The Level and Timing of Systemic Exposure to Fluoride with Respect to Caries Resistance

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Material related to water fluoridation and fluoride availability has been examined for changing patterns of fluoride intake by humans over recent years. The difficulty of separating systemic and topical fluoride action from water and foods from that found in fluoride agents used in preventive treatment programs is discussed.

Recommendations are made that water fluoridation is a well-proven program and should be continued, but that fluoride supplementation programs under the control of the individual should be carefully evaluated and, if used, should be restricted to periods after the secretory stage of enamel formation is normally finished for anterior teeth, with supplements commenced during the pre-eruption maturation period and continuing until permanent tooth eruption is complete. Although supplements can also give a topical source to the teeth, depending on the way the supplement is consumed and the duration of time it is available in the mouth, other methods of topical fluoride provision are endorsed, and these should continue through life. It is suggested, in respect of epidemiology studies, that data collected before the availability of fluoride dentifrices in 1971 should be re-examined.


Introduction.

In 1989, an international symposium, jointly supported by the International Association for Dental Research and the European Organization for Caries Research, examined the mechanisms of action and recommendations for use of fluoride (J Dent Res 69 (Spec Iss):505-836, 1990).

From these and other studies, the changing patterns of systemic fluoride intake by humans over recent years were highlighted.

It is increasingly difficult to separate the systemic and topical role of fluorides and fluoride-containing agents from, on one hand, the systemic sources available in water and foods and, on the other hand, the universal availability of fluorides providing a topical action from sources such as dentifrices and fluorides given by the dental profession in preventive treatment programs (Margolis and Moreno, 1990).

The systemic use of fluorides can, like many other nutrients and drugs, have both a beneficial and a harmful action, depending on the agents used, the amounts given, and the timing of availability during growth and throughout life.

The following discussion paper will examine specifically the beneficial action of systemic fluorides related to timing and caries resistance.

When one is looking at studies completed, it is necessary, particularly in regard to epidemiology studies in man, to look again at data collected prior to the ready availability of over-the-counter sales of fluoride-containing toothpastes and mouthrinses. It is difficult for systematic outcomes in epidemiological data collection to be assessed, since no one should be encouraged to act as controls and be denied access to home-fluoride products. This means going back to before 1971 in most European studies and before 1975 for studies undertaken in the US, the time when fluoride dentifrices became readily available through over-the-counter sales.

Animal experiments.

Animal experimentation has provided considerable evidence on the role of fluoride during tooth development and incorporation into the tooth structures; much of this research has examined not only dental caries but also other conditions, such as dental fluorosis and osteoporosis (Suga, 1982; Fejerskov et al., 1983; Angmar-Mansson and Whitford, 1984; DenBesten and Heffernan, 1989; Suckling, 1989).

Richards et al. (1986) showed, in pigs given daily doses of 2 mg F/kg body weight for eight months, that only enamel exposed to F at the pre-eruption maturation stage became fluorosed. Richards (1990), in reviewing animal experiments, also showed evidence on the relation concerning the production of fluorosis, the plasma F concentration, and the stage of enamel development at which F was given.

Human studies.


Systemic fluoride and dental caries in human permanent teeth.

As mentioned above, studies undertaken before the availability of fluoride-containing dentifrices need to be re-assessed critically.

In this light, Thylistrup (1990) looked at some of the early epidemiological evidence, specifically the studies of Klein (1945, 1946), those from Grand Rapids after 15 years of fluoridation (Arnold et al., 1962), and the reviews of Møller (1965), Backer Dirks et al. (1978), and Nikiforuk (1985). The early workers' concept was that increased caries resistance was provided to teeth by pre-eruptive incorporation of fluoride, and that this was the widely accepted explanation for this phenomenon. It is now realized that low concentrations of F ions in the dental environment reduce apatite solubility and favor mineralization (ten Cate and Duijsters, 1983a, b; Borsboom et al., 1985). Weatherell et al. (1977) have shown clearly that much of the enamel F acquired during development of the anterior teeth is removed later by abrasion and can play no part in reducing caries. In the cervical regions, however, the F concentration increases with age and may contribute to the caries-preventive effect. Crabb (1976), in an important study, demonstrated that human premolars have an outer porous layer of enamel at the time of eruption, which is presumably mineralized during post-eruption maturation, and that this is accelerated by topical F. The role of fluoride in

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pre-eruptive maturation and post-eruptive maturation is clearly possible during these periods. Beltran and Burt (1988) concluded that both pre- and post-eruptive F contributed to the decline of caries in the 1970's and 1980's. Groeneveld et al. (1990) reviewed fluoride pre- and post-eruptive effects using longitudinal data from the Culemborg (non-F) and Tiel (F) studies in The Netherlands. They stated that 66% of the greatest reduction in pit- and fissure caries came from pre-eruptive fluoride while in smooth surfaces this effect was reduced to 25%. For approximal surfaces, the reduction was due half to pre- and half to post-eruptive fluoride, although the total reduction in surfaces was greater for smooth surfaces compared with pits and fissures.

Hargreaves and Chester (1973) suggested, from longitudinal studies with fluoride dentifrices on the non-fluoridated Isle of Lewis, that the reduction of dental caries found in schoolchildren was due to the topical post-eruptive effect of fluoride from the dentifrice.

An analysis of studies of fluoridation of water supplies and reduction of dental caries in Toronto, Canada (Lewis, 1976), convincingly shows the effect of water fluoridation at 1 ppm on this community related to the age of fluoridation onset (see below). These studies demonstrated that fluoride over a ten-year period reduced DMFT values by between 40 and 50% (Fig. 1) if the fluoride was available from birth.

Higher levels of drinking-water fluoride—i.e., up to 7 ppm—although having a significantly greater effect than 1 ppm on reduction of caries, would be expected to result in enamel fluorosis, as shown by Englander and DePaola (1979). A review of the early history of fluorides as antacaries is given by Cawson and Stocker (1984). Interpretation of these studies has resulted in changing recommendations over the years by use of such criteria as age; height and weight of individuals related to fluoride safety; toxic levels of fluoride; ambient air temperatures and fluid intake; fluoride from food sources and other environmental conditions; fluoride availability throughout the life of an individual; and the types and forms of different fluoride sources, among other factors (Subba Rao, 1984; Hargreaves, 1990; Whitford, 1990). The US Environmental Protection Agency prepared a report in 1985 as a result of the Surgeon General's request. This gave a safe fluoride range of from 0.1 to 0.5 mg/day for infants less than six months old to 1.5 to 4.0 mg/day (0.7 to 2.0 mg/L in drinking water) as the appropriate range for adults. Clovis and Hargreaves (1988) and Clovis et al. (1988) endorsed 1 mg/L of fluoride in drinking water for maximum prevention against dental caries with minimum risk of objectionable fluorosis, these data being based on available evidence of fluorides in fluids in a temperate zone.

Hargreaves et al. (1988a) looked at commencement date of supplementation of 1.0 mg fluoride per day and showed that, for children aged 11-13 years of age, those starting supplementation before 3 months of age had significantly less dental caries compared with those children starting supplementation at a later date, i.e., between 6 months and 3 years of age. Both supplemental groups had significantly less dental caries than a group of children not taking any form of fluoride supplement. The earlier starting date did marginally increase fluorosis compared with the other two groups (Hargreaves et al., 1988b). However, more recently, Stephen et al. (1991) found no significant differences in enamel mottling between child cohorts who had never used fluoride supplements and those who commenced fluoride drop/tablet regimens from birth to seven years of age.

Systemic incorporation of fluoride into the permanent dentition reduces dental caries, mainly by (a) inhibition of demineralization (Isaac et al., 1958; Jenkins, 1963; Healey and Ludwigs, 1966; Cutress, 1972; Tyler et al., 1986); (b) enhancement of remineralization by F released from dissolved enamel (although a greater effect of remineralization occurs from F acquired topically by saliva and plaque); (c) a small effect on the morphology of the teeth, e.g., shallow fissures (Cooper and Ludwigs, 1965; Simpson and Castaldi, 1969; Aasenden and Peebles, 1974); and (d) an effect on oral bacteria, as shown in an extensive current review of antibacterial effects of fluorides (Murray et al., 1991).

Brunelle and Carlos (1990) suggested that when the 'background' effect of topical fluoride was controlled for US schoolchildren in the second national epidemiological survey completed in 1987, those living in a water-fluoridated community had approximately 25% less caries, and that water fluoridation was playing a dominant role in the US caries decline.

### Systemic fluoride and dental caries in primary teeth

Several well-proven statements related to the timing of fluoride availability and the reduction of dental caries in the primary dentition are available in the literature (Poulsen and Larsen, 1975; Lewis, 1976; Driscoll and Horowitz, 1978; Review of Perspectives on the Use of Prenatal Fluorides, a symposium, 1981).

Gedalia (1964a,b) showed in Israeli studies that primary teeth, examined from regions with different levels of fluoride in the drinking water, had higher levels of fluoride in the tooth structures with increasing fluoride levels in the water supplies. Hargreaves (1972) also showed that fluoride levels in primary enamel, from studies in the North of England, increased with fluoride levels of the drinking water up to 2.2 mg/L.

Glenn (1977, 1979) and Glenn et al. (1984) examined the caries protection conveyed by a fluoride supplement during pregnancy. Glenn's studies suggested that prenatal fluorides...
were beneficial in reducing dental caries, but her studies need to be repeated with the use of sound scientific principles. Edelstein (1979) and others expressed concerns about uncontrolled aspects of her studies.

Several studies of the placenta acting as a possible barrier to fluorides have been positive when fluoride was increased to high levels in experimental animals (Ericsson and Malms, 1962), but fluoride can be incorporated into tooth enamel and dentin of developing human teeth during pregnancy in increasing concentrations as fluoride levels in the drinking water rise up to 2 mg/L (Gedalia, 1964a,b; Hargreaves, 1972; LeGeros et al., 1985). How much of the fluoride available is incorporated during pre-natal tooth development is not known, but it would be small when related to the primary molar teeth because of their developmental pattern before birth.

Other factors that must be taken into account are the availability of fluoride from human milk of breast-fed children during the first year after birth (Ekstrand et al., 1984; Hargreaves, 1989) and from fluoride levels found in baby formulae and baby foods. Many of these manufactured baby products, prior to the mid-1980's, had significant levels of fluoride (up to 16 ppm), which could have influenced early research studies (Singer and Ophau, 1979).

Fluoride levels are always much higher in dentin than in enamel. In the resorption of primary tooth roots, a reservoir of fluoride may be readily available to developing successional permanent teeth (but not to teeth that do not have primary tooth predecessors, i.e., permanent molars) from the primary tooth dentin (Weatherell and Hargreaves, 1986), during the period of pre-eruptive maturation.

Lewis (1976), in examining the Toronto findings related to dental caries activity in the primary dentition over a ten-year period of water fluoridation and covering individuals with lifetime exposure to fluoridated water, found, on comparison with data prior to water fluoridation, that caries-free rates of 5-year-olds entering school increased from 27% to 58%; the need for extraction of teeth decreased from 25% to 8% (Fig. 2), and for the 5-to-9-year-olds, def values were reduced by approximately 50% (Fig. 3). In a study in Scotland, where fluoride was removed from water supplies, Stephen et al. (1987) found that 5-year-old children had a 39.6% increase in dmfs and that there was a 10.1% reduction in those children who were caries-free, when compared with the time of water fluoridation only five years earlier. Driscoll (1974), in looking at the use of fluoride supplementation in young children and the effect on the primary dentition, reviewed 18 studies and showed that the majority (15) had positive effects in reducing dental caries in the primary teeth. The earlier the children started taking the supplements after birth, the better were the findings related to a reduction in dental caries in the primary teeth.

Confounding factors relating to effectiveness of fluoride drops and tablets.

A current review of the dosage of fluoride tablets and drops is given by Murray et al. (1991). The earlier the time the fluoride is given, the greater the effectiveness of caries reduction. Confounding factors such as socio-economic status appear to have little effect (Andersson and Grahnén, 1976); parental co-operation, however, needs a high level of motivation related to adequate compliance. Diet and oral hygiene of the child have been suggested as influencing the outcome. Granath et al. (1978) showed that caries reductions from fluoride tablet supplementation for 4-year-olds were not as significant for children taking fluoride tablets when compared with children having no tablets if diet and oral hygiene were kept constant in the analysis. Tijmstra et al. (1978), in studies with 15-year-old children, also found a difference: Caries experience for children who had not taken tablets fell over 10% when the data were standardized on diet, oral hygiene, and father's occupation.

Factors such as the ones listed above should be considered when fluoride supplementation data are being analyzed.

Recommendations.

It appears, in assessment of information that is available with use of four established criteria of fluoride action for the reduction of dental caries—(a) by reduction of enamel solubility when incorporated into the mineral structure, (b) by fostering the remineralization of incipient enamel lesions and the deposition of fluoride within dental plaque, (c) by reduction in the net rate of transport of matter out of the enamel surface, under acidic conditions, by induction of the re-precipitation of fluoridated hydroxyapatite phases within enamel, and (d) by reduction of the rate of acid production of cariogenic oral bacteria (reviewed by Murray et al., 1991)—that maximum caries reduction is produced when fluoride is available for incorporation during all stages of tooth formation and by topical effect after eruption. A meeting on fluoride ingestion and dosage of fluoride dietary supplements, held in London in 1990, examined the use of fluorides in the UK, and although many issues were raised, the decision was that there be no change in the current fluoride supplement dosage for the UK (James, 1990). The timing of when fluoride should be incorporated without causing fluorosis of permanent tooth enamel, however, must be realized, and benefits and adverse findings cannot be looked at in isolation. The timing of the fluoride availability would involve all stages of tooth development, although the most effective time seems to be during the pre- and post-eruptive maturation periods.

It is recommended, from the many research studies to date, that good benefit is achieved with respect to the permanent dentition: (1) from water fluoridation to 1.0 mg/L in temperate zones and to 0.7 mg/L in tropical zones, throughout life (Hargreaves, 1980); (2) from fluoride supplementation started before the pre-eruptive maturation period (i.e., at approximately 5 years of age) until completion of permanent tooth eruption, which would give good protection against dental caries [Fluorosis, if produced, should not be severe at this time of fluoride incorporation into tooth structures (Fejerskov et al., 1988). Compliance, however, would always remain a problem, since fluoride supplementation of this type would be under the control of the individual, and fluoride intake could be either neglected or excessive]; and (3) from availability of fluoride through established topical sources, after tooth eruption. These sources would be beneficial and would not cause dental fluorosis.
Future research.

Further studies that need to be undertaken in respect of timing of systemic fluorides and dental caries prevention include:

(1) timing and amounts of fluoride given to mothers during the perinatal period related to dental caries prevention of their children's teeth;

(2) epidemiology studies focusing on the starting of fluoride supplementation during the pre-eruptive maturation periods compared with fluoride supplementation from birth;

(3) social factors that might influence compliance in fluoride tablet/drop studies;

(4) methods of consumption of fluoride supplements (drops/tablets) for the provision of systemic incorporation as well as topical effects on tooth enamel in the mouth before actual ingestion;

(5) further evaluation of data collected from epidemiological and clinical trial studies completed before the ready availability of fluoride from topical sources—i.e., studies in Europe prior to 1971 and in North America prior to 1975—since it would not be possible for many of these well-conducted investigations to be repeated;

(6) examination of the release of fluoride during primary tooth resorption and incorporation of the released fluoride into developing permanent successional teeth. Such studies could demonstrate a secondary beneficial aspect of fluoride incorporation in the primary teeth; and

(7) effects of different starting times of systemic fluoride availability on dental caries reduction for specific teeth and specific tooth surfaces.

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