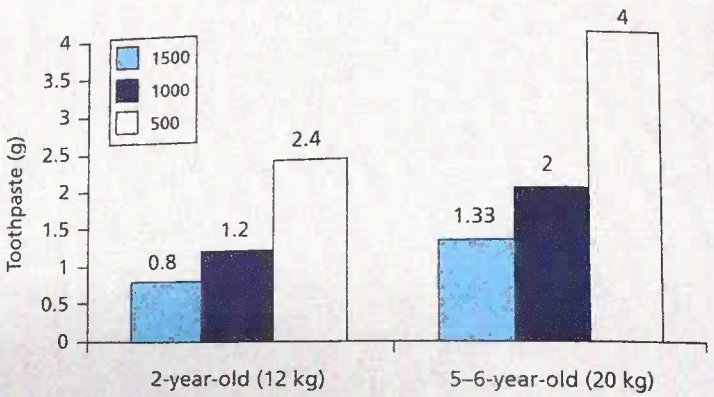

Figure 14.21 Daily amounts of toothpaste (grams) required to be ingested to constitute an intake of 0.1 mg F^-/kg for 12 and 20 kg children for three different F^- levels in toothpaste (1500, 1000, and 500 ppm F^-).

toothpastes containing the higher levels of F^-. Young children tend to swallow a greater percentage of toothpaste than older ones [104], with 2-year-olds swallowing on average half the toothpaste used and 6-year-olds swallowing one-quarter (Tables 14.4 and 14.5). Therefore, we must, on average, multiply the amounts shown by factors of 2 and 4 for the 2-year-old and 5–6-year-old children respectively.

In addition, the amount of F^- absorbed from ingested toothpaste will depend on the gastric contents at time of ingestion and the type of toothpaste. Toothbrushing is usually conducted after meals, and this can significantly reduce F^- bioavailability. In fact, F^- bioavailability from an 1100 ppm toothpaste ingested after lunch can be very similar to that of a 550 ppm toothpaste ingested on fasting (Fig. 14.22). Regarding toothpaste composition, it should be considered that many affordable toothpastes are formulated with a calcium-based abrasive agent, and with MFP as the F^- salt. In these formulations, about 20–30% of F^- is

Table 14.4 Amount of dentifrice used per brushing (grams) or F^- per brushing (milligrams)[a] by age.

Study	Age range (years)						
	2–3	4	5	6–7	8–10	11–13	16–35
Ericsson and Forsman [65][b]		0.45		0.45			
Hargreaves *et al.* [88][c]			0.38			1.10	
Barnhart *et al.* [11][b]	0.86			0.94			1.39
Glass *et al.* [83][b]					1.04[d]		
Dowell [55][c]	0.55						
Bruun and Thylstrup [21][c]	0.55[d]			0.75[e]	1.10[d]		1.55[d]
Simard *et al.* [156][b]	0.46	0.78	0.65				
Naccache *et al.* [125][b]	0.50		0.47				
Naccache *et al.* [155][b]	0.55	0.45	0.52	0.50			
Mean value	0.58	0.56	0.50	0.66	1.07	1.10	1.5
(no. of studies)	(6)	(3)	(4)	(4)	(3)	(1)	(2)

Source: [147].
[a]If one assumes that the dentifrice contains 0.1% (1000 ppm), then the ingestion of *x* g of dentifrice results in the ingestion of *x* mg of fluoride.
[b]Supervised dentifrice use study.
[c]Home-use study.
[d]No attempt was made to control for spillage of dentifrice.

Table 14.5 Percentage ingestion of dentifrice fluoride by age.

Study	Age range (years)						
	2–3	4	5	6–7	8–10	11–13	16–35
Ericsson and Forsman [65][a]		30		26			
Hargreaves *et al.* [88][b]			28				
Barnhart *et al.* [11][a]	35			14		6	3
Glass *et al.* [83][a]					12[c]		
Simard *et al.* [156][a]	59	48	34				
Naccache *et al.* [125][a]	41		30				
Naccache *et al.* [126][a]	57	49	42	34			
Mean value	48	42	34	25	12	6	3
(no. of studies)	(6)	(3)	(4)	(3)	(1)	(1)	(1)

Source: [132].
[a]Supervised dentifrice use study.
[b]Home-use study.
[c]No attempt was made to control for spillage of dentifrice.

bound to calcium, being insoluble and not absorbable. Therefore, if total F^- in such formulations is considered to calculate the dose to which children are exposed by inadvertent ingestion during toothbrushing, a dose twice as high would be found when compared with a formulation in which all F^- is soluble (e.g., a silica-base, NaF toothpaste). However, if only the soluble (bioavailable) F^- fraction in both types of formulations is considered, the bioavailable dose would be similar [133] (Table 14.6). Unfortunately, this has not been considered when the risk of fluorosis by toothpaste ingestion is discussed; and as most publications overestimate the effect of toothpaste alone or the relative contribution of F^- toothpaste to total daily F^- ingestion by young children, this has had implications on the recommendations of toothpaste use by children [66].

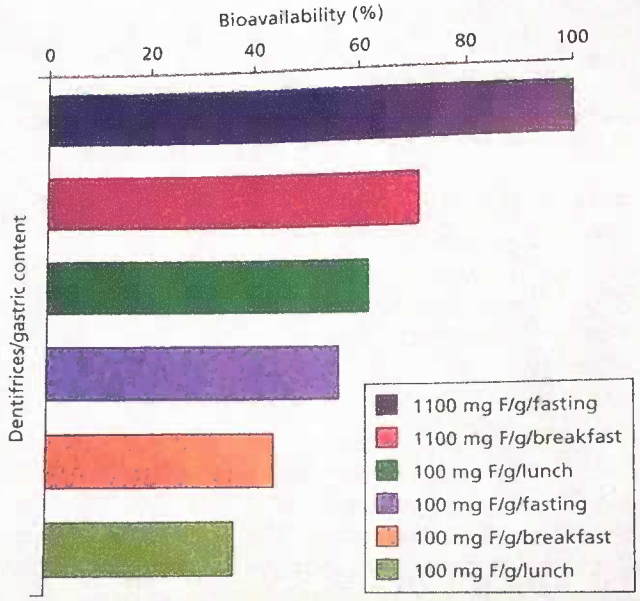

Figure 14.22 Bioavailability of F^- ingested from toothpastes, depending on the content of the stomach. From [42].

Table 14.6 Estimated dose of F^- (mg F^-/kg body weight per day) to which a sample of Brazilian children were subjected during toothbrushing with MFP/$CaCO_3$ or NaF/silica formulations, based on total or soluble F^- concentrations in toothpastes (mean ± SD).

Toothpaste formulations	Dose based on F^- concentration determined in toothpaste	
	Total F^-	Soluble F^-
MFP/$CaCO_3$[a] (n=80 children)	0.074 ± 0.007	0.039 ± 0.005
NaF/silica (n=79 children)	0.039 ± 0.003	0.039 ± 0.005
All (n=159 children)	0.057 ± 0.004	0.039 ± 0.003

From [133].
[a]MFP/$CaCO_3$ toothpastes formulated with a higher total F^- concentration (1500 ppm F^-) but with similar soluble F^- concentration (1000–1100 ppm F^-) when compared with NaF/silica toothpastes (1000–1100 ppm F^-).

Tables 14.4 and 14.7 show that the amount of toothpaste children use is fairly consistent between the ages of 2 and 7. This has important consequences for fluorosis risk. Young children not only swallow more toothpaste and are often not supervised when brushing, but they also are at greater risk of fluorosis as their body weight is lower than older children. Therefore, we must be particularly cautious when using F^- toothpaste in the youngest children and ensure that small (pea-sized or in Brazil rice sized!) amounts are used and they are encouraged to spit out the waste toothpaste slurry as efficiently as possible [14, 15].

Although the quantity of F^- swallowed from toothpaste is not as high as often anticipated, F^- in toothpaste will add to an increase in overall F^- consumption and hence increase the risk of developing more fluorosis in populations living in areas with F^- in the drinking water or using other forms

Table 14.7 Estimated median weights of children [54] and fluoride intake according to age estimated from twice daily use of a 1000 ppm F toothpaste [86].

Age	Median weight of child (kg)	Toothpaste use per day (g)	Toothpaste ingested (%)	(mg F^-/kg for 1000ppm F^- toothpaste)
2	11.9	1.16	48	0.047
3	14.3	1.16	48	0.039
4	16.3	1.12	42	0.029
5	18.3	1.00	34	0.019
6	20.6	1.32	25	0.013

Source: [76].

of systemic F^-, such as tablets or salt. In regions with fluoridated drinking water there are a number of studies reporting a relationship between F^- ingestion from toothpaste and milder forms of dental fluorosis [120, 134, 137–139, 149, 180]. In countries, like the USA and Brazil, where water fluoridation is widespread and the use of F^- toothpaste is common, the most prevalent degree of dental fluorosis found is claimed to be 'mild' and not of 'public health concern' [31, 53, 123, 140, 141]. Whether a degree of dental fluorosis is of 'public health concern' is very culturally dependent. If living in an area with widespread milder forms of fluorosis, this is often considered 'normal'.

Where is fluoride found in nature?

F^- is a trace element widely present in the environment. F^- gets into the hydrosphere by leaching from soils and minerals into ground waters. Volcanic eruptions and dust storms in areas rich in volcanic rocks add to the F^- in the atmosphere.

Owing to the small radius of the fluorine atom, it is the most electronegative and reactive element and is rarely found in its elemental state. It is most commonly found in combination in the ionic F^- and the electrovalent or covalent form. Most of the ionic fluorides are soluble in water, although some, such as CaF_2, are only slightly soluble. Further information is available from the detailed textbook chapters by Smith and Ekstrand [158] and Glemser [84].

Water is by far the most common natural source of F^-; but even in areas with levels of F^- in the drinking water less than 0.5–0.7 mg/L, the importation of commercially prepared beverages and other foods from areas where water supplies contain higher levels can add substantially to the amount of F^- ingested. Some fruit-flavored, carbonated soft drinks and mineral water may also contain significant (0.7–0.9 mg/L) amounts of F^- [38, 152]. Fish is a particularly good source of F^-, as are tea leaves, although they differ on F^- bioavailability. A cup of tea [56] or iced tea [89] may have a F^- concentration of 0.5–4 mg/L. An assessment of the total exposure of a given population to F^- requires not only a thorough knowledge of the F^- concentrations of foods and beverages and an understanding of the open markets of a modern society, but also a careful assessment of potential F^- ingestion from dental products.

Fluoride absorption, distribution, and elimination in the body

F^- ingestion is particularly important in infants as dental fluorosis can only occur when teeth are developing. F^- is poorly transported from plasma to breast milk, even when the mother or animal has a high intake of F^-, and human and other mammalian milks contain very low concentrations of F^- [159]. In contrast, commercially prepared formula milks may have a highly variable F^- conten, and if they are prepared with fluoridated water, children may potentially ingest considerable amounts of F^- from this source [78, 105].

It is outside the scope of this textbook to deal in detail with F^- metabolism in humans, but any dentist should be expected to have a thorough knowledge about the pharmacokinetics of F^- and are referred to authoritative texts (see Ekstrand [60] and Whitford [179] for reviews). Following ingestion, soluble F^- is rapidly absorbed into the blood plasma, predominantly in the stomach. The stomach contents are important in determining the rate of absorption. Milk, calcium-rich breakfasts, and even lunch may reduce the degree of absorption from about 90% to about 60%. The time of F^- ingestion in relation to meals is critical with respect to how much of the F^- will become bioavailable [42, 64]. Also, when toothpastes are ingested by children the amount of F^- that is absorbed depends on toothpaste formulation because in those containing calcium in the abrasive only part of the F^- is bioavailable [150].

F^- not absorbed in gastrointestinal tract is excreted by feces, which usually accounts for less than 10% of the amount ingested each day by diet [63]. F^- is distributed all over the body by plasma, predominantly as ionic F^-. Plasma F^- concentrations vary considerably over the day depending on the intake of F^-. With increasing age, plasma F^- levels gradually increase because there is a direct relationship between the amounts of F^- accumulating in bone, which, as time passes by, is gradually released from the bone as part of bone remodeling [135]. There is no homeostatic mechanism to maintain the F^- concentration in any body compartment, and blood F^- levels are largely dependent upon daily intake. This has important implications for the oral environment, as will be described further in this chapter.

F^- is distributed from the plasma to all tissues and organs in body. Naturally, the degree of blood flow through the different types of tissues determines how rapidly distribution occurs. Of particular interest is that the kidney in general has a higher concentration of F^- than the corresponding concentration in plasma (high ratio tissue/plasma). In contrast, the central nervous system, like

adipose tissue, only contains about 20% of the concentration of that of plasma [160].

As previously stressed, F^- is a highly reactive agent and it reacts rapidly with mineralizing tissues. Over time the F^- gradually becomes incorporated into the crystal lattice structure in the form of fluorhydroxyapatite. It is during the growth phase of the skeleton, during active mineralization, that the highest proportion of an ingested F^- dose will be deposited. Thus, retention of F^- in infants may be as high as 90%, whereas in adults only about 50% of the F^- may be retained in the bone.

F^- in the bone is not irreversibly bound to the crystals. Bone in humans constantly undergoes remodeling and F^- is thus mobilized slowly from the skeleton. Therefore, when studying cross-sectional samples, F^- concentrations in plasma and urine will not only be determined by the immediate past intake of F^- but also by earlier F^- exposure and the degree of accumulation of F^- in bone. Moreover, with age the mobilization rate from bone and how efficient the kidneys are at excreting F^- will strongly influence such data [62]. Thus, bone might be considered a F^- reservoir that maintains F^- concentration in the body fluids between the periods that F^- is not being ingested.

F^- absorbed and not incorporated in bone is eliminated mainly by urine during the excretion. If the pH of urine is low, F^- is reabsorbed in renal tubules, returning to the blood [179]. This mechanism may be important regarding the chronic effect of F^- because the duration of high plasma F^- concentration is prolonged.

Fluoride concentrations in teeth

Concentrations of F^- in all mineralized tissues will vary depending on the actual F^- intake and the length of time during which such an intake has taken place. The F^- concentration in bulk enamel is fairly constant but increases steeply at the surface within the outer 100 µm. Recently, this has been suggested to be a result of the fluctuating pH changes in the surface of enamel caused by the ameloblasts during the long-lasting phase of enamel maturation, which in permanent teeth may last for several years before eruption [96]. The F^- concentration of dentin is generally slightly higher than that of bulk enamel and usually increases as we go deeper into the tooth (Fig. 14.23). As dentin formation continues slowly throughout life, F^- steadily accumulates at the dentin–pulpal interface.

It can be seen in Fig. 14.23 that the overall shape of the F^- profile from the surface of the enamel to the enamel–dentin junction is a characteristic 'hockey stick' shape. The relative concentrations of F^- in the different layers of enamel reflect the F^- exposure during tooth development. Hence, the higher the dose of F^- occurring during development, the higher the concentration of F^- is to be found in enamel. The effect of different levels of F^- exposure can be seen in Fig. 14.24. Clearly, teeth with the more severe forms of fluorosis (TF scores 7+8+9) have significantly higher levels of F^- in the enamel than those with less severe forms, and this difference is maintained even deeper in the enamel. The concentration of F^- at the outermost surface of the enamel is not only an indicator of F^- exposure during the developmental period of the tooth but also highly dependent upon post-eruptive changes (see Fig. 14.25).

Once the enamel is fully formed and mineralized, the F^- content in human enamel can only be permanently altered as a result of chemical traumas to the tooth (dental caries and erosions) or through mechanical abrasion. Unless chemical interactions take place with substantial fluctuations in pH over a prolonged period of time it is in fact not easy to significantly change the F^- content in the surface enamel even after several topical F^- treatments. However, the F^- concentration in the surface layers increases whenever de- and remineralization processes are ongoing [40, 146, 178]. This means that, in cervical regions, where dental plaque accumulates, F^- concentrations will gradually increase over time. It is also the reason why the surface zone covering a subsurface carious lesion contains significantly higher amounts of F^- than the surrounding normal enamel (Fig. 14.26).

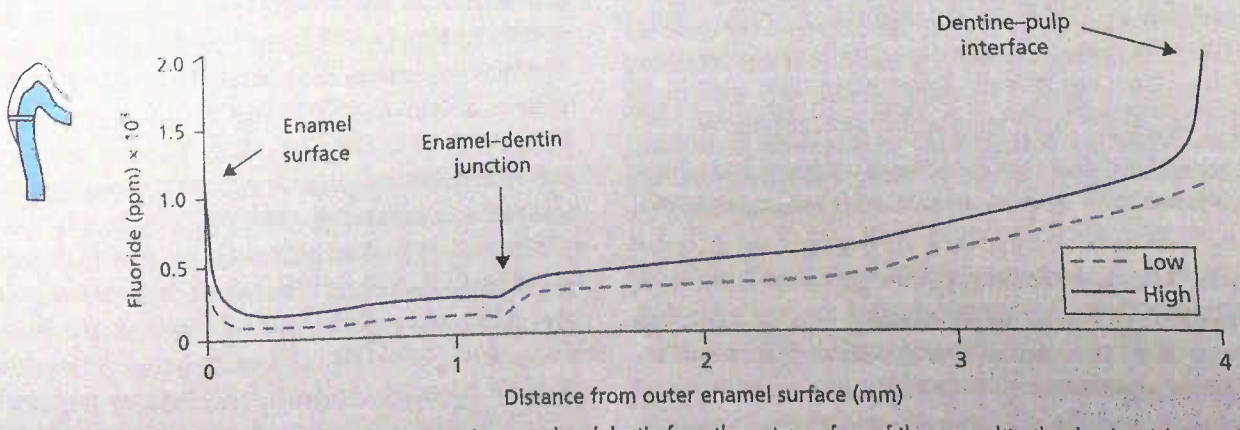

Figure 14.23 Schematic representation of the F^- concentration in enamel and dentin from the outer surface of the enamel to the dentin–pulp interface for subjects with a low and higher F^- intake.

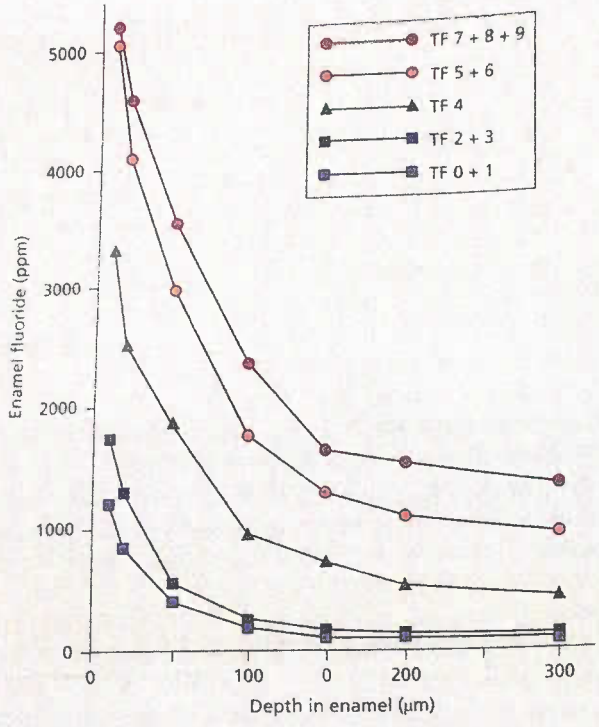

Figure 14.24 Enamel F^- concentrations in the outer 300 µm of the enamel for erupted teeth with different degrees of fluorosis. See Fig. 14.16 for explanation of the TF index [146].

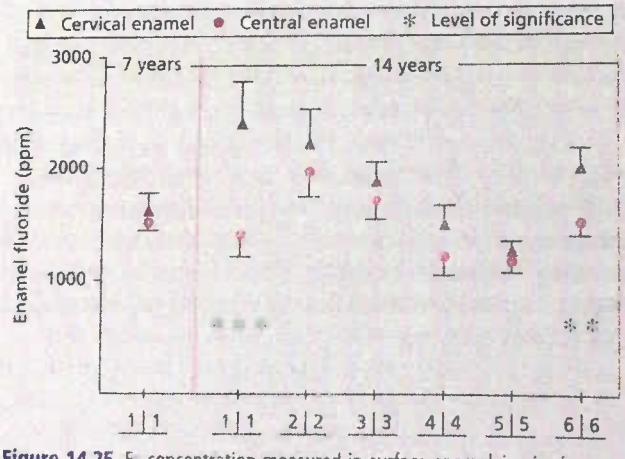

Figure 14.25 F^- concentration measured in surface enamel *in vivo* in upper central incisors at the age of about 7 years (shortly after eruption). The concentration is the same in central and cervical enamel. However, after 7 years in the oral environment it is apparent that F^- in the cervical enamel (where plaque accumulates) increases, whereas it remains unchanged or gradually drops in central parts that have been exposed to attrition/toothbrushing [144].

The difference in F^- content of enamel formed in low F^- areas (<0.2 ppm F^- in the water supply) and an area with about 1 ppm of F^- is so small that it cannot explain differences in caries experience in populations living in low and higher F^- areas. Also, even in the enamel surface, where F^- concentration is 'maximum,' it represents only a substitution

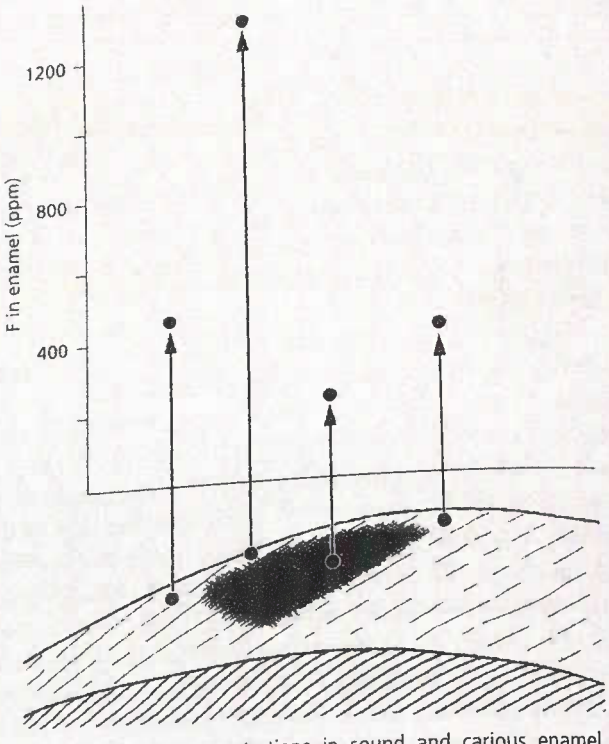

Figure 14.26 Fluoride concentrations in sound and carious enamel. The lowest concentrations are found in body of the lesion and then the sound bulk enamel. The surface enamel layer covering the lesion has picked up considerable amounts of F^- from the surrounding fluids. Modified from [178].

of 5–10% of hydroxyl by F^- ions and it is necessary to have 60% of substitution to form a mineral that is more acid resistant. Moreover, there is no association between the F^- concentration in the surface zone of teeth and the individual's caries experience for either the primary or permanent teeth (Fig. 14.27).

Pathogenesis of dental fluorosis

Until the 1970s it was generally assumed that F^- caused dental fluorosis by interfering with the process of enamel matrix formation and mineralization and that the secretory ameloblast was highly sensitive to slightly elevated plasma concentrations of F^-. However, microscopic studies of human enamel [69, 70] showed that enamel fluorosis was a hypomineralization of the enamel in an otherwise normal enamel maturation. Therefore, it was suggested that F^- predominantly affected enamel by retarding the processes of pre-eruptive enamel maturation [71]. Moreover, the studies showed that enamel pits resulted from mechanical damage to the enamel after eruption of the tooth [10, 73]. To test the hypothesis that dental fluorosis might be a result of F^- delaying otherwise normal enamel maturation, Richards and coworkers [5, 145] conducted a series of experiments in domestic pigs which clearly showed that F^- given systemically during enamel maturation only, in dosages comparable to humans, would result in subsurface hypomineralized

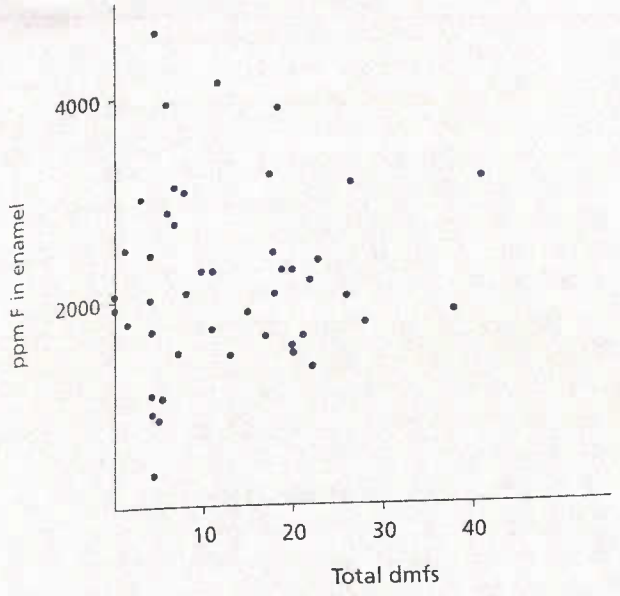

Figure 14.27 F^- concentrations in the surface enamel of deciduous canines and dental caries prevalence in the deciduous dentition. No relationship between the two is apparent [143]. Reproduced with permission of Karger Publishers.

enamel at the time of eruption. How F^- ingested in just slightly elevated concentrations over several years can influence enamel maturation at the time of pre-eruptive maturation is still unknown!

It should be understood that once the full width of enamel is laid down the enamel is far from fully mineralized. The transformation of soft, protein-rich enamel into highly mineralized, hard mature enamel is a result of growth in size of the already seeded crystals. Once a matrix is laid down, the apatite crystals are instantaneously seeded and mineral increase occurs as a result of longitudinal growth of the crystals. In fact, in rats it has been calculated that the enamel contains only about 18–20% of mineral after being fully formed (see [157] for a review). Following this the enamel matrix proteins have to be broken down and removed from the enamel while calcium and phosphates have to be simultaneously transported into the enamel and allowed to precipitate onto the growing crystal surfaces. The hydroxyl apatite crystals grow predominantly in width and thickness until the enamel contains about 96% mineral by weight. Enamel crystals grow very slowly, and pre-eruptive enamel maturation may last for several years in humans! Despite extensive studies on normal enamel maturation in experimental animals, the processes leading to a fully mineralized enamel are far from understood [96]. Therefore, it is speculative as to how F^- in small elevated dosages in plasma may interfere with the processes.

In a review, Aoba and Fejerskov [6] discussed in depth the various possibilities for how F^- ions may influence enamel mineralization during tooth development. Enamel mineralization is highly sensitive to free F^- ions promoting the hydrolysis of acidic precursors to apatite formation, such as octacalcium phosphate. This results in precipitation of fluoridated apatite crystals.

The effectiveness of fluorides in the control of dental caries: evidence from systematic reviews

Evidence from comprehensive systematic reviews on fluorides for caries prevention and control has come to occupy a key position between research and practice in the last decade. As reliable summaries of accumulated knowledge, they inform decisions, are the basis for recommendations about the appropriate use of F^--based caries preventive interventions, and are making clearer the scientific justification for future research on the subject. Cochrane reviews are systematic reviews that employ rigorous research methods and are published in full in *The Cochrane Library* (http://www.thecochranelibrary.com) following a detailed editorial process that is common to all reviews. Cochrane reviews have answered important questions regarding the effects of F^- on caries prevention. Consequently, they have become very influential as a foundation for preventive practice and policy in dentistry.

The UK National Health Service (NHS) Centre for Reviews and Dissemination's (CRD's) review of the effects of water fluoridation was the first systematic review undertaken on the subject. This systematic review was set up by the University of York and is colloquially known as the York review. It was conducted as an open process and to the highest standards [118]. This review has shown that research carried out over the past half century has been of a much lower methodological quality than had previously been reported. This review pointed out that the evidence of a benefit of a reduction in dental caries should be considered together with the evidence of an increased prevalence of dental fluorosis, and that there would continue to be a need for high-quality studies providing more definite current evidence on the effects, both positive and negative, of water fluoridation. The findings of this review published in 2000, which have been interpreted in quite different ways on both sides of the fluoridation debate, reinforced the importance of systematic reviews of the large body of experimental evidence on the effects of all the main forms of F^- treatments used for caries prevention/control.

The series of Cochrane systematic reviews on the effectiveness and safety of F^- toothpastes, mouthrinses, gels, and varnishes published throughout the last decade are considered the most comprehensive and most detailed on the subject to date [109–115, 176, 180]. They bring together, in a consistent manner, the available evidence on the effects of the main modalities of topically applied F^- interventions currently used for the prevention/control of dental caries,