Systemic Benefits of Fluoride and Fluoridation

Ernest Newbrun, DMD, PhD

Abstract

Clinical trials, animal studies, and in vitro tests demonstrate effectiveness of exposure to topical (posteruptive) fluoride in caries prevention and reduction of enamel dissolution. However, careful analyses of human epidemiologic data on caries increments, following communal water fluoridation, show unquestionably that fluoride has an important preeruptive effect on caries in permanent teeth, particularly on pit and fissure surfaces. These preeruptive or systemic benefits also apply to the use of fluoride supplements or fluoridated salt when used continuously during the period of tooth formation. The role of systemic fluoride in caries prevention is neither "minimal" nor "of borderline significance." On the contrary, it is a major factor in preventing pit and fissure caries, the most common site of tooth decay. Maximal caries-preventive effects of water fluoridation are achieved by exposure to optimal fluoride levels both pre- and posteruptively.

Key Words: dental caries, extraction, fluoride, systemic, topical.

Homage to Herschel Horowitz (1932–2003)

I have known our dear colleague Herschel S. Horowitz since he came to San Francisco as chief of the Epidemiology Branch at Dental Health Center in 1966. How can I condense into two minutes of my assigned time a friendship of almost 40 years? How can I do justice to Hersh's career and his manifold contributions to dental research in the areas of epidemiology, prevention, dental public health, ethical study design, and of course fluorides? Obviously, I can only be selective in pointing out some of the salient issues that Hersh thought were important. In relation to this symposium, Dr. Horowitz was a tireless advocate of communal water fluoridation, nationally and internationally, speaking to city councils, government entities, water boards, and court hearings all over the world. In those countries where water fluoridation was impractical, he actively promoted salt fluoridation.

Hersh had strong convictions on which he willingly spoke out in public, especially on important public health issues like fluoridation or nutrition. I recall one instance in the 1970s when he wanted to testify at hearings of the FCC on the deleterious effects of television advertising on children's dental health. At that time Hersh was a commissioned officer of the USPHS, and as chief, Community Programs Section, Caries Prevention and Research Branch, National Institute of Dental Research, he had to obtain permission from his immediate superior, Dr. James Carlos, who refused his request. Accordingly, Hersh took vacation time to testify as a private citizen. Nevertheless, Jim Carlos wrote a negative report in Hersh's annual personnel file. Maybe that is why he never made it to admiral.

Seriously though, this illustrates the sort of person Hersh was, always willing to stand up for his principles. We served on committees and councils together and often argued about details, minutiae, pilpul (penetrating investigation, disputation, searching debate, and drawing of conclusions). I thought that dental public health investigators needed to have a better biological basis for their training and research. Hersh thought that too many basic scientists lacked thorough statistical and epidemiologic preparation. But on important principles we generally agreed—namely, that no matter what the findings were of in vitro studies or animal testing, the ultimate proof lay in clinical epidemiologic studies, preferably in carefully conducted and suitably designed human clinical trials.

Introduction

The concept that fluoride action was exclusively systemic or preeruptive was very short lived, from the early 1940s until no later than the mid-1950s, by which time there was growing evidence of both systemic and topical benefits of fluoride exposure. In this presentation we will focus on the epidemiologic data documenting that the systemic benefits of fluoride are significant, not minimal or borderline, as some have suggested. We should not throw out the baby with the bathwater in claiming the predominant fluoride benefits are topical, but recognize that for maximal fluoride protection there needs to be both systemic and topical exposure.

Early Studies on the Benefits of Fluoride in Prevention of Dental Caries

When the link between fluoride in the drinking water and enamel fluorosis and later with reduced caries prevalence was first recognized in the 1940s and 1950s, the emphasis was on fluoride ingestion "at least during the formative period" of the teeth (1,2). Fluoride was thought to exert its effect in reducing caries only when taken in the diet during tooth development and would be of little benefit to persons who were more than 5 or 6 years of age at the time that fluoride ingestion began (3). It did not take long to find that this was not the case. Japanese American children, 8–10 years old, who were relocated during World War II in 1943 to the Arizona Center where the water contained 3 ppm fluoride, experienced considerably less decay in their first permanent molars, which had erupted when fluoride exposure began (4). Later, Arnold ac-

Dr. Newbrun is professor emeritus at the University of California San Francisco, Department of Stomatology, 1823 8th Avenue, San Francisco, CA 94122. E-mail: newbrun@itsa.ucsf.educ. [J Public Health Dent 2004;64(Spec Iss 1):35-9]

knowledged a posteruptive benefit of optimal levels of fluoride as used in communal water fluoridation. In the Grand Rapids study, he rationalized that if the benefits were exclusively preeruptive, one would not expect any caries reduction in teeth whose crowns had already formed at the time of fluoridation. "The results of the 16-year-olds, for example, do not support this hypothesis. There have been definite reductions in dental caries in this group of children. It is to be remembered that these children in most cases were those who presumably had the coronal portion of their permanent teeth already calcified when fluoridation started" (5).

Marthaler, Driscoll, and others have shown a clear-cut posteruptive benefit to first permanent molars of children, aged 6 to 14 years, participating in school-based fluoride tablet programs (6-8). However, late-erupting teeth benefited twice as much as early-erupting teeth, demonstrating the importance of preeruptive fluoride exposure in addition to posteruptive exposure. In regard to water fluoridation, Marthaler stated that: "From all the data presented, it is evident that the systemic fluoride effect is most pronounced with respect to the prevention of fissure caries." He also concluded that: "Systemic fluorides are important for obtaining maximum benefit regarding pit and fissure caries and to a lesser degree, regarding approximal surfaces. However, continued posteruptive supply of fluorides is indispensable since otherwise the advantage of systemic fluoride will be lost" (9).

A preeruptive benefit of fluoride in reducing caries has been demonstrated in rats fed by gastric intubation, thereby avoiding any topical contact of fluoride (10). In this study the caries reduction on the third molars, which had the longest preeruptive fluoride exposure, was 93 percent on smooth surfaces and 30 percent on sulcal surfaces, not an insignificant effect. Of course the benefit was greater when rats ingested fluoride orally, so that there was both systemic and topical exposure—but the preeruptive benefit was indisputable (Table 1).

TABLE 1
Effect of Fluoride Administered by Stomach Tube or Orally on Smooth Surface and Sulcal Caries in Third Molars of Rats

Treatment	Caries Score Smooth	% Reduction	Caries Score Sulcal	% Reduction
Control: no F	7.0	—	2.3	—
F stomach tube	0.5	93	1.6	30
F orally	0.0	100	0.8	65

Source: adapted from Larson et al. (10).

It was recognized that a major fraction of absorbed fluoride was deposited in mineralized tissue, mostly the skeleton, but also the teeth, by incorporation into the apatite crystal (11), thereby reducing the solubility of enamel on acid exposure. Although it was also known that topically applied fluoride in paste or liquid form would also reduce caries (12,13), it was thought that this required relatively higher concentrations of fluoride acting externally.

Analyses of Epidemiologic Studies on the Preeruptive Effect of Fluoride in Caries Prevention

Let us examine some human epidemiologic data. In the United States, early studies noticed that children who drank water with a high natural fluoride level (8 ppm) water and subsequently consumed fluoride-deficient water experienced less than half the caries (DMFT) of children who had ingested fluoride-deficient water from birth (14). These findings were also confirmed in adults who had ingested fluoridated water only during the first eight years of childhood, yet had 32 percent less DMFT (15). Similarly, appreciable caries reduction in the deciduous teeth was seen only in children who had been exposed to fluoridated water since birth (16). These epidemiologic observations led DePaola to conclude "that [they] can only be explained in terms of preeruptive fluoride effects" (17).

In a later study by Burt and colleagues, children who moved from fluoridated communities to nonfluoridated Coldwater, MI, before their permanent first molars had erupted, developed less caries than children who had lived in that nonfluoridated community all their lives. These findings forced Burt, who considers the benefits of fluoridated water ingestion are topical, to grudgingly concede "that preeruptive benefits cannot be ruled out" (18).

Dutch investigators have looked at the relative pre- and posteruptive effect of fluoride by comparing the effectiveness in caries prevention in children of different ages at the onset of water fluoridation. They compared caries increments in the Netherlands in fluoridated Tiel and Culemborg, the nonfluoridated control community (19,20). They concluded that fluoride had an important pre- and posteruptive effect on caries in permanent teeth. On approximal surfaces 50 percent of the benefit was preeruptive and 50 percent of the benefit was posteruptive, whereas in pits and fissures 66 percent of the caries prevention was preeruptive and 33 percent was posteruptive. On free smooth surfaces, reduction was 25 percent preeruptive and 75 percent posteruptive. Limeback has criticized these Dutch analyses for ignoring first permanent molars that erupted before age 6 years and would have had a longer posteruptive exposure: "Age 6 years should not be used as the absolute cutoff age for the eruption of first permanent molars prior to which the effects are considered only preeruptive" (21). Limeback ignores the fact that eruption tables are based on averages; that while some first permanent molars may erupt early, others erupt later than 6 years of age and would have had longer preeruptive benefit; and that 6 years is an average eruption age.

More recently, investigators studied caries prevalence in 6- to 15-year-old schoolchildren in South Australia (n=9,690) and Queensland (n=10,195) to determine relative pre- and posteruptive benefits (22). In their analyses, they not only factored in eruption dates in boys and girls, but also lifetime fluoride exposure based on residential history, to allow for mobility of each individual (22). In addition, socioeconomic status measures and use of discretionary fluoride were determined by questionnaire. Overall

TABLE 2
Bivariate Associations: Mean DMFS by Exposure Categories

Exposure (% Lifetime)	DMFS 6	$DMFS_{p\&f}$	$DMFS_{app}$	$DMFS_{free}$
Pre & post=0	0.670	0.590	0.058	0.023
Pre<post	0.682	0.605	0.056	0.021
Pre=post	0.632	0.548	0.067	0.016
Pre>post	0.513*	0.452*	0.046	0.015†
Pre & post ≥90	0.484*	0.447*	0.025*	0.012*

Ordinary least squares regression against reference category (pre and post=0).
*Significant at $P<.01$.
†Significant at $P<.05$.
Source: Singh et al. (22).

DMFS scores for first molars and surface types (pit and fissure, approximal, free) and different fluoride exposure categories are shown in Table 2.

The conclusions of these Australian studies were that a high pre- and posteruptive fluoride exposure (≥90 percent of lifetime) had the maximum caries preventive effect on all surface types of permanent first molars. There was an exposure-response relationship between preeruptive exposure and caries. Exposure to posteruptive fluoride alone did not suffice in restricting caries to low levels. Pit and fissure surfaces benefit the most from preeruptive exposure to fluoride, confirming the earlier Dutch studies.

The Naysayers

In a lengthy review paper presented at a joint IADR/ORCA symposium in 1989, Thylstrup misinterpreted some clinical studies, stating that: "The similarities in caries reductions obtained in water fluoridation studies and long-term studies with topically administered fluoride regimens, including fluoride-containing dentifrices, indicate that the preeruptive effect of fluoride is of borderline significance to the more significant posteruptive effect" (23). Actually, no statistical analyses were included to substantiate this claim. I have always felt that some of our Scandinavian and Dutch colleagues have reacted to water fluoridation like the fabled fox and the grapes. For political or legal reasons they have not succeeded in achieving communal water fluoridation. Also, they have a surplus of dentists, and many are kept employed delivering preventive treatments such as topical fluoride applications. By a combination of such intensive fluoride therapy, including supervised fortnightly rinsing and home use of fluoride-containing dentifrices, caries prevalence has indeed been lowered (24). However, in Ireland, maximum caries reduction was only achieved when children were exposed to both systemic fluoride in the water supplies and topical fluoride such as in dentifrices (25).

North America has not been without our naysayers, who have trivialized the importance of preeruptive fluoride exposure, stating that: "Fluoride incorporated during tooth development is insufficient to play a role in caries protection" (26), or "The role of systemically ingested fluoride on caries is minimal" (27). Others have taken up the mantra that the benefits of water fluoridation are primarily topical/posteruptive (18,21,28,29). The authors of the CDC recommendations for using fluoride cite some epidemiologic analyses supporting the benefits of preeruptive fluoride exposure (9,20,30). Nevertheless, they put little stock in the value of preeruptive fluoride exposure, stating that "laboratory and epidemiological research ... indicates that fluoride's predominant effect is posteruptive and topical" (28). Actually, their basis for this conclusion is not supported by any epidemiologic studies; rather, they cite two references to physicochemical laboratory research and a chapter in a textbook arguing against a systemic route on a mechanistic and theoretical basis (31). One of Hersh Horowitz's last publications pointed out these shortcomings in the CDC report (32).

The apparent reason offered for the claim that the major effect of fluoride is posteruptive is: "a high fluoride concentration in sound enamel cannot alone explain the marked reduction in dental caries that fluoride produces" and rests on papers on physicochemical perspectives on the cariostatic mechanisms (33,34), not on any epidemiologic data. It may well be that the mechanism of fluoride action is by fostering remineralization and that fluoride on the surface of the apatite crystal is more important than fluoride within the crystal; however, these are proposed models of the caries process, not clinical findings.

Discussion

I have been involved in both clinical and laboratory research throughout my academic career. I recognize the value of in vitro models where factors are under close experimental control, more so than in clinical trials and certainly more so than in epidemiologic studies. The ultimate test of a laboratory-based hypothesis is whether it can be substantiated by epidemiologic findings in humans. If not, then the hypothesis must be rejected.

Let me remind you of a similar mistaken, oft-repeated, statement: "After 35 years of age more teeth are lost because of periodontal disease than dental caries." This widely accepted adage was based on the observation that the prevalence of periodontal disease increases directly with aging and early studies on tooth extractions on various convenience populations, showing periodontal disease as an increasing factor in tooth extraction after about age 35 years (35,36). It found its way into textbooks (37), statements from dental organizations, and on the Web. There was a widely used diagram (similar to those used to "prove" fluoride acts only topically) that showed tooth extraction due to dental caries peaking at age 20, then declining, while tooth extraction due to periodontal disease started at about age 20 and kept increasing, supposedly surpassing caries extraction rates at age 35. But simply repeating an incorrect claim over and over again does not make it correct.

Extractions for periodontal reasons increase with age (38) and various studies have reported that extractions for periodontal disease exceeded those for caries after the age of 40, 50, or 60 years. However, teeth requiring extraction for periodontal reasons are extremely rare in the United States

TABLE 3
Reason for Tooth Extractions

Author	Year	Country	Proportion of Extractions (%)		
			Caries	Periodontal Disease	Other*
Allen	1944	USA	46	46	8
Ainamo et al.	1984	Finland	60	18	22
Cahen et al.	1985	France	48	32	20
Agerholm & Sidi	1988	England, Wales	40	27	33
Kay & Blinkhorn	1986	Scotland	50	21	29
Brown et al.	1989	USA	70	19	11
Chancey et al.	1989	USA	33	19	48
Niessen & Weyant	1989	USA	63	33	4
Klock & Haugejorden	1991	Norway	35	19	46
Stephens et al.	1991	Canada	63	34	23
Murray et al.	1997	Canada	29	36	35
Haddad et al.	1999	Jordan	28	33	39
McCaul et al.	2001	Scottland	55	17	28
Cardona et al.	2002	Spain	50	34	16

*Orthodontics, prosthodontics, third molars, root fracture, etc.

(39). Epidemiologic studies in most countries reveal that overall caries continues to be the leading cause of tooth extractions in adults (Table 3) (39-53). Fewer teeth are now being extracted and the reason for tooth extraction has changed as oral hygiene has improved and caries prevalence has fallen.

When viewed through the "retrospectroscope," a magical instrument for anachronistic hindsight, the Dutch and Australian analyses (20,22) fall short of the ideal. Convenience samples of populations were used, and few large-scale studies of communal water fluoridation have done otherwise (54). The examiners were not "blinded," yet in other studies, when the clinical diagnosis of carious lesions have been performed using blind clinical and radiological examination of children and strictly objective criteria such as missing permanent molars, no evidence of examiner bias has been found (55). These sorts of disparagements have been raised by opponents of communal water fluoridation, e.g., Sutton, Groth, Diesendorf, Colquhoun, and Limeback over many years (21,56-60) and have little real validity (61). A more serious criticism is the fact that US investigators have undertaken no similar analyses since water fluoridation was first initiated in Grand Rapids, Michigan, almost 60 years ago (62). Why has the NIDCR or CDC not issued requests for proposals to conduct such studies and why have they failed to fund such investigations?

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